

THE MD ANDERSON MANUAL OF MEDICAL ONCOLOGY

FOURTH EDITION

HAGOP M. KANTARJIAN
ROBERT A. WOLFF
ALYSSA G. RIEBER

Mc Graw Hill

The MD Anderson Manual of Medical Oncology

NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

The MD Anderson Manual of Medical Oncology

Fourth Edition

Editors

Hagop M. Kantarjian, MD
Professor of Medicine
Chair, Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, Texas

Robert A. Wolff, MD
Professor of Medicine
Department of Gastrointestinal Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Alyssa G. Rieber, MD
Professor of Medicine
Department of General Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Mc Graw Hill Education

New York Chicago San Francisco Athens London Madrid Mexico City
Milan New Delhi Singapore Sydney Toronto

Copyright © 2022 by McGraw Hill, LLC. All rights reserved. Except as permitted under the United States Copyright Act of 1976, no part of this publication may be reproduced or distributed in any form or by any means, or stored in a database or retrieval system, without the prior written permission of the publisher.

ISBN: 978-1-26-046765-9
MHID: 1-26-046765-1

The material in this eBook also appears in the print version of this title: ISBN: 978-1-26-046764-2,
MHID: 1-26-046764-3.

eBook conversion by codeMantra
Version 1.0

All trademarks are trademarks of their respective owners. Rather than put a trademark symbol after every occurrence of a trademarked name, we use names in an editorial fashion only, and to the benefit of the trademark owner, with no intention of infringement of the trademark. Where such designations appear in this book, they have been printed with initial caps.

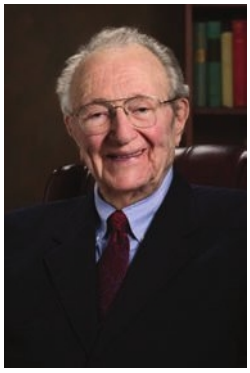
McGraw-Hill Education eBooks are available at special quantity discounts to use as premiums and sales promotions or for use in corporate training programs. To contact a representative, please visit the Contact Us page at www.mhprofessional.com.

TERMS OF USE

This is a copyrighted work and McGraw-Hill Education and its licensors reserve all rights in and to the work. Use of this work is subject to these terms. Except as permitted under the Copyright Act of 1976 and the right to store and retrieve one copy of the work, you may not decompile, disassemble, reverse engineer, reproduce, modify, create derivative works based upon, transmit, distribute, disseminate, sell, publish or sublicense the work or any part of it without McGraw-Hill Education's prior consent. You may use the work for your own noncommercial and personal use; any other use of the work is strictly prohibited. Your right to use the work may be terminated if you fail to comply with these terms.

THE WORK IS PROVIDED "AS IS." McGRAW-HILL EDUCATION AND ITS LICENSORS MAKE NO GUARANTEES OR WARRANTIES AS TO THE ACCURACY, ADEQUACY OR COMPLETENESS OF OR RESULTS TO BE OBTAINED FROM USING THE WORK, INCLUDING ANY INFORMATION THAT CAN BE ACCESSED THROUGH THE WORK VIA HYPERLINK OR OTHERWISE, AND EXPRESSLY DISCLAIM ANY WARRANTY, EXPRESS OR IMPLIED, INCLUDING BUT NOT LIMITED TO IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. McGraw-Hill Education and its licensors do not warrant or guarantee that the functions contained in the work will meet your requirements or that its operation will be uninterrupted or error free. Neither McGraw-Hill Education nor its licensors shall be liable to you or anyone else for any inaccuracy, error or omission, regardless of cause, in the work or for any damages resulting therefrom. McGraw-Hill Education has no responsibility for the content of any information accessed through the work. Under no circumstances shall McGraw-Hill Education and/or its licensors be liable for any indirect, incidental, special, punitive, consequential or similar damages that result from the use of or inability to use the work, even if any of them has been advised of the possibility of such damages. This limitation of liability shall apply to any claim or cause whatsoever whether such claim or cause arises in contract, tort or otherwise.

Dedication



Emil J Freireich, MD
March 16,1927 – February 1, 2021

Dedication of the fourth Edition of "The MD Anderson Manual of Medical Oncology" to Emil J Freireich, a Legendary Trailblazer in Cancer and Leukemia Research and Therapy

Emil J Freireich was a founding father of modern cancer research, and leader of the world's first generation of cancer research pioneers.

Following his medical training at the University of Illinois College of Medicine at Chicago, and internal medicine training at Cook County Hospital and Presbyterian Hospital, he moved to the National Cancer Institute (1955-1965), where he made his first seminal discoveries: the benefit of platelet transfusions in reducing bleeding; the design of the first-ever continuous-flow blood cell separator that extracted platelets from whole blood; the development of multidrug regimens that paved the way for the cure of childhood acute lymphoblastic leukemia (ALL).

In 1965, Freireich moved to Houston and spent the next 55 years at MD Anderson, his real home. He was a founding member of the institution, which owed much of its early success and reputation to his work and that of his mentees. Freireich's name became synonymous with that of MD Anderson. He created a department of Developmental Therapeutics (DT), dedicated to medical cancer research and to developing novel cancer strategies. Over the next 15 years, he attracted hundreds of cancer researchers from all over the world who, like him, were convinced that cancer was curable and were determined to accomplish this. Many of the early chemotherapy drugs (cytarabine, Adriamycin, cisplatin, others) were developed during this period, and became building blocks for curative combinations. Together with Dr Gerald Bodey, Freireich discovered the association between neutropenia and increased risk of infections and developed the concept of empiric antibiotic therapy to prevent and treat fever and infections in patients with cancer. This, along with platelet transfusions, made cancer care safer and opened the research venues for intensive chemotherapy and stem cell transplantation in hematologic and solid tumors. The pheresis machines he helped to create were later used to collect stem cells for the purpose of transplantation.

In DT, and later as a senior leader at MD Anderson, Freireich trained and mentored hundreds of oncologists, many of whom later created their own legacies and helped hundreds of thousands of patients with cancer. He also created in 1966 the first training fellowship program in cancer and established clinical-translational research and care as a new critical discipline in oncology.

To the hundreds of us who trained under Freireich, he and his stories and education are indelibly cemented in our memories. In recognition of his massive contributions to education in cancer research and care, we dedicate this fourth edition to Emil J Freireich.

This page intentionally left blank

Contents

Contributors xi

A Brief History of MD Anderson Cancer Center xxv

Foreword xxix

Preface xxxi

I LEUKEMIA

Section Editor: *William G. Wierda*

1. **Acute Lymphoblastic Leukemia 3**
   Hind Rafei, Sergej N. Konoplev, Sa A. Wang, Nicholas J. Short, Hagop M. Kantarjian, Elias J. Jabbour
2. **Adult Acute Myeloid Leukemia 23**
   Tapan M. Kadia, Joseph D. Khoury, Farhad Ravandi
3. **Chronic Lymphocytic Leukemia and Associated Disorders 49**
   Nitin Jain, Philip Thompson, Carlos Bueso-Ramos, Susan M. O'Brien, William G. Wierda
4. **Chronic Myeloid Leukemia 67**
   Koji Sasaki, Elias Jabbour, Jorge Cortes, Hagop Kantarjian
5. **Myelodysplastic Syndromes: The MD Anderson Cancer Center Approach 91**
   Kelly Chien, Carlos Bueso-Ramos, Guillermo Garcia-Manero
6. **Philadelphia Chromosome-Negative Myeloproliferative Neoplasms 119**
   Prithviraj Bose, Lucia Masarova, Hesham M. Amin, Srdan Verstovsek

II LYMPHOMA AND MYELOMA

Section Editor: *Nathan H. Fowler*

7. **Follicular Lymphoma 165**
   Paolo Strati, Jillian R Gunther, L. Jeffrey Medeiros, Loretta J. Nastoupil
8. **Marginal Zone and Other Small Cell Lymphomas 183**
   Melody Becnel, Felipe Samaniego
9. **Aggressive B-Cell Lymphomas 191**
   Raphael Steiner, Jason R. Westin, Sergej N. Konoplev, Luis E. Fayad, L. Jeffrey Medeiros
10. **Mantle Cell Lymphoma 227**
    Preetesh Jain, Michael Wang
11. **Nodal Peripheral T-Cell Lymphoma 253**
    Ranjit Nair, Francisco Vega, Swaminathan P. Iyer
12. **Cutaneous Lymphomas 269**
    Auris Huen
13. **Hodgkin Lymphoma 291**
    Collin K. Chin, L. Jeffrey Medeiros, Fredrick B. Hagemeister, Hun J. Lee
14. **Systemic Immunoglobulin Light Chain Amyloidosis 323**
    Gregory P. Kaufman, Muzaffar H. Qazilbash, Krina Patel, Sheeba Thomas, Robert Z. Orlowski, Hans C. Lee
15. **Waldenström Macroglobulinemia 333**
    Melody Becnel, Gregory P. Kaufman, Elisabet E. Manasanch, Krina Patel, Hans C. Lee, Robert Z. Orlowski, Sheeba Thomas
16. **Multiple Myeloma 341**
    Paul Lin, Gregory P. Kaufman, Hans C. Lee, Elisabet E. Manasanch, Melody Becnel, Sheeba Thomas, Donna Weber, Robert Z. Orlowski, Krina Patel
17. **Cellular Therapy for Lymphoma 363**
    Sairah Ahmed, Simrit Parmar, Sattva Neelapu

III STEM CELL TRANSPLANTATION

Section Editor: *Elizabeth J. Shpall*

18. **Autologous Hematopoietic Progenitor-Cell Transplantation 383**
    Neeraj Saini, Yago Nieto
19. **Allogeneic Transplantation 397**
    Rohtesh S. Mehta, Chitra Hosing
20. **Alternative Donor Transplants: Cord Blood Transplant 427**
    Hind Rafei, Amanda Olson, Rohtesh S. Mehta, Betul Oran, Katayoun Rezvani, Elizabeth J. Shpall

21. **Alternative Donor Transplants: Haploidentical Hematopoietic Stem Cell Transplantation 447**
Samer A. Srour, Richard E. Champlin, Stefan O. Ciurea

22. **Cellular Therapy in Allogeneic Hematopoietic Cell Transplantation 457**
Amanda Olson, Jeremy Ramdial, Uri Greenbaum, Paul Lin, Katayoun Rezvani, Partow Kebriaei

IV LUNG CANCER
Section Editor: *Bonnie S. Glisson*

23. **Small Cell Carcinoma of the Lung 475**
Jeremy A. Ross, Lauren A. Byers, Carl M. Gay

24. **Non–Small Cell Lung Cancer: General Principles, Management of Localized Disease, and Treatment of Metastatic Disease without Oncogene Drivers 495**
Mehmet Altan, Joshua M Gulvin, George Simon, Bonnie Glisson

25. **Targeted Therapies in Non–Small Cell Lung Cancer 535**
Yasir Y. Elamin, Don L. Gibbons, Marcelo V. Negrao

V HEAD AND NECK CANCER
Section Editor: *Bonnie S. Glisson*

26. **Head and Neck Cancer 555**
Ruth Sacks, David Boyce-Fappiano, Amy Moreno, Frank Mott

VI GASTROINTESTINAL CANCER
Section Editor: *Robert A. Wolff*

27. **Gastric, Gastroesophageal Junction, and Esophageal Cancers 579**
Mariela Blum Murphy, Elena Elimova, Ahmed Abdelhakeem, Jaffer Ajani

28. **Pancreatic Cancer 619**
Jonathan D. Mizrahi, Anirban Maitra, Robert A. Wolff

29. **Biliary Tract Cancer 647**
Shalini Makawita, Sunyoung Lee, Yun Shin Chun, Millicent A. Roach, Eugene J. Koay, Milind Javle

30. **Hepatocellular Carcinoma 677**
Sunyoung S. Lee, Hao Chi Zhang, Hop S. Tran Cao, Sudha Kodali, Joshua D. Kuban, Eugene J. Koay, Rony Avritscher, Ahmed O. Kaseb

31. **Small Bowel Cancer and Appendiceal Tumors 707**
Pat Gulhati, John Paul Shen, Kanwal P. Raghav, Michael J. Overman

32. **Colorectal Cancer 733**
Arvind Dasari, Benny Johnson, Christine Parseghian, Kanwal P. Raghav, Scott Kopetz

33. **Anal Cancer 765**
Emma Holliday, Van Morris, Craig A. Messick

34. **Neuroendocrine Tumors 781**
Jessica E. Maxwell, James C. Yao, Daniel M. Halperin

VII BREAST CANCER
Section Editor: *Gabriel N. Hortobagyi*

35. **Early-Stage and Locally Advanced Breast Cancer 803**
Demetria Smith-Graziani, Mariana Chavez-MacGregor

36. **Metastatic Breast Cancer 829**
Haven R. Garber, Meghan S. Karuturi, Gabriel N. Hortobagyi

37. **Management of Locally Advanced Breast Cancer, Including Inflammatory Breast Cancer 863**
Bora Lim, Gabriel N. Hortobagyi

38. **Special Situations in Breast Cancer 875**
Rachel M. Layman

VIII GYNECOLOGIC MALIGNANCIES
Section Editor: *Karen H. Lu*

39. **Ovarian Cancer 897**
Roni Nitecki, Lauren P. Cobb, Amir A. Jazaeri, J. Alejandro Rauh-Hain

40. **Tumors of the Uterine Corpus 931**
Michaela A. Onstad, Shannon N. Westin, Karen H. Lu

41. **Tumors of the Uterine Cervix 955**
Gloria Salvo, Mila P. Salcedo, Sol Basabe, Pedro T. Ramirez

42. **Gestational Trophoblastic Disease 983**
Han T. Cun, Aaron Shafer

IX GENITOURINARY MALIGNANCIES
Section Editor: *Nizar M. Tannir*

43. **Renal Cell Carcinoma 1005**
Andrew W. Hahn, Jose A. Karam, Christopher G. Wood, Nizar M. Tannir

44. Bladder Cancer 1027
Alexander Y. Andreev-Drakhlin, Ashish M. Kamat, Arlene O. Siefker-Radtke

45. Prostate Cancer 1049
Patrick Pilié, Paul Viscuse, Christopher J. Logothetis, Paul G. Corn

46. Penile Cancer 1071
Jad Chahoud, Curtis A. Pettaway

47. Germ Cell Tumors 1081
Joseph A. Moore, Shi-Ming Tu

X NEUROLOGIC TUMORS
Section Editor: *John de Groot*

48. Tumors of the Central Nervous System 1105
Shiao-Pei Weathers, Barbara O'Brien, Ashley Aaroe, Debra Yeboa, Sujit Prabhu, John de Groot

XI MALIGNANT MELANOMA
Section Editor: *Michael A. Davies*

49. Melanoma 1133
Houssein Safa, Jane Mattei, Andrew J. Bishop, Emily Z. Keung, Sirisha Yadugiri, Michael A. Davies, Isabella C. Glitza Oliva

XII SARCOMAS
Section Editor: *Shreyaskumar Patel*

50. Soft Tissue and Bone Sarcomas 1159
J. Andrew Livingston, Anthony P. Conley, Ravin Ratan, Vinod Ravi, Shreyaskumar Patel

XIII OTHER TUMORS AND CANCER TOPICS OF INTEREST
Section Editor: *Alyssa G. Rieber*

51. Endocrine Malignancies 1189
Ha Nguyen, Mouhammed Amir Habra

52. The Acquired Immunodeficiency Syndrome–Related Cancers 1223
Adan Rios, Fredrick B. Hagemeister

53. Carcinoma of Unknown Primary 1253
Gauri R. Varadhachary, Kanwal P. Raghav, Ryan W. Huey

54. Pediatric Cancers 1271
Branko Cuglievan, Wafik Zaky, Richard Gorlick, Douglas Harrison

55. Cancer Genomics 1283
Jason A. Willis, Jennifer B. Goldstein, Zhijing Zhang, Andy Futreal

56. Immuno-oncology 1297
Bilal A. Siddiqui, Sangeeta Goswami, James P. Allison, Padmanee Sharma

57. Targeted Therapy in Cancer 1323
Rabih Said, Apostolia-Maria Tsimberidou

58. Viral Infections in Patients with Cancer 1345
Fareed Khawaja, Roy F. Chemaly

59. Fungal Infections in Patients with Cancer 1363
Bruno P. Granwehr, Dimitrios P. Kontoyiannis

60. Endocrine and Metabolic Complications of Cancer Therapy 1381
Rachael Hosein, Sara Bedrose, Rebecca Jeun, Jeena M. Varghese, Sonali N. Thosani

61. Oncologic Emergencies 1407
Sai-Ching Jim Yeung, Ellen F. Manzullo, Patrick Chaftari

62. Oncocardiology 1435
Elie Mouhayar, Danielle El-Haddad, Peter Kim, Kara Thompson, Cezar Iliescu, Abdulrazzak Zarifa

63. Pulmonary Complications of Cancer Therapy 1461
Audra J. Schwalk, Saadia A. Faiz, Horiana B. Grosu, Lara Bashora, Vickie R. Shannon

64. Cancer-Associated Thrombosis 1493
Kelly A. Casteel, Michael H. Kroll

XIV SUPPORTIVE AND PALLIATIVE CARE
Section Editor: *Eduardo Bruera*

65. Inpatient Supportive and Palliative Care 1509
Ahsan Azhar, Ali Haider, Eduardo Bruera

66. Integrated Outpatient Supportive Care 1519
Akhila Reddy, David Hui, Eduardo Bruera

67. Rehabilitation 1529
Brian Fricke, An Ngo-Huang, Ekta Gupta

68. Pain Management and Symptom Control 1553
Kaoswi K. Shih, Rony Dev, Shalini Dalal

XV BIOSTATISTICS

Section Editor: *Xuelin Huang*

69. Statistical Designs for Oncology Clinical Trials 1579

Xuelin Huang, Wei Qiao, Fang Xia, E Lin, Liang Zhu, Jing Ning

70. Big Data and Machine Learning in Oncology 1593

Peng Wei, Hai Shu

71. Value-Based Oncology 1603

Casey J. Allen, Aileen Chen, Ryan W. Huey, Ya-Chen Tina Shih

Index 1619

The fourth edition of *The MD Anderson Manual of Medical Oncology* is also available online as part of the excellent **accesshemonc.com** website, with direct links to a comprehensive drug therapy database and to other important medical texts that include *Hematology-Oncology Therapy*. The online edition of *The MD Anderson Manual of Medical Oncology* also includes PubMed links to journal articles cited in the references.

New in this edition is the online-only presentation of clinical cases, *The MD Anderson Manual of Medical Oncology Cases*, for readers to explore, with each case linked to the relevant chapter.

Contributors

Hind Rafei, MD
Instructor
Department of Stem Cell Transplantation and Cellular Therapy
Fellow, Hematology and Oncology
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Sergej N. Konoplev, MD, PhD
Associate Professor
Department of Hematopathology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Sa A. Wang, MD
Professor
Department of Hematopathology
Division of Pathology/Lab Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Nicholas J. Short, MD
Assistant Professor
Department of Leukemia
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Hagop M. Kantarjian, MD
Professor and Chairman
Department of Leukemia
Samsung Distinguished University Chair in Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Elias J. Jabbour, MD
Department of Leukemia
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Tapan M. Kadia
Department of Leukemia
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Joseph D. Khoury, MD
Assistant Professor
The University of Texas MD Anderson Cancer Center
Houston, Texas

Farhad Ravandi, MD
Professor
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, Texas

Nitin Jain, MD
Associate Professor
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, Texas

Philip Thompson, MD
Associate Professor
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, Texas

Carlos Bueso-Ramos, MD, PhD
Professor
Department of Hematopathology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Susan M. O'Brien, MD
Associate Director for Clinical Science
Chao Family Comprehensive Cancer Center
University of California Irvine
Irvine, California

William G. Wierda, MD, PhD
Professor
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, Texas

Koji Sasaki, MD, PhD
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, Texas

Elias Jabbour, MD
Professor
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, Texas

Jorge Cortes, MD
Director
Georgia Cancer Center at Augusta University
Medical College of Georgia
Augusta, Georgia

Hagop Kantarjian, MD
Professor and Chairman
Department of Leukemia
Samsung Distinguished University Chair in Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Kelly Chien, MD
Assistant Professor
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, Texas

Carlos Bueso-Ramos, MD, PhD
Professor
Department of Hematopathology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Guillermo Garcia-Manero, MD
Professor
Chief, Section of Myelodysplastic Syndromes
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, Texas

Prithviraj Bose, MD
Associate Professor
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, Texas

Lucia Masarova, MD
Assistant Professor
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, Texas

Hesham M. Amin, MD, MSc
Professor
Department of Hematopathology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Srdan Verstovsek, MD, PhD
Professor
United Energy Resources, Inc.
Department of Leukemia
Director, Hanns A. Pielenz Clinical Research Center for Myeloproliferative Neoplasms (MPN)
The University of Texas MD Anderson Cancer Center
Houston, Texas

Paolo Strati, MD
Assistant Professor
Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas

Jillian R. Gunther, MD, PhD
Assistant Professor
Department of Radiation Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

L. Jeffrey Medeiros, MD
Professor
Department of Hemato-Pathology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Loretta J. Nastoupil, MD
Associate Professor
Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas

Felipe Samaniego, MD
Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas

Raphael Steiner, MD
Assistant Professor
Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas

Jason R. Westin, MD
Associate Professor
Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas

Sergej N. Konoplev, MD, PhD
Associate Professor
Department of Hematopathology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Luis E. Fayad, MD
Professor
Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas

Preetesh Jain, MBBS, MD, DM, PhD
Assistant Professor
Department of Lymphoma and Myeloma
Mantle Cell Lymphoma Program of Excellence
The University of Texas MD Anderson Cancer Center
Houston, Texas

Michael Wang, MD
Professor
Department of Lymphoma/Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas

Ranjit Nair, MD
Assistant Professor
Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas

Francisco Vega, MD, PhD
Professor
Department of Hematopathology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Swaminathan P. Iyer, MD
Professor
Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas

Auris Huen, PharmD, MD
Associate Professor
Department of Dermatology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Collin K. Chin, MBBS
Bloodwise Clinic
Perth, Australia

Fredrick B. Hagemeister
Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas

Hun J. Lee
Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas

Gregory P. Kaufman, MD
Assistant Professor
Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas

Muzaffar H. Qazilbash, MD
Professor
Department of Stem Cell Transplantation and Cellular Therapy
The University of Texas MD Anderson Cancer Center
Houston, Texas

Krina Patel, MD
Associate Professor
Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas

Sheeba Thomas, MD
Professor
Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas

Robert Z. Orlowski, MD, PhD
Professor
Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas

Elisabet E. Manasanch, MD, MHSc
Associate Professor
Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas

Paul Lin
Assistant Professor
Department of Stem Cell Transplantation and Cellular Therapy
The University of Texas MD Anderson Cancer Center
Houston, Texas

Hans C. Lee, MD
Assistant Professor
Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas

Melody Becnel, MD
Assistant Professor
Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas

Donna Weber
Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas

Sairah Ahmed
Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas

Simrit Parmar
Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas

Sattva Neelapu
Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas

Neeraj Saini, MD
Assistant Professor
Department of SCT and Cellular Therapy
Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas

Yago Nieto, MD
Professor
Department of SCT and Cellular Therapy
The University of Texas MD Anderson Cancer Center
Houston, Texas

Rohtesh S. Mehta, MD, MPH, MS
Assistant Professor
Department of Stem Cell Transplantation and Cellular Therapy
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Chitra Hosing, MD
Professor
The University of Texas MD Anderson Cancer Center
Houston, Texas

Betul Oran, MD
Associate Professor
Department of Stem Cell Transplantation and Cellular Therapy
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Katayoun Rezvani, MD, PhD
Professor
Department of Stem Cell Transplantation and Cellular Therapy
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Elizabeth J. Shpall, MD
Professor
Department of Stem Cell Transplantation and Cellular Therapy
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Samer A. Srour, MB ChB, MS
Assistant Professor
Department of Stem Cell Transplantation and Cellular Therapy
The University of Texas MD Anderson Cancer Center
Houson, Texas

Richard E. Champlin, MD
Chairman
Department of Stem Cell Transplantation and Cellular Therapy
The University of Texas MD Anderson Cancer Center
Houston, Texas

Stefan O. Ciurea, MD
Associate Professor
Department of Stem Cell Transplantation and Cellular Therapy
The University of Texas MD Anderson Cancer Center
Houston, Texas;
Professor, Director of the Hematopoietic Stem Cell
Transpalntation and Cellualr Therapy Program
University of California, Irvine, California

Amanda Olson, MD
Associate Professor
Department of Stem Cell Transplantation and Cellular Therapy
The University of Texas MD Anderson Cancer Center
Houston, Texas

Jeremy Ramdial
Assistant Professor
Department of Stem Cell Transplantation and Cellular Therapy
The University of Texas MD Anderson Cancer Center
Houston, Texas

Uri Greenbaum
Department of Stem Cell Transplantation and Cellular Therapy
The University of Texas MD Anderson Cancer Center
Houston, Texas

Partow Kebriaei
Professor
Department of Stem Cell Transplantation and Cellular Therapy
The University of Texas MD Anderson Cancer Center
Houston, Texas

Jeremy A. Ross, MD
Medical Oncologist
Center for Cancer and Blood Disorders
Fort Worth, Texas

Lauren A. Byers, MD
Professor
Department of Thoracic/Head and Neck Medical Oncology
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Carl M. Gay, MD, PhD
Assistant Professor
Department of Thoracic/Head and Neck Medical Oncology
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Mehmet Altan
Department of Thoracic/Head and Neck Medical Oncology
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Joshua M. Gulvin, MD
Hematology/Oncology
St. Charles Health System
Redmond, OR

George Simon, MD
Executive Director, Clinical Research Unit
Moffitt Cancer Center-Advent Health
Celebration, FL

Bonnie Glisson
Department of Thoracic/Head and Neck Medical Oncology
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Yasir Y. Elamin
Assistant Professor
Department of Thoracic / Head and Neck Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Don L. Gibbons
Professor
Department of Thoracic / Head and Neck Medical Oncology;
Department of Molecular and Cellular Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Marcelo V. Negrao
Assistant Professor
Department of Thoracic / Head and Neck Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Ruth Sacks, MD
Assistant Professor
Department of Hematology and Medical Oncology
Winship Cancer Center of Emory University
Atlanta, Georgia

David Boyce-Fappiano, MD
Resident Physician
Department of Radiation Oncology
The University of MD Anderson Cancer Center
Houston, Texas

Amy Moreno, MD
Assistant Professor
Department of Radiation Oncology, Head and Neck Service
The University of MD Anderson Cancer Center
Houston, Texas

Frank Mott, MD, FACP
Professor
Department of Thoracic/Head and Neck Medical Oncology
The University of MD Anderson Cancer Center
Houston, Texas

Mariela Blum Murphy
Department of Gastrointestinal Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Elena Elimova, MD
Medical Oncologist
Princess Margaret Cancer Centre
Toronto, ON

Ahmed Abdelhakeem, MD
Internal Medicine Resident
Department of Medicine

Jaffer Ajani
Department of Gastrointestinal Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Jonathan D. Mizrahi, MD
Assistant Professor
Department of Hematology and Oncology
The Oschner Clinic

Anirban Maitra, MBBS
Professor
Department of Anatomical Pathology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Robert A. Wolff, MD
Professor
Department of GI Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Shalini Makawita, MD
Medical Oncologist
Baylor College of Medicine
Houston, Texas

Sunyoung Lee, MD, PhD
Assistant Professor
Department of Gastrointestinal Medical Oncology
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Yun Shin Chun, MD, FACS
Associate Professor
Department of Surgical Oncology
Division of Surgery
The University of Texas MD Anderson Cancer Center
Houston, Texas

Millicent A. Roach, BS
Assistant Clinical Research Coordinator
Department of Radiation Oncology
Division of Radiation Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Eugene J. Koay, MD, PhD
Associate Professor
Department of Radiation Oncology
Division of Radiation Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Milind Javle, MD
Professor
Department of Gastrointestinal Medical Oncology
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Sunyoung S. Lee
Professor
Department of Gastrointestinal Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Hao Chi Zhang
Assistant Professor
Department of Gastroenterology, Hepatology, and Nutrition,
The University of Texas MD Anderson Cancer Center
Houston, Texas

Hop S. Tran Cao
Associate Professor
Department of Surgical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Sudha Kodali
Transplant Hepatology, Houston Methodist Hospital
Houston, Texas

Joshua D. Kuban
Associate Professor
Department of Interventional Radiology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Eugene J. Koay
Associate Professor
Department of Radiation Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Rony Avritscher
Professor
Department of Interventional Radiology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Ahmed O. Kaseb
Professor
Department of Gastrointestinal Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Pat Gulhati, MD, PhD
Assistant Professor
Cancer Institute of New Jersey
Rutgers University

John Paul Shen
Department of Gastrointestinal Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Michael J. Overman
Department of Gastrointestinal Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Arvind Dasari, MD, MS
Associate Professor
Department of Gastrointestinal Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Benny Johnson, DO
Assistant Professor
Department of Gastrointestinal Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Christine Parseghian, MD
Assistant Professor
Department of Gastrointestinal Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Kanwal P. Raghav, MD
Associate Professor
Department of Gastrointestinal Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Scott Kopetz, MD, PhD
Professor and Deputy Chair
Department of Gastrointestinal Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Emma Holliday, MD
Department of Radiation Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Van Morris, MD
Department of Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Craig A. Messick, MD, FACS, FASCRS
Associate Professor
Department of Colon and Rectal Surgery;
Department of Surgical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Jessica E. Maxwell, MD, MBA
Assistant Professor
Department of Surgical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

James C. Yao, MD
Professor and Chair
Department of Gastrointestinal Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Daniel M. Halperin, MD
Assistant Professor
Department of Gastrointestinal Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Demetria Smith-Graziani, MD
Fellow, Hematology and Medical Oncology
The University of Texas MD Anderson Cancer Center; Instructor
Department of Medicine, Section of Hematology and Oncology,
Baylor College of Medicine
Houston, Texas

Mariana Chavez-MacGregor, MD
Associate Professor
Department of Health Services Research
The University of Texas MD Anderson Cancer Center
Houston, Texas

Haven R. Garber, MD, PhD
Assistant Professor
Department of Breast Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Meghan S. Karuturi, MD
Associate Professor
Department of Breast Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Gabriel N. Hortobagyi, MD, FACP
Professor
Department of Breast Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Bora Lim, MD
Associate Professor
Department of Medicine-Oncology
Baylor College of Medicine
Houston, Texas

Gabriel N. Hortobagyi, MD, FACP
Professor
Department of Breast Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Rachel M. Layman, MD
Associate Professor
The University of Texas MD Anderson Cancer Center
Houston, Texas

Roni Nitecki, MD, MPH
Clinical Fellow
Department of Gynecologic Oncology and Reproductive
Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Lauren P. Cobb, MD
Assistant Professor
Department of Gynecologic Oncology and Reproductive
Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

J. Alejandro Rauh-Hain, MD, MPH
Assistant Professor
Gynecologic Oncology and Reproductive Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Amir A. Jazaeri, MD
Professor
Department of Gynecologic Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Michaela A. Onstad, MD, MPH
Assistant Professor
Gynecologic Oncology and Reproductive Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Shannon N. Westin, MD, MPH
Associate Professor
Department of Gynecologic Oncology and Reproductive
Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Karen H. Lu, MD
Chair and Professor
Department of Gynecologic Oncology and Reproductive Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Gloria Salvo, MD
Clinical Research
Department of Gynecologic Oncology and Reproductive Medicine
The University of Texas MD Anderson Cancer Center
Houston Texas

Mila P. Salcedo, MD
Visiting Scientist
Department of Gynecologic Oncology and Reproductive Medicine
The University of Texas MD Anderson Cancer Center, Houston, Texas; Associate Professor, Chair of Gynecology
The Obstetrics and Gynecology Department, Federal University of Health Sciences of Porto Alegre/Santa Casa de Misericordia of Porto Alegre Hospital, Brazil

Sol Basabe, MD
Postdoctoral Fellow
Department of Gynecologic Oncology and Reproductive Medicine,
The University of Texas MD Anderson Cancer Center
Houston, Texas

Pedro T. Ramirez, MD
Professor, Editor-in-Chief
International Journal of Gynecological Cancer, David M. Gershenson Distinguished Professor in Ovarian Cancer Research, Director of Minimally Invasive Surgical Research and Education, Department of Gynecologic Oncology and Reproductive Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Han T. Cun, MD
Clinical Fellow
Department of Gynecologic Oncology and Reproductive Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Aaron Shafer, MD
Associate Professor
Department of Gynecologic Oncology and Reproductive Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Andrew W. Hahn, MD
Medical Oncology Fellow
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Jose A. Karam, MD, FACS
Associate Professor
Department of Urology
Division of Surgery and Department of Translational Molecular Pathology
Division of Pathology and Laboratory Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Christopher G. Wood, MD, FACS
Professor
Deputy Chairman, Department of Urology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Nizar M. Tannir, MD, FACP
Professor
Department of Genitourinary Medical Oncology
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Alexander Y. Andreev-Drakhlin, MD, PhD
Genentech, San Francisco, California

Arlene O. Siefker-Radtke, MD
Professor
Department of Genitourinary Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Ashish M. Kamat, MD
Professor
Department of Urology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Patrick Pilié, MD
Assistant Professor
Department of GU Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Paul Viscuse, MD
Clinical Fellow
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Christopher J. Logothetis, MD
Professor
Department of GU Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Paul G. Corn, MD
Professor
Department of GU Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Jad Chahoud, MD, MPH
GU Department, Moffitt Cancer Center, Tampa, Florida

Curtis A. Pettaway, MD
Urology Department
The University of Texas MD Anderson Cancer Center
Houston, Texas

Joseph A. Moore, MD
Staff Oncologist
Cancer Center of Kansas
Wichita, Kansas

Shi-Ming Tu, MD
Professor
Department of GU Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Shiao-Pei Weathers, MD
Assistant Professor
Department of Neuro-Oncology
Division of Cancer Medicine; Clinical Medical Director, Brain and Spine Center
The University of Texas MD Anderson Cancer Center
Houston, Texas

Barbara O'Brien, MD
Assistant Professor
Department of Neuro-Oncology
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Ashley Aaroe, MD
Clinical Fellow, Department of Neuro-Oncology
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Debra Yeboa, MD
Assistant Professor
Department of Radiation Oncology
Division of Radiation Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Sujit Prabhu, MD, FRCS (Ed)
Professor
Department of Neurosurgery
Division of Surgery
The University of Texas MD Anderson Cancer Center
Houston, Texas

John de Groot, MD
Professor
Department Chair ad interim, Department of Neuro-Oncology
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Houssein Safa, MD
Internal Medicine Resident
Montefiore Health System
Bronx, New York

Jane Mattei
Clinical Fellow
Department of Melanoma Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Andrew J. Bishop, MD, AM
Assistant Professor
Department of Surgical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Emily Z. Keung, MD
Assistant Professor
Department of Surgical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Sirisha Yadugiri, PhD, MHA
Sr. Technical Writer, Department of Melanoma Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Michael A. Davies, MD, PhD
Professor and Chair
Department of Melanoma Medical Oncology
Professor, Translational Molecular Pathology, Genomic Medicine, Systems Biology, Anne and John Mendelsohn Chair in Cancer Research
The University of Texas MD Anderson Cancer Center
Houston, Texas

Isabella C. Glitza Oliva
Department of Melanoma Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

J. Andrew Livingston, MD
Assistant Professor
Department of Sarcoma Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Anthony P. Conley
Associate Professor
Department of Sarcoma Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Ravin Ratan, MD
Assistant Professor
Department of Sarcoma Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Vinod Ravi, MD
Associate Professor
Department of Sarcoma Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Shreyaskumar Patel, MD
Professor
Department of Sarcoma Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Ha Nguyen, MD
Assistant Professor
Department of Medicine
Baylor College of Medicine
Houston, Texas

Mouhammed Amir Habra, MD
Professor
Department of Endocrine Neoplasia
The University of Texas MD Anderson Cancer Center
Houston, Texas

Adan Rios, MD
Associate Professor
Division of Medical Oncology
The University of Texas Health Science Center-Houston
Houston, Texas

Gauri R. Varadhachary, MD†
Professor
Department of GI Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Branko Cuglievan, MD
Assistant Professor
Section Chief ad Interim, Pediatric Leukemia, and Lymphoma
The University of Texas MD Anderson Cancer Center
Houston, Texas

Wafik Zaky, MD
Associate Professor
Department of Pediatrics
The University of Texas MD Anderson Cancer Center
Houston, Texas

Richard Gorlick, MD
Professor
Division Head and Department Chair,
Department Chair ad interim, Sarcoma Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Douglas Harrison, MD, MS
Associate Professor
Center Medical Director
The University of Texas MD Anderson Cancer Center
Houston, Texas

Jason A. Willis, MD
Assistant Professor
Department of GI Medical Oncology (or Gastrointestinal Medical Oncology)
The University of Texas MD Anderson Cancer Center
Houston, Texas

Jennifer B. Goldstein, MD, PhD
Medical Oncologist
University of California-Irvine
Irvine, California

Zhijing Zhang
College Student
Department of Genomic Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Andy Futreal
Department of Genomic Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Bilal A. Siddiqui, MD
Assistant Professor
Department of Genitourinary Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Sangeeta Goswami, MD, PhD
Assistant Professor
Departments of Genitourinary Medical Oncology and Immunology
The University of Texas MD Anderson Cancer Center
Houston, Texas

James P. Allison, PhD
Chair and Regental Professor, Department of Immunology, MD Anderson Cancer Center
The University of Texas MD Anderson Cancer Center
Houston, Texas

Padmanee Sharma, MD, PhD
Professor, Departments of Genitourinary Medical Oncology and Immunology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Rabih Said, MD, MPH
Associate Professor, Oncology Division, St George Hospital University Medical Center, University of Balamand, Beirut, Lebanon

Apostolia-Maria Tsimberidou, MD, PhD
Professor
Department of Investigational Cancer Therapeutics
The University of Texas MD Anderson Cancer Center
Houston, Texas

Fareed Khawaja, MD
Assistant Professor
Department of Infectious Diseases
The University of Texas MD Anderson Cancer Center
Houston, Texas

Roy F. Chemaly, MD
Professor
Department of Infectious Diseases
The University of Texas MD Anderson Cancer Center
Houston, Texas

Bruno P. Granwehr, MD, MS, FACP, CMQ
Professor
Department of Infectious Diseases
The University of Texas MD Anderson Cancer Center
Houston, Texas

Dimitrios P. Kontoyiannis, MD, ScD, PhD(Hon.), FACP, FIDSA, FECMM, FAAM, FAAAS
Professor
Department of Infectious Diseases, Texas 4000, Distinguished Endowed Professor for Cancer Research, Deputy Head
Division of Internal Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Rachael Hosein, MD
Aurora Health Care, 2414 Kohler Memorial Dr, Sheboygan, Wisconsin; Division of Endocrinology, Diabetes, and Metabolism, McGovern Medical School
The University of Texas Health Science Center
Houston, Texas

Sara Bedrose, MD
Department of Endocrinology, Diabetes and Metabolism, Baylor College of Medicine
Houston, Texas

Rebecca Jeun, MD
Department of Endocrinology, Diabetes and Metabolism, Baylor College of Medicine
Houston, Texas

Sonali N. Thosani, MD
Associate Professor
Department of Endocrine Neoplasia and Hormonal Disorders
Section Chief, Diabetes and Metabolic Disorders
Certified in Medical Quality (CMQ)
Division of Internal Medicine Quality Council, Chair
Patient Safety and Quality Officer, Endocrine Department
The University of Texas MD Anderson Cancer Center
Houston, Texas

Jeena M. Varghese, MD
Assistant Professor
Endocrine Neoplasia and Hormonal Disorders
The University of Texas MD Anderson Cancer Center
Houston, Texas

Sai-Ching Jim Yeung
Professor
Department of Emergency Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Ellen F. Manzullo, MD, FACP
Professor
Deputy Division Head (Clinical) Internal Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Patrick Chaftari, MD, MBA, FACP
Associate Professor
Department of Emergency Medicine
Clinical Medical Director, Clinical Decision Unit (CDU)
The University of Texas MD Anderson Cancer Center
Houston, Texas

Elie Mouhayar, MD, FACC, FSVM
Professor
Department of Cardiology.
The University of Texas M. D. Anderson Cancer Center
Houston, Texas

Danielle El-Haddad, MD
Clinical research resident, Department of Cardiology.
The University of Texas M. D. Anderson Cancer Center
Houston, Texas

Peter Kim, MD
Associate Professor
Department of Cardiology.
The University of Texas M. D. Anderson Cancer Center
Houston, Texas

Kara Thompson, MD
Associate Professor
Department of Cardiology.
The University of Texas M. D. Anderson Cancer Center
Houston, Texas

Cezar Iliescu, MD
Professor
Department of Cardiology.
The University of Texas M. D. Anderson Cancer Center
Houston, Texas

Kaoswi K. Shih, MD
Assistant Professor
Palliative Care Medicine
University of Texas MD Anderson Cancer Center
Houston, Texas

Rony Dev, MD
Associate Professor
Palliative Care Medicine
University of Texas MD Anderson Cancer Center
Houston, Texas

Shalini Dalal, MD
Professor
Palliative Care Medicine
University of Texas MD Anderson Cancer Center
Houston, Texas

Abdulrazzak Zarifa, MD
Department of Cardiology.
The University of Texas M. D. Anderson Cancer Center
Houston, Texas

Audra J. Schwalk, MD
Assistant Professor
Department of Internal Medicine-Pulmonary and Critical Care Medicine
University of Southwestern Medicine Center
Dallas, Texas

Saadia A. Faiz, MD
Professor
Department of Pulmonary Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Horiana B. Grosu, MD
Associate Professor
Department of Pulmonary Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Lara Bashora, MD
Professor
Department of Pulmonary Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Vickie R. Shannon, MD
Professor
Department of Pulmonary Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Kelly A. Casteel
Assistant Professor
Department of Benign Hematology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Michael H. Kroll, MD
Professor
Department of Benign Hematology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Ali Haider, MD
Assistant Professor
Department of Palliative, Rehabilitation and Integrative Medicine Department
The University of Texas MD Anderson Cancer Center
Houston, Texas

Ahsan Azhar, MD
Assistant Professor
Palliative, Rehabilitation and Integrative Medicine Department
The University of Texas MD Anderson Cancer Center
Houston, Texas

Eduardo Bruera, MD
Professor and Chair, Palliative, Rehabilitation and Integrative Medicine Department
The University of Texas MD Anderson Cancer Center
Houston, Texas

Akhila Reddy, MD
Associate Professor
Department of Palliative, rehabilitation, and Integrative Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

David Hui, MD
Associate Professor
Department of Palliative, Rehabilitation, and Integrative Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Brian Fricke, MD
Fellow, Department of Palliative, Rehabilitation, and Integrative Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

An Ngo-Huang, DO
Assistant Professor
Department of Palliative, Rehabilitation, and Integrative Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Ekta Gupta, MD
Assistant Professor
Department of Palliative, Rehabilitation, and Integrative Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Xuelin Huang, PhD
Professor
Deputy Chair, Department of Biostatistics
The University of Texas MD Anderson Cancer Center
Houston, Texas

Wei Qiao, PhD
Senior Biostatistician, Department of Biostatistics
The University of Texas MD Anderson Cancer Center
Houston, Texas

Fang Xia, PhD
Biostatistics Manager, Gilead Sciences, Foster City, California

E Lin, MD, PhD
Associate Director of Biostatistics, PTC Therapeutics, Inc., South Plainfield, New Jersey

Liang Zhu, PhD
Associate Professor, Department of Internal Medicine
The University of Texas Health Science Center at Houston
Houston, Texas

Jing Ning, PhD
Associate Professor
Department of Biostatistics
The University of Texas MD Anderson Cancer Center
Houston, Texas

Peng Wei, PhD
Department of Biostatistics
The University of Texas MD Anderson Cancer Center
Houston, Texas

Hai Shu, PhD
Department of Biostatistics, School of Global Public Health, New York University, New York, New York

Casey J. Allen, MD
Fellow, Department of Surgical Oncology
Division of Surgery
The University of Texas MD Anderson Cancer Center
Houston, Texas

Aileen Chen, MD, MPP
Associate Professor
Department of Radiation Oncology and Department of Health Services Research
The University of Texas MD Anderson Cancer Center
Houston, Texas

Ryan W. Huey, MD
Assistant Professor
Department of Gastrointestinal Medical Oncology
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Ya-Chen Tina Shih, PhD
Professor
Department of Health Services Research, Chief, Section of Cancer Economics and Policy
Division of Cancer Prevention and Population Sciences
The University of Texas MD Anderson Cancer Center
Houston, Texas

This page intentionally left blank

A Brief History of MD Anderson Cancer Center

Houston's evolution into the fourth largest city in the United States was propelled by four seminal events. First was the Great Galveston Hurricane of 1900, which destroyed the city port of Galveston and led to the realization that Houston could become a viable and safer deep-water port; this led to the widening of the Ship Channel to offer direct access to Houston. Second was the discovery of oil at Spindletop in Beaumont, Texas in 1901. This prompted the development of the oil industry in Texas and transformed Houston from a small town into a large city. Third was (of course) the commercialization of air conditioning in 1950's, which made Houston (and many Southern cities of the United States) more livable. And lastly, the allocation of land for the Texas Medical Center created the largest medical center in the world with one of the highest densities of clinical facilities for patient care, basic science, and translational research. The Texas Medical Center is a major contributor to Houston's economy and growth.

Several additional factors contributed to the creation of The University of Texas MD Anderson Cancer Center in Houston and its development into one of the most important cancer centers in the world. First was the generous philanthropy of visionary Texans such as Monroe Dunaway Anderson (Fig. 1) (his nephew died of leukemia in 1936) and his partner Will Clayton, who founded the charitable MD Anderson Foundation, which helped create the Texas Medical Center in 1945.



FIGURE 1.



FIGURE 2.

The charter of the Anderson Foundation did not specify how the money should be used, but Mr. Anderson's trustees and close friends—Colonel William Bates, John Freeman and Horace Williams—leaned strongly in favor of health care. Soon after taking possession of the estate from its executors, the trustees turned to Dr. Ernest Bertner (Fig. 2) for advice. Dr. Bertner was a prominent Houston surgeon and gynecologist who was well known to the trustees because of his care for cancer patients, despite inadequate facilities and treatment options (he was later called the "father of the Texas Medical Center").

The trustees and Dr. Bertner noted that the 1941 Texas legislature authorized the University of Texas to create a hospital for cancer research and treatment, allocating $500,000 for the purpose. Today, that figure would be approximately $8 million. The Anderson trustees, with Dr. Bertner's guidance, seized the opportunity and offered to match the $500,000 legislative appropriation, if the hospital was to be named for Monroe Dunaway Anderson and located in Houston. The legislature accepted their offer. The trustees then purchased 134 acres of mosquito-infested land to create the Texas Medical Center, stating that the new cancer hospital would be located there. They made it known that the new state hospital should be an academic institution. In fact, MD Anderson was the first comprehensive cancer hospital to be associated with a major university as an independent free-standing unit.

In 1942, The University of Texas Board of Regents appointed Dr. Bertner as the director of the new hospital. A 6-acre property near downtown was purchased from the estate of Captain James A. Baker, grandfather of former Secretary of State James Baker III, and became the first campus of the hospital. An empty carriage house became the office and stables were the research laboratories. Twelve surplus army barracks were procured for patient clinics (Figs. 3A-C). With the addition of 22 leased beds at Hermann Hospital, the dream became realityA small faculty of physicians and scientists was recruited from the University

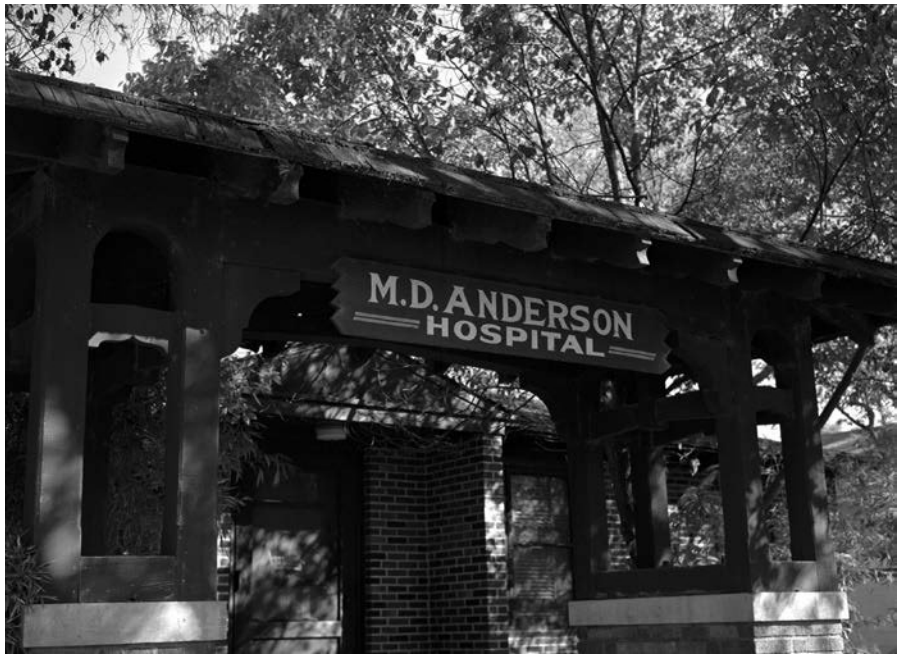


FIGURE 3A.

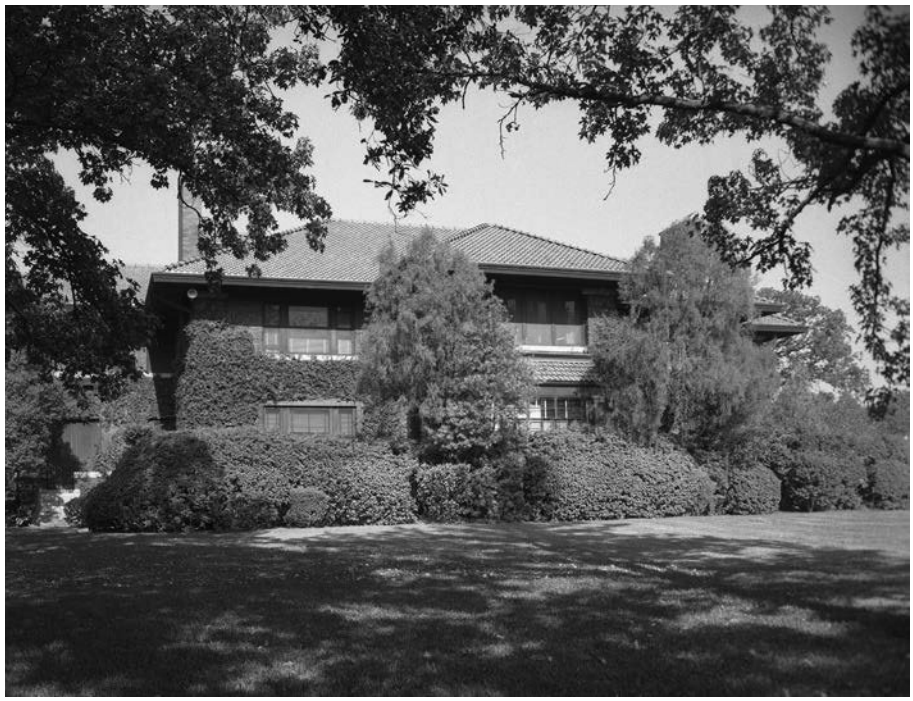


FIGURE 3B.



FIGURE 3C.

of Texas Medical Branch in Galveston, and cancer patients finally had a home. The name proposed in 1941 was the "Texas State Cancer Hospital and the Division of Cancer Research", which was changed to "M.D. Anderson Hospital for Cancer Research of The University of Texas" (to acknowledge the donation of M.D. Anderson). The name was again changed in 1955 to "The University of Texas M.D. Anderson Hospital and Tumor Institute at Houston" (to avoid the word "cancer" which elicited fear and avoidance). In 1988 the name was finally changed to its current "The University of Texas MD Anderson Cancer Center".

In 1946, Dr. Bertner persuaded Dr. Randolph Lee Clark, a native Texan, to become president of what was to become The University of Texas MD Anderson Cancer Center. Dr. Clark, a widely recognized surgeon, concentrated on recruiting an excellent surgical faculty and then set upon acquiring all the basic and clinical scientists and clinicians. From the outset, all efforts, whether administrative, clinical or research, were focused on developing excellence in research-driven cancer care. Forty-six patients were receiving treatment in these early quarters when the hospital moved to its current site in March 1954 (Figs. 4A and B).



FIGURE 4A.



FIGURE 4B.

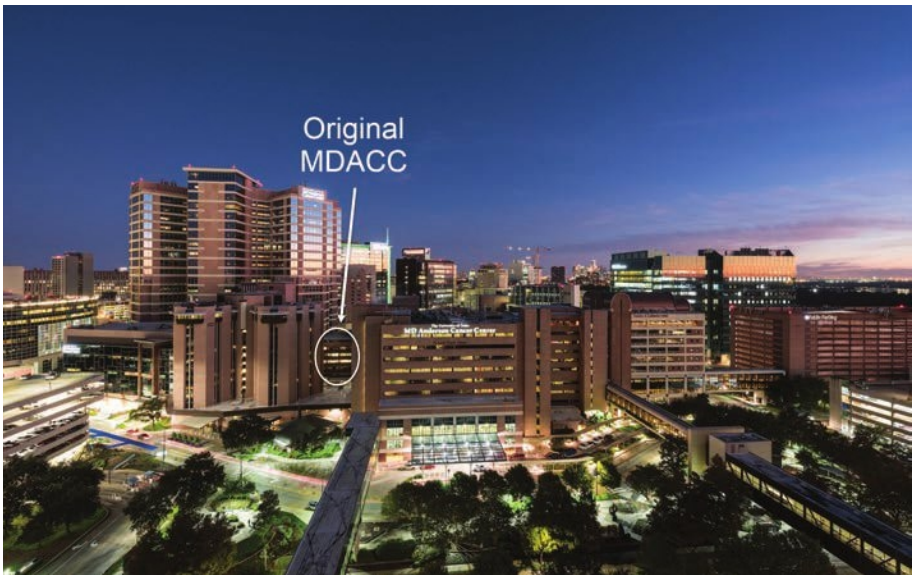


FIGURE 5.



FIGURE 6A.



FIGURE 6B.

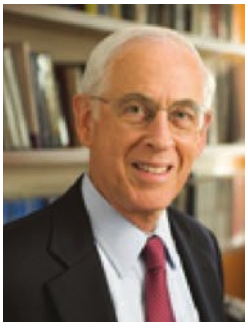


FIGURE 6C.

Additional resources to expand the MD Anderson infra-structure (Fig. 5) and research capacities came from several venues: (1) generous donations from the oil industry; (2) the visionary research and administrative leadership under its five presidents, Drs. Randolph Lee Clark (1946–1978) (Fig. 6A), Charles A. LeMaistre (1978–1996) (Fig. 6B), John Mendelsohn (1996–2011) (Fig. 6C), Ronald DePinho (2011–2017) (Fig. 6D), and Peter WT Pisters (2017-present) (Fig. 6E); (3) the recruitment of world-renowned cancer research pioneers (some of the early legends included Drs. Emil J. Freireich, Emil Frei, Gilbert Fletcher, James Butler, Felix Rutledge, Gerald Dodd, and Sidney Wallace); and (4) the relentless research efforts of the cancer experts on the MD Anderson's faculty.

Today, MD Anderson is one of the largest cancer centers in the world, with more than 21,000 employees and 1800 faculty; serving more than 150,000 patients with cancer in Houston every year; operating a 700-bed cancer hospital; and being ranked as



FIGURE 6D.



FIGURE 6E.

the No. 1 hospital for cancer care by the *U.S. News and World Report* in 11 of the past 14 years. The MD Anderson Cancer Center research has resulted in numerous discoveries that became standards of care across many types of cancers, and that have saved the lives and/or improved survivals and outcomes of millions of patients with cancer around the world.

One component of MD Anderson's mission is to spread its knowledge about cancer research and discoveries across the globe. This educational mission is furthered by the hematology/oncology fellowship that currently trains more than 40 medical hematology-oncology cancer specialists on its premises. *The MD Anderson Manual of Medical Oncology*, created as part of our educational mission, is often written by our fellows as first authors (many of whom later join the MD Anderson faculty) and supported in depth by senior tumor specialty faculty as co-authors. We envision this fourth edition expanding into a continuously updated electronic version that educates and spreads knowledge and discoveries in cancer research and therapy rapidly and widely.

Hagop M. Kantarjian, MD
Robert A. Wolff, MD
Alyssa G. Reiber, MD

Foreword

The MD Anderson Manual of Medical Oncology, fourth edition, articulates the personalized, multidisciplinary approach to cancer management pioneered by The University of Texas MD Anderson Cancer Center. Our unique perspective has evolved from decades of clinical practice and research with more than 1.6 million patients turning to MD Anderson for care. We are expanding our reach, making it easier for the patients and communities we serve to access our expertise. We are enabling high-impact discovery and introducing novel therapies through a leading clinical trials network. And we are setting new standards for high-touch, high-value cancer care.

This book is designed to bring a pragmatic approach to cancer management that may serve as a guide for oncologists around the world. The text reflects how MD Anderson currently operates, including many patient care practices that would not have been recognized by practitioners just a decade ago. Since the first edition, MD Anderson's experts have improved our ability to identify biomarkers that are predictive for survival, a major triumph in medical oncology that is demonstrated throughout the text.

Reflecting new advances in our research and our approach to cancer management, the fourth edition of *The MD Anderson Manual of Medical Oncology* features a wealth of new material. The sections on Lymphoma and Myeloma and Gastrointestinal Cancer contain additional chapters focused on recently defined subsets of disease and their treatment modalities. New targeted therapies are described in Lung Cancer. Additional Cancer Topics of Interest chapters detail updated knowledge in viral and fungal infections, for example, as well as oncocardiology and thrombosis. Biostatistics now has its own section, underscoring the extraordinary wealth of information brought about by big data analytics and its application to influence value-based oncology care. Supportive and Palliative Care content reflects current approaches in advanced symptom management concurrent with a patient's entire cancer journey, starting at diagnosis.

Every chapter includes abundant tables and diagrams, including algorithms and decision trees developed at MD Anderson for specific cancers or disease subtypes; promising novel therapy targets and the latest clinical trial phase of drugs targeting them; and new molecular therapies recommended to overcome resistance to previously effective therapies.

Emphasis on safety is even more relevant now than in prior editions of this book. MD Anderson's core value of Safety drives our colleagues each day, and this was especially highlighted during the COVID-19 pandemic when we came together with diligence, determination and evidence-based protocols to ensure the safest possible environment for our immunocompromised patients. Additionally, we remain laser focused on survivorship, as advances in cancer care have increased the number of people who are cancer free or who are living with cancer as a chronic condition rather than a fatal one. We remain dedicated to our bold aspiration of maximizing our impact on humanity through research-driven patient care, education, prevention and science that contribute to Making Cancer History®.

Peter WT Pisters, MD, MHCM
President, The University of Texas MD Anderson Cancer Center
Houston, Texas
January, 2022

This page intentionally left blank

Preface

When we first envisioned *The MD Anderson Manual of Medical Oncology*, we hoped that it would fill an important void in oncology reference material by serving as a hands-on resource for the practicing oncologist. The first edition, published in 2006, was written exclusively by our faculty and fellows with the idea of giving a bird's-eye view of how multidisciplinary care was practiced at our institution. We were proud of that initial effort and pleased that the book received positive reviews from several high-impact journals, including *JAMA*, *The Lancet*, and *The New England Journal of Medicine*.

The second edition, published in 2011, moved closer to the aims of providing more illustrations, figures, tables, and algorithms. In addition, the second edition included new chapters on myelodysplastic syndromes, Philadelphia chromosome-negative myeloproliferative neoplasms, T-cell lymphomas, small bowel cancer and appendiceal tumors, inflammatory breast cancer, and penile cancer.

In the third edition, we have continued the tradition of including evidence-based management algorithms in the form of flowcharts and diagrams, shaped by the clinical experience of our world-class faculty at MD Anderson. Readers are also provided with a practical guide to the diagnostic and therapeutic strategies used at MD Anderson.

The new edition of *The MD Anderson Manual of Medical Oncology* contains new chapters on cord blood transplant, haploidentical stem cell transplantation, cellular therapy in allogeneic hematopoietic cell transplantation, pediatric cancers, molecular biomarkers and cancer, immuno-oncology, targeted therapies in cancer, applied biostatistics, oncocardiology, pulmonary complications of cancer therapy, and cancer-associated thrombosis. In addition, there is expanded coverage of the rapidly growing areas of biological and immune therapies of cancer, with one chapter co-authored by our very own Nobel Laureate, Jim Allison.

The new edition of *The MD Anderson Manual of Medical Oncology* will also be a continually updated version of the book, online, with the latest science and clinical recommendations from the world-renowned clinical investigators at MD Anderson.

We hope that this edition serves to help oncologists everywhere provide high-quality, state-of-the-art cancer care to their patients.

Hagop M. Kantarjian, MD
Robert A. Wolff, MD
Alyssa G. Reiber, MD

This page intentionally left blank

Section I Leukemia

Section Editor: William G. Wierda

1 Acute Lymphoblastic Leukemia

2 Adult Acute Myeloid Leukemia

3 Chronic Lymphocytic Leukemia and Associated Disorders

4 Chronic Myeloid Leukemia

5 Myelodysplastic Syndromes: The MD Anderson Cancer Center Approach

6 Philadelphia Chromosome–Negative Myeloproliferative Neoplasms

This page intentionally left blank

1 Acute Lymphoblastic Leukemia

Hind Rafei
Sergej N. Konoplev
Sa A. Wang
Nicholas J. Short
Hagop M. Kantarjian
Elias J. Jabbour

KEY CONCEPTS

- Acute lymphoblastic leukemia (ALL) is classified into B-cell ALL, T-cell ALL, and natural killer cell ALL. Cytogenetics are key in the diagnosis of ALL because they hold a predictive and prognostic value. A Philadelphia chromosome–like signature that lacks the expression of BCR-ABL1 fusion protein but does have a gene expression profile similar to *BCR-ABL1*+ ALL has been recently defined.
- Measurement of measurable residual disease (MRD) using multiparameter flow cytometry, quantitative polymerase chain reaction, and next-generation sequencing is standard of care in the treatment of patients with ALL, and it holds prognostic as well as predictive significance. Treatment of patients with MRD-positive disease after achievement of response consists of the use of immunotherapy, such as blinatumomab or combinatorial agents.
- The frontline therapy of patients with ALL consists of four major components: induction of remission, consolidation, maintenance, and central nervous system prophylaxis. Intensive induction chemotherapy regimens are modeled after either the pediatric-inspired roadmap regimens or the hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) regimen. Consolidation depends on the risk category and consists of either consolidation chemotherapy (e.g., high-dose methotrexate and cytarabine) or allogeneic hematopoietic stem cell transplant. Maintenance consists of POMP (Purinethol, Oncovin, methotrexate, and prednisone) or DOMP (Dexamethasone, Purinethol, Oncovin, and methotrexate) chemotherapy for 2 to 3 years. Clinical trials are evaluating the use of novel agents, such as antibody–drug conjugates and bispecific antibodies, in the frontline setting.
- The combination of chemoimmunotherapy is the mainstay of treatment of patients with ALL and is a field of ongoing research to identify the best combinations as well as timing of their use.
- In adolescents and young adults, pediatric regimens and the hyper-CVAD regimen showed similar complete remission rates, remission duration, and survival outcomes.
- The role of allogeneic hematopoietic stem cell transplantation (AHSCT) in first remission remains currently valid in certain high-risk circumstances, such as (1) KMT2A-rearranged ALL, (2) early T-cell precursor ALL, and (3) ALL with complex cytogenetics and hypodiploidy.
- In the salvage setting, a number of novel agents have been approved, including monoclonal antibodies, bispecific antibodies, and chimeric antigen receptor T-cell therapies.

EPIDEMIOLOGY AND ETIOLOGY

Acute lymphoblastic leukemia (ALL) is characterized by the proliferation and accumulation of lymphoid progenitor cells in the blood, bone marrow, and other tissues. It has a bimodal distribution. The overall age-adjusted incidence is 1.7 per 100,000 persons, with a peak in early childhood and then a smaller peak in older adults. Approximately 60% of cases are diagnosed in patients who are 20 years old or younger. In 2020, the American Cancer Society estimated that 6150 individuals would be diagnosed with ALL in the United States that year, and 1520 patients would succumb to the disease.[1] ALL is projected to represent 20% of adult leukemias and 46% of leukemias in teenagers (15–19 years old) and will be the most common childhood acute leukemia in children 14 years old and younger, representing approximately 75% in this patient population.[1]

The cause of ALL is unknown in most cases.[2–6] Chromosomal translocations occurring in utero during fetal hematopoiesis have suggested genetic factors as the

primary cause of pediatric ALL and postnatal genetic events as secondary contributors. Monozygotic and dizygotic twins of patients with ALL and individuals with genetic disorders, such as Klinefelter (XXY and variants) and Down (trisomy 21) syndromes, or inherited diseases with excessive chromosomal fragility, such as Bloom syndrome, Fanconi anemia, and ataxia telangiectasia, have all been found to have higher incidence of ALL, implicating a possible genetic predisposition. Additional studies have postulated infectious causes.[3]

CLINICAL PRESENTATION AND LABORATORY ABNORMALITIES

The presenting symptoms can be nonspecific, particularly in children. They largely reflect bone marrow failure and include malaise, fatigue, bleeding or bruising, and secondary infections. The B symptoms, such as fever, night sweats, and weight loss, are frequent. White blood cell (WBC) count at presentation varies widely, and circulating blasts are generally noted. Symptoms related to hyperleukocytosis are rare in ALL, given the lymphoblast morphology, even when WBC counts are high.

Leukemic involvement of the central nervous system (CNS), ranging from cranial neuropathies to meningeal infiltration, occurs in fewer than 10% of patients at presentation. It is more common in mature B-cell acute lymphoblastic leukemia (B-ALL) or Burkitt leukemia.[7] A history or findings of abdominal masses, significant spontaneous tumor lysis syndrome, and chin numbness (mental nerve) indicating cranial nerve involvement are also more common in this subtype of ALL.[8] Lymphadenopathy and hepatosplenomegaly, although rarely symptomatic, are observed in approximately 20% of patients.[8]

DIAGNOSIS

The revised World Health Organization (WHO) classification recognizes three types of ALL: B-ALL, T-cell acute lymphoblastic leukemia (T-ALL), and natural killer cell acute lymphoblastic leukemia (NK-ALL)[9] (Table 1–1). ALL can involve predominantly bone marrow or predominantly extramedullary sites. In patients with extramedullary lymphoblastic lymphoma, an arbitrary cut-off of 25% blasts in bone marrow was applied to distinguish lymphoblastic leukemia from lymphoma in the past.[10] Currently, this distinction has been practically abandoned, and the current WHO classification uses a combined term "lymphoblastic leukemia/lymphoma." In contrast to acute myeloid leukemia, there is no agreed-upon minimal blast percentage required for a diagnosis of ALL. The current WHO classification states that the diagnosis of ALL "should be avoided when there are <20% blasts" but at the same time does recognize that cases of ALL with blasts of less than 20% do exist.[9]

Morphologically, ALL is characterized by the presence of a large number of lymphoblasts. Blasts may show significant variation in cell size, nuclear shape, visibility of nucleoli, amount of cytoplasm, and cytoplasmic basophilia or vacuolization. Auer rods are consistently absent. In the past, the French-American-British (FAB) Cooperative Group recommended the separation of ALL cases into three subtypes (L1, L2, and L3) based on cytologic characteristics;[11] this cytologic classification is no longer used. In fact, Burkitt lymphoma/leukemia, which was a part of B-ALL in the FAB classification scheme under the L3 subtype, has been moved to the mature B-cell lymphoma category.[9] Table 1–2 summarizes lineage assignment.

The initial diagnosis of ALL is largely based on flow cytometric immunophenotyping (FCI). FCI successfully assigns lineage in more than 95% of cases. True mixed-phenotype acute leukemia is rare.[12] Aberrant myeloid antigen expression of markers is reported in 15% to 50% of adult and 5% to 35% of pediatric ALL cases.[13–15] ALL blasts are negative for myeloperoxidase (MPO), although a low-level MPO positivity (<3%) may occur in rare cases that otherwise are typical for ALL.[16] The diagnosis of ALL requires the detection of

Table 1–1 Classification of Acute Lymphoblastic Leukemia

I.	B-lymphoblastic leukemia/lymphoma (B-ALL)
	1. B-ALL, not otherwise specified
	2. B-ALL with recurrent genetic abnormalities
	B-ALL with t(9;22)(q34.1;q11.2); *BCR-ABL1*
	B-ALL with t(v;11q23.3); *KMT2A* rearranged
	B-ALL with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
	B-ALL with hyperdiploidy
	B-ALL with hypodiploidy
	B-ALL with t(5;14)(q31.1;q32.3); *IL3-IGH*
	B-ALL with t(1;19)(q23;p13.3); *TCF3-PBX1*
	B-ALL, *BCR-ABL1*–like[a]
	B-ALL with iAMP21[a]
II.	T-lymphoblastic leukemia/lymphoma (T-ALL)
	Early T-cell precursor lymphoblastic leukemia (ETP-ALL)[a]
	Near ETP ("close to" ETP) ALL[b]
III.	Natural killer (NK) cell lymphoblastic leukemia/lymphoma[a]

[a]Provisional entities in the current World Health Organization (WHO) classification.
[b]This entity is not recognized in the current WHO classification but is widely used.
Data from Swerdlow SH. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. International Agency for Research on Cancer; 2017 and Jain N, Lamb AV, O'Brien S, et al. Early T-cell precursor acute lymphoblastic leukemia/lymphoma (ETP-ALL/LBL) in adolescents and adults: a high-risk subtype. *Blood*. 2016 Apr 14;127(15):1863-1869.

Table 1–2 Diagnosis of Acute Lymphoblastic Leukemia by Immunophenotype

	Lineage-Defining Markers	Frequent Positive Markers	Important Negative Markers	Diagnosis Requirement
B-ALL	CD19, CD22, cytoplasmic CD79a, cytoplasmic IgM,[a] PAX5	CD10, HLADR, TDT, CD34	Cytoplasmic CD3, MPO, and monocytic markers	CD19, if strong and uniform, one of B markers or CD10; if CD19 weak and partial, two more B markers or CD10
T-ALL	Cytoplasmic CD3	CD7 (bright), variable CD1a, CD2, CD4, CD5, CD8, TDT	MPO and monocytic markers;. B-lineage markers[a]	Cytoplasmic CD3 and negative for other lineage markers
NK-ALL	CD56, CD94, CD161	CD7, CD2, TDT May express cytoplasmic CD3[b,c]	MPO, and monocytic markers; TCR gene rearrangement	CD56+, CD94, CD161, TCR gene rearrangement germline

[a]PAX5 is an excellent B-lineage marker, but it is performed by immunohistochemistry.
[b]May express partial or dim CD19, CD56, or CD79a but often negative for PAX5. Overall, not sufficient to assign B lineage.
[c]Depending on the clone of CD3 with reactivity to cytoplasmic CD3 epsilon chain.
B-ALL, B-cell acute lymphoblastic leukemia; MPO, myeloperoxidase; NK-ALL, natural killer cell acute lymphoblastic leukemia; T-ALL, T-cell acute lymphoblastic leukemia; TCR, T-cell receptor.

immature markers, such as CD34 or terminal deoxynucleotidyl transferase (TdT), as well as lineage-specific markers. For B-ALL, it requires a combination of strong CD19 and at least one additional B-cell marker, such as CD22 and cytoplasmic CD79a or CD10; if CD19 is weak, it requires at least two additional markers. Cytoplasmic CD3 is the lineage-defining marker for T-ALL. In addition, T-ALL is often bright positive for CD7, with variable expression of other markers. CD19 can be aberrantly expressed in 10% to 20% of T-ALL blasts.

The immunophenotypic classification of ALL is summarized in Table 1–2. The original classification proposed by the European Group for the Immunological Characterization of Leukemias in 1995 separated B-ALL cases into four categories according to the stages of maturation: pro-B-ALL, early pre-B-ALL, pre-B-ALL, and mature B-ALL.[17] The mature B-ALL group was subsequently removed from B-ALL categories. This immunophenotypic classification of B-ALL is still used in some practice, but with the advances in genetic and molecular characterization of B-ALL, its clinical importance became obsolete.

In contrast to B-ALL, the immunophenotypic classification of T-ALL has acquired a critical clinical importance since the concept of early T-cell precursor lymphoblastic leukemia (ETP-ALL) was introduced.[18] As with B-ALL, the European Group for the Immunological Characterization of Leukemias separated T-ALL cases according to the stages of maturation in four categories: pro-T, pre-T, cortical T, and medullary T.[17] In 2009, gene expression profiling studies in pediatric patients identified a unique subgroup within the pro-T category, which was associated with high risk of induction failure and relapse and thereafter designated as ETP-ALL.[18] The study conducted at our institution confirmed a poor clinical outcome of patients with ETP-ALL in adolescent and adult patient populations.[19] Immunophenotypically, ETP-ALL is defined by the lack of CD8 and CD1a, negative or dim expression of CD5 (as defined by CD5 expression in <75% lymphoblasts or 1 log scale dimmer than normal T-cells), and expression of at least one myeloid or stem cell marker (e.g., CD13, CD33, CD34, CD65, CD117, or HLA-DR).[18]

Although the original description of ETP-ALL phenotype stresses the absent or weak CD5 expression on lymphoblasts, an original study described three patients with an immunophenotype similar to ETP except for no decrease in CD5 but showing a gene expression profile of ETP-ALL.[19] These findings were confirmed in subsequent studies,[20] which led to the introduction of the term of "near ETP-ALL" (also known as "close to ETP-ALL") to describe T-ALL with a phenotype typical for ETP-ALL with an exception of normal or bright CD5.

NK-ALL has been recently added to the WHO classification as a provisional entity.[9] The entity remains ill-defined and extremely challenging to diagnose,[9] in part because of the limited knowledge about early stages of NK cell development. The information mostly comes from ex vivo analyses of normal CD34-positive progenitor populations;[21] the information regarding its malignant counterpart is sparse. The true frequency of NK-ALL remains unknown. The neoplastic cells are reported to express CD56, CD94, and CD161 and cytoplasmic CD3-epsilon. CD2, CD7, and even CD5 could be positive, but CD16 is usually absent.[9] T-cell receptor (TCR) gene rearrangement is germline.

Cytogenetic and Molecular Profiling

Frequent cytogenetic and molecular abnormalities associated with adult ALL offer insight into

leukemogenesis and leukemic progression (Table 1–3).[22] They are of both prognostic and predictive significance and have varying frequencies in children and adults, which explains some of the differences in outcomes in these two groups. This is particularly true in the case of B-ALL harboring Philadelphia chromosome [t(9;22)] (Ph) or other chromosomal changes with prognostic relevance, such as t(4;11)/mixed lineage leukemia (*KMT2A)-AF4*. Cytogenetic alterations provide an important basis for B-ALL subclassification. In T-ALL, an abnormal karyotype is found in about 50% to 70% of cases, commonly involving *TCR* loci, 14q11.2/*TCR* alpha/delta, 7p14-15/*TCR* gamma, or 7q35/*TCR* beta. The partner genes involve 10q24/*HOX11*,5q35/*HOX11L2*,1q32/*TAL1*,11p15/*LMO1*, or 8q24/*MYC*. del(9p) with the loss of *CDKN2A* is also common. Activating mutations in *NOTCH1* are detected in around 50% and *FBXW7* in about 30% of cases of T-ALL. The presence of *NOTCH1/FBXW7* mutations in the absence of *KRAS/NRAS* or *PTEN* abnormalities is associated with a good outcome.[23] On the other hand, the absence of *NOTCH1/FBXW7* mutations, the presence of *KRAS/NRAS* mutations, and the presence of *PTEN* mutations are associated with a poor prognosis in T-ALL.[24] Next-generation sequencing (NGS), expression proteomics, and oligonucleotide microarrays have transformed our understanding of the genomic landscape of ALL, yielding new molecular subgroups with actionable targets.[25–27]

Recently, a Ph-like signature has been defined using genome-wide gene expression arrays, which is found in 10% of children with standard-risk ALL and as many as 25% to 30% of young adults with ALL. This subgroup lacks the expression of BCR-ABL1 fusion protein but does have a gene expression profile similar to *BCR-ABL1*+ ALL.[28–30] The vast majority of these patients have deletions in genes encoding key transcription factors involved in B-cell signaling, such as *IKZF1*, *TCF3*, *EBF1*, *PAX5*, and *VPREB1*, as well as kinase-activating alterations involving *ABL1*, *ABL2*, *CRLF2*, *CSF1R*, *EPOR, JAK2, NTRK3, PDGFRB, PTK2B, TSLP*, or *TYK2* and sequence mutations involving *FLT3*, *IL7R*, or *SH2B3*. The most common alterations (~60% in adults) are rearrangements of *CRLF2*, which activate downstream signaling through Janus kinases (JAKs), and approximately half of *CRLF2*-rearranged cases

Table 1–3 Cytogenetic and Molecular Abnormalities in Acute Lymphoblastic Leukemia

Category	Cytogenetics	Involved Genes	Adult Frequency (%)	Children Frequency (%)
Hyperdiploid			2–15	10–26
Hypodiploid			5–10	5–10
Pseudodiploid	t(9;22)(q34;q11)	*BCR-ABL1*	15–25	2–6
	del(9)(q21-22)	*p15, p16*	6–30	20
	t(4;11);t(9;11);	*KMT2A*	5–10	<5
	t(11;19); t(3;11)			
	del(11)(q22-23)	*ATM*	25–30[a]	15[a]
	t(12;21)(p12;q22)	*TEL-AML1*	<1[b]	20–25[b]
	t(1;19)	*E2A-PBX1*	<5	<5
	t(17;19)	*E2A-HLF*	<5	<5
	t(1;14)(p32;q11)	*TAL1*	10–15	5–10
	t(7;9)(q34;q32)	*TAL2*	<1	<1
	t(10;14)(q24;q11)	*HOX11*	5–10	<5
	t(5;14)(q35;q32)	*HOX11L2*	1	2–3
	t(1;14)(p32;q11)	*TCR*	20–25[ac]	20–25[c]
	del(13)(q14)	*miR15/miR16*	<5	<5
	t(8;14); t(8;22); t(2;8)	*C-MYC*	5	2–5
	+ 8	?	10–12	2
	del(7p)	?	5–10	<5
	del(5q)	?	<2	<2
	del(6q); t(6;12)	?	5	<5

[a]As determined by loss of heterozygosity.
[b]As determined by polymerase chain reaction.
[c]In T-cell acute lymphoblastic leukemia, overall incidence <10%.

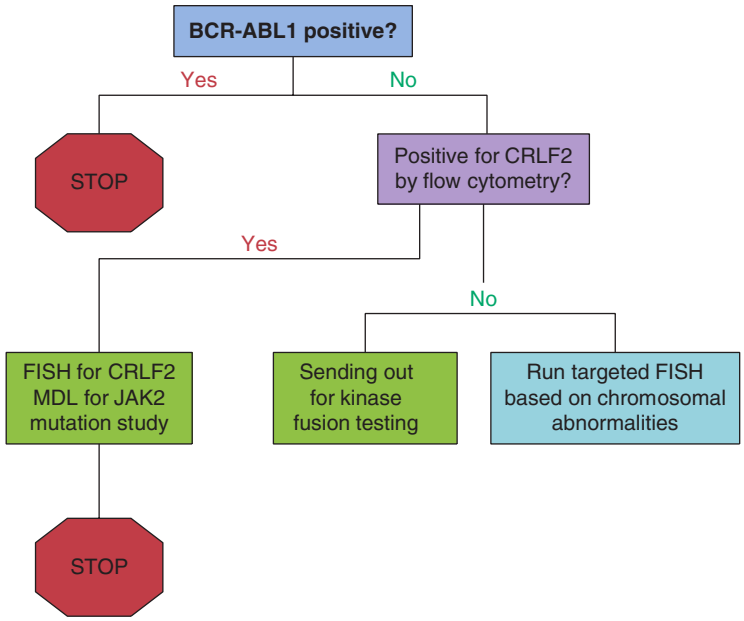


FIGURE 1-1 Philadelphia chromosome–like acute lymphoblastic leukemia molecular lesions and associated molecular fusions or mutations. FISH, fluorescence in situ hybridization.

have activating mutations in *JAK1* or *JAK2* (Fig. 1–1). *CRLF2* expression can be rapidly detected by flow cytometry, and a positive *CRLF2* expression correlates 100% with *CRLF2* rearrangement by fluorescence in situ hybridization (FISH).[31] Importantly, Ph-like ALL with *ABL1, ABL2, CSF1R*, and *PDGFRB* expression fusions (the ABL class) has been shown sensitive to tyrosine kinase inhibitors (TKIs; e.g., dasatinib) both by in vitro and in vivo human xenograft models. On the other hand, rearrangements in *EPOR, IL-7R*, and *JAK2* are sensitive to JAK inhibitors (e.g., ruxolitinib); and the *ETV6-NTRK3* fusion is sensitive to ALL kinase inhibitors (e.g., crizotinib).[29] The identification of kinase alterations expands therapeutic options in this subgroup of ALL with a poor outcome (Table 1–4).

At our institution, we use the following algorithm to stratify B-ALL cases (see Fig. 1–1). For every new patient with B-ALL, we perform FISH for *BCR/ABL1* and test for *CRLF2* expression by FCI. If FCI detects *CRLF2* expression, FISH studies are ordered to confirm *CRLF2* rearrangement, and molecular studies are ordered to check for *JAK2* (or *JAK1, JAK3*) mutations. In the absence of

Table 1–4 Genetic Determinants in Acute Lymphoblastic Leukemia by Lineage

ALL Lineage	Cytogenetic Aberration	Involved Genes	Protein
B-cell	BCR/ABL+ (Ph+)	*IKZF1*	Ikaros
		CRLF2 + the Ig heavy chain locus or an interstitial *PAR1* deletion	CRLF2
	BCR/ABL-like	*IKZF1* deletions; rearrangements/mutations in *CRLF2*, *IGH-CRLF2*, and *NUP214-ABL1*; in-frame fusions of *EBF1-PDGFRB*, *BCR-JAK2*, or *STRN3-JAK2*; cryptic *IGH-EPOR* rearrangements	
	Near hypodiploid	*NRAS*, *KRAS*, *FLT3*, and *NF1*	
	Low hypodiploid	*IKZF2*, and by *TP53* disruptions, *CDKN2A/B* locus deletion	
	Hyperdiploid	*CREBBP*	
		NT5C2 mutations	NT5C2
		TP53 mutations	
T-cell		*PICALM-MLLT10*, *NUP214-ABL1* fusion, *EML-ABL1*, *SET-NUP214* fusion, *MLL*, *NOTCH1*, *FBW7*, *BCL11B*, *JAK1*, *PTPN2*, *IL7R*, *PHF6*, *RAS/PTEN*	

ALL, acute lymphoblastic leukemia; Ig, immunoglobulin; mTOR, mammalian target of rapamycin; TKI, tyrosine kinase inhibitor.

BCR/ABL1 rearrangement and *CRLF2* expression, the sample is sent out for additional molecular testing.

Measurable Residual Disease

Measurable residual disease (MRD), or minimal residual disease, is defined as residual leukemic blasts detected after cytoreductive chemotherapy despite apparent morphologic remission (<5% blasts in the bone marrow). Assessment of MRD has become a standard-of-care practice in the management of patients with ALL because of its powerful prognostic value as a predictor of relapse and survival.[32] The significant prognostic value of MRD spans across all subtypes of ALL and supersedes that of historical parameters, such as age, WBC count, and cytogenetics.[24] A meta-analysis of 13,637 pediatric and adult ALL patients showed that across all subgroups and covariates, MRD negativity has a hazard ratio (HR) of 0.23 in pediatric patients and 0.28 in adults for event-free survival (EFS) and an HR of 0.28 in both children and adults for overall survival (OS).[33] In adult patients, this translated to 10-year OS rates of 60% and 15% for patients who were MRD negative and MRD positive, respectively.

There are different methods to assess MRD after treatment, including multiparameter flow cytometry (MFC), quantitative polymerase chain reaction (PCR), and NGS. Ideally, MRD should be tested on a bone marrow sample because it can be 1 to 3 logs higher in MRD levels than that in the peripheral blood.[34–36] MRD assessment is recommended to perform on bone marrow with morphologic remission after induction, at approximately 3 months, and every 3 to 6 months thereafter. MRD information is currently used to guide postinduction therapy. Bassan et al.[37] assigned patients who achieved complete remission (CR) after intensive chemotherapy to either maintenance or allogeneic hematopoietic stem cell transplantation (AHSCT) based on their MRD status and found a 75% OS rate for patients who achieved MRD negativity and did not undergo AHSCT, regardless of their cytogenetic or clinical risk stratification at diagnosis. Another example of the use of MRD to guide therapies is the use of blinatumomab in patients with poor MRD clearance. In a multicenter single-arm phase II study of blinatumomab in MRD-positive ($\geq 10^{-3}$) B-ALL in morphologic CR, MRD negativity was achieved in 88 of 113 (78%) patients. Complete MRD responders had longer relapse-free survival (RFS) (23.6 vs 5.7 months; $P = .002$) and OS (38.9 vs 12.5 months; $P = .002$) compared with patients whose MRD did not clear after blinatumomab. The 4-year OS rate was 52% among MRD responders.[38] These findings were further confirmed using propensity score matching by comparing them with historical data.[39]

The time to achieve MRD negativity is also a strong prognostic factor, particularly in Ph-negative ALL. A study from our institution analyzed 215 patients with newly diagnosed Ph-negative B-ALL who received intensive chemotherapy and had available MRD assessment by MFC at CR and around 12 weeks. Early responders defined as MRD negativity at CR had better outcome, with 3-year EFS rates of 65% vs 42% in late responders ($P < .001$) and 3-year OS rates of 76% vs 58% ($P = .001$). On multivariate analysis, the *KMT2A* rearrangement and MRD positivity at CR were the only factors that correlated with worse OS.[40]

FRONTLINE THERAPY

The treatment of patients with ALL consists of four major components: induction of remission, consolidation, maintenance, and CNS prophylaxis.[41] The goal of induction is to induce remission by eradicating leukemic cells from the bone marrow. Intensive induction chemotherapy regimens are modeled after either the pediatric-inspired roadmap regimens or the hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) regimen developed at MD Anderson Cancer Center (MDACC). Pediatric-inspired regimens have previously been studied in patients of all ages, but their use in patients older than 40 years has largely fallen out of favor because of higher rates of toxicity and treatment-related mortality rates in this patient population, and they are generally reserved for use in the adolescent and young adult (AYA) population.[42] After achieving CR, the consolidation phase aims to eradicate any residual leukemia cells remaining after induction and, depending on the risk category, consists of either consolidation chemotherapy (e.g., high-dose methotrexate and cytarabine) or AHSCT. Consolidation is followed by maintenance therapy to prevent relapse and prolong remission. Maintenance consists of daily 6-mercaptopurine, weekly methotrexate, and monthly pulses of vincristine and prednisone or dexamethasone, given over 2 to 3 years (POMP [Purinethol, Oncovin, methotrexate, and prednisone] or DOMP (Dexamethasone, Purinethol, Oncovin, and methotrexate), depending on corticosteroid used).[43] Maintenance is omitted in mature B-ALL because of high cure rates, and BCR-ABL1 TKIs are included in all phases for patients with Ph-positive ALL.

One extensively studied regimen used in treatment of adult ALL is the hyper-CVAD regimen, in which patients receive hyper-CVAD alternating with high-dose methotrexate and cytarabine for a total of eight alternating cycles approximately every 3 to 4 weeks.[42] This is followed by 2.5 years of POMP maintenance therapy interspersed with intensification courses during months 6, 7, 18, and 19.

The advances made in the field of immunotherapy and the remarkable results achieved in the salvage

setting of ALL led to the investigation of chemoimmunotherapy in the frontline setting. To improve outcomes of younger patients with newly diagnosed B-ALL, an ongoing phase II trial is investigating the sequential use of hyper-CVAD and blinatumomab with promising safety and efficacy. The regimen consists of four cycles of hyper-CVAD followed by four cycles of blinatumomab. Blinatumomab is started after two cycles of chemotherapy for patients at high risk for relapse, including those with Ph-like ALL, complex karyotype, t(4;11), low-hypodiploidy, or near triploidy or who are MRD positive. Four cycles of blinatumomab are also incorporated in the POMP maintenance (three cycles of POMP followed by one cycle of blinatumomab) for a total of 16 cycles (i.e., 18 months) of maintenance therapy. Among 27 patients treated, the median age was 27 years (range, 18–57 years). The CR rate was 100%, and MRD negativity was achieved in 96%. There were no induction deaths. One-third of patients underwent AHSCT because of the presence of high-risk disease features. With a median follow-up period of 17 months, 93% of patients were still alive; one patient died after of AHSCT-related complication, and one died of sepsis during reinduction after relapse. The 1-year RFS and OS rates were 76% and 89%, respectively. This trial is currently ongoing at our institution (NCT02877303).[44]

Central Nervous System Prophylaxis and Treatment

Regularly scheduled lumbar punctures with intrathecal (IT) chemotherapy are a mainstay of ALL therapy to prevent or treat CNS disease and are implemented throughout the eight courses of the hyper-CVAD regimen in a risk-adapted manner. In Ph-negative B-ALL and T-ALL, a total of eight IT treatments (two per course for the first four courses) are given, which has decreased the rate of isolated CNS relapse to approximately 6%.[42,45] Because outcomes for patients with Ph-positive B-ALL improved with the addition of BCR-ABL TKIs to the hyper-CVAD regimen, leading to better survival, a higher percentage of CNS relapse is observed with only eight IT courses (~10%).[46] The addition of four more IT courses (12 IT in total) in Ph-positive B-ALL reduced the CNS relapse rate to 0% and hence is our current practice.[47] In patients with Burkitt leukemia or mature B-ALL, prophylaxis is further intensified to include 16 IT doses, a dosing strategy that has successfully reduced the risk of isolated CNS relapse in this patient population.[45]

During hyper-CVAD courses, IT chemotherapy alternating methotrexate and cytarabine is given on days 2 and 8, respectively. However, to avoid the simultaneous administration of IT methotrexate and systemic high-dose methotrexate during the even cycles, we have changed practice during the methotrexate and cytarabine (even) courses, reversing the sequence of IT therapy to avoid increased risk of neurotoxicity. Therefore, IT cytarabine is administered on day 2 and methotrexate on day 8.[48]

CNS disease is diagnosed by the presence of more than five lymphoblasts per microliter in the cerebrospinal fluid (CSF). Patients with CNS involvement are treated with triple IT therapy (hydrocortisone 50 mg, cytarabine 40 mg, and methotrexate 12 mg) twice per week until the CSF is negative for malignant cells on two occasions, then weekly IT for four to eight doses followed by every other week for four doses, and then the normal prophylaxis schedule is resumed with the remaining chemotherapy treatment. After this, consolidative craniospinal irradiation is considered in select patients with a curative intent, particularly before AHSCT.

Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia

The combination of cytotoxic chemotherapy with TKIs has been the mainstay of the frontline treatment of patients with Ph-positive ALL, with the early introduction and continuous administration of TKIs leading to best results.[49–52] Imatinib, a first-generation TKI, combined with intensive and nonintensive chemotherapy, results in CR rates greater than 90% and OS rates ranging from 33% to 50%.[53,54] The best results are achieved when imatinib is administered in a continuous fashion. Despite the improved outcomes with the addition of imatinib to chemotherapy, imatinib resistance is common and leads to a high incidence of relapse, which led to the evaluation of more potent TKIs for the frontline treatment of patients with Ph-positive ALL.

The second-generation TKI dasatinib has better potency and selectivity than the first-generation TKIs.[55] It was first developed for chronic myeloid leukemia in patients who could not tolerate or developed resistance to imatinib. Dasatinib is also reported to cross the blood–brain barrier.[56] A single-institution study conducted at MDACC of 72 patients with Ph-positive ALL treated with hyper-CVAD and dasatinib in the frontline setting led to 96% CR rate, 83% complete cytogenetic response (CCyR) rate after the first course, and 65% complete molecular response (CMR) rate. The 5-year OS rate was 46%.[55] These results were confirmed by a multicenter SWOG study of 94 patients with newly diagnosed Ph-positive ALL. At a median follow-up period of 26 months, the CR rate was 88%, and the 3-year OS rate was 71%.[57] Dasatinib in combination with low-intensity chemotherapy was also evaluated. The the European Working Group on Adult ALL (EWALL) study number 01 for Ph(+) ALL

(EWALL-PH-01) study investigated the combination of dasatinib with low-intensity chemotherapy in patients 55 years of age or older with newly diagnosed Ph-positive ALL, showing a 96% CR rate, 28% 5-year RFS, and 36% 5-year OS rate.[58] The majority (75%) of patients who relapsed had the T315I mutation, which confers resistance to all first- and second-generation TKIs.[58]

Nilotinib is another second-generation TKI with activity against most imatinib-resistant mutants of *ABL1*.[59] The EWALL international trial investigated the combination of low-intensity chemotherapy with nilotinib in older adult patients (median age, 65 years) with Ph-positive ALL. The regimen was well-tolerated. The CR rate was 94%, the 4-year EFS rate was 42%, and the OS rate was 47%. Thirty-two percent of patients underwent AHSCT, and the 4-year OS rate for transplanted patients was 61%.[60]

Because the emergence of T315I mutation is a driving force of relapse and the achievement of CMR is associated with better survival, an improvement of outcome relies on more potent TKIs that can suppress the emergence of T315I mutation. Ponatinib is a third-generation TKI that is active against the T315I mutation. In a phase II single-arm trial, patients with newly diagnosed Ph-positive ALL were treated with ponatinib and hyper-CVAD.[61] Ponatinib was given orally at 45 mg/day for the first 14 days of cycle 1 and then continuously at 45 mg/day for the subsequent cycles. After treating 37 patients, the protocol was amended after the occurrence of two fatal myocardial events to reduce the dose of ponatinib to 30 mg/day at cycle 2, with further reduction to 15 mg when a CMR (defined as absence of quantifiable BCR-ABL1 transcripts) was achieved. After the protocol amendment, no further vascular events occurred. A recent update was reported of 86 patients treated with hyper-CVAD and ponatinib with a median follow-up period of 43 months. The 3-month CMR rate was 74%, and the cumulative CMR rate was 84%. Only 18 patients (21%) underwent AHSCT in first CR (CR1). With a median follow-up period of 44 months, 71% of patients remain alive in remission, and only three relapses were observed in patients while still taking ponatinib. The 5-year CR duration and OS rates were 68% and 74%, respectively. A landmark analysis performed at 6 months showed a trend toward better OS in patients who did not undergo AHSCT in first remission (5-year OS rate of 66% for patients who underwent AHSCT compared with 83% for patients who did not [$P = .07$]).[62] The grade 3/4 toxicities included infections, liver function test abnormalities, thrombotic events, myocardial infarction, pancreatitis, and rash.[61–63]

The Gruppo Italiano Malattie Ematologiche Ddell'Adulto (GIMEMA) 1811 phase II trial included 42 patients with newly diagnosed Ph-positive ALL who were treated with ponatinib at 45 mg/day (for eight consecutive courses of 6 weeks) and steroids (prednisone days –14 to 29 during course 1). Complete hematologic response occurred in 95% of patients at 6 weeks and 91% at 24 weeks. The CMR rate at 24 weeks was 46%. The estimated 24-month OS rate was 60%.[64]

It is worth noting that although none of the TKIs has been compared head to head in Ph-positive ALL, one meta-analysis showed that ponatinib is more efficacious than earlier-generation TKIs in the frontline setting, with a higher percentage of patients achieving CMR with ponatinib-based therapy than with earlier-generation TKI-based therapies (79% vs 34%) and a higher OS with ponatinib (2-year, 83% vs 58%; 3-year, 79% vs 50%),[65] and one propensity-score analysis showed that ponatinib is superior to dasatinib: 3-month CMR rates were 82% versus 65% ($P = .03$); 3-year EFS and OS rates were 69% vs 46% ($P = .04$) and 83% versus 56% ($P = .03$), respectively.[66] The sequential combination of ponatinib combined with low-intensity chemotherapy followed by blinatumomab and ponatinib in patients with newly diagnosed Ph-positive ALL is currently being investigated in a clinical trial (NCT03147612).

The combination of blinatumomab with TKIs (mainly ponatinib) has been shown to be safe and effective in a small case series of 15 patients from MDACC with 50% CR rate and 75% CMR rate.[67] The GIMEMA group has recently presented early results from D-ALBA, the first trial investigating the sequential use of TKIs–steroid (in induction) and blinatumomab (in consolidation). Sixty-three patients were treated with this regimen of prednisone, dasatinib, and blinatumomab. The CR rate was 98%, and the 1-year disease-free survival (DFS) rate was 88%. Deep molecular response increased throughout therapy (29% after induction, 60% after two cycles of blinatumomab, and 80% after four cycles). Notably, T315I mutation was noted in 6 of 15 patients with rising MRD in the induction phase, all of which was cleared after blinatumomab.[68] However, T315I resistance mutation and patients harboring *IKZF1* and/or *PAX5* and/or *CDKN2A/B* deletions remain a therapeutic challenge. Several similar trials are evaluating the combination of blinatumomab with dasatinib (NCT02143414, NCT04329325) and ponatinib (NCT03263572) in both frontline and relapsed or refractory settings. At our institution, we are evaluating the combination of ponatinib with blinatumomab with promising early results.

Philadelphia Chromosome–Like Acute Lymphoblastic Leukemia

The treatment of patients with Ph-like ALL remains challenging because of the poor prognosis that this subtype confers. In a retrospective study from MDACC investigating the outcomes of patients with Ph-like ALL treated with standard intensive chemotherapy,

148 patients with untreated Ph-like ALL received hyper-CVAD or the pediatric-inspired augmented Berlin-Frankfurt-Münster (aBFM) regimen. Of the 148 patients, 56 patients (median age, 34 years) had Ph-like ALL, 37 of whom (61%) had *CRLF2* overexpression. The majority of patients with *CRLF2* rearrangements (84%) had concurrent *IKZF1* deletion. Patients with Ph-like ALL had lower rates of MRD negativity at CR and a worse 5-year survival rate (23% vs 59%; $P = .006$).[69]

Recently, the outcomes of 24 patients with B-ALL harboring *ABL*-class fusions and treated with a combination of TKIs and chemotherapy were reported in both frontline ($n = 19$) and relapse ($n = 5$) settings. The median age was 24 years (range, 5–72 years). Eleven patients (46%) harbored *IKZF1* deletions. After induction therapy, only 16 of 24 patients (67%) achieved CR, all with detectable MRD, including 7 with MRD of 10^{-2} or greater. In 14 of 18 patients (78%), an MRD level below 10^{-4} was achieved within a median time of 2.5 months (range, 1.4–14.8 months) after TKI initiation. The median remission duration and OS were not reached after a median follow-up period of 36 months. The 3-year EFS and OS rates were 55% and 77%, respectively.[70] Given that patients are more likely to remain MRD positive after induction therapy, the use of blinatumomab as frontline or for MRD in CR1 may improve outcomes.

Our current treatment strategies in patients with Ph-like ALL include the use of TKIs in patients with *ABL*-class fusions and blinatumomab and inotuzumab ozogamicin combinations mainly among patients with *CRLF2* and *JAK* activations.

Mature B-Cell and Burkitt Acute Lymphoblastic Leukemia

The addition of rituximab to short intensive chemotherapy has improved outcomes in adults with Burkitt and Burkitt-type lymphoma or ALL.[71–73] Its addition to hyper-CVAD resulted in a 3-year survival rate of 89% compared with 53% with chemotherapy alone. This was confirmed in a randomized, open-label, phase III trial, in which 260 patients with newly diagnosed Burkitt lymphoma/leukemia received intensive chemotherapy with or without rituximab. The addition of rituximab improved EFS (3-year rate, 75% vs 62%; $P = .024$) and OS (3-year rate, 83% vs 70%; $P = .011$).[74]

To further reduce early morbidity and mortality, a pilot study investigated dose-adjusted EPOCH (etoposide phosphate, prednisone, Oncovin, cyclophosphamide, and hydroxydaunorubicin) in combination with rituximab in 30 patients (median age, 33 years; age older than 40 years, 40%) diagnosed with Burkitt lymphoma. The treatment was safe and highly effective. The PFS and OS rates were 95% to 100% and 90% to 100%, respectively. Of note, the majority of patients (90%) had low- and intermediate-risk disease: only 13% had marrow involvement, and 3% had CNS involvement, both being known adverse factors.[75] One concern with the DA-EPOCH-R (dose-adjusted etoposide phosphate, prednisone, Oncovin, cyclophosphamide, hydroxydaunorubicin, and rituximab) regimen is the lack of highly CNS-penetrating chemotherapy agents, such as high-dose methotrexate and cytarabine, which are essential components of high-intensity chemotherapy for Burkitt leukemia. A recent report showed significantly higher 3-year rates of CNS relapse in patients with Burkitt leukemia treated with DA-EPOCH compared with regimens that incorporate agents with good CNS penetration, such as hyper-CVAD and CODO-M/IVAC (cyclophosphamide, Oncovin, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine) (12% compared with 3%–4%), despite the use of IT CNS prophylaxis with DA-EPOCH.[76] A phase III clinical trial comparing R-CODOX-M/R-IVAC (cyclophosphamide, doxorubicin, vincristine, methotrexate/ifosfamide, etoposide, high-dose cytarabine) with DA-EPOCH-R in patients with newly diagnosed high risk mature B-ALL is underway (EudraCT Number: 2013-004394-27).

CD20-Positive Precursor B-Cell Acute Lymphoblastic Leukemia

Expression of cell surface marker CD20 in adult ALL ranges from 35% to ubiquitous, depending on the subtype, and has been associated with an inferior prognosis.[77] The addition of two doses of monoclonal CD20 antibody (rituximab) administered with the first four cycles of chemotherapy and during maintenance intensification at months 6 and 18 resulted in improved OS in younger patients compared with similar chemotherapy historical control participants (75% vs 47% at 3 years; $P = .003$).[45] Similar results were reported by the German Multicenter Study Group for ALL (GMALL).[78] The addition of rituximab to chemotherapy in the GRAAL-R 2005 randomized study improved the 2-year EFS and OS rates from 52% to 65% ($P = .038$) and 64% to 71% ($P = .095$; censoring for AHSCT, $P = .018$), respectively.[79]

Ofatumumab is a second-generation anti-CD20 monoclonal antibody that has a different binding site than rituximab, targeting a membrane proximal small-loop epitope on the CD20 molecule.[80] Ofatumumab in combination with hyper-CVAD was found to be highly effective in a phase II study of 69 patients with newly diagnosed Ph-negative CD20-positive B-ALL. All but one patient (98%) achieved CR, and the MRD negativity rate was 93% overall. At a median follow-up period of 44 months, the median RFS was 52 months, and the median OS was not reached. The 4-year RFS and OS

rates were 60% and 68%, respectively. For AYAs, the 4-year OS rate was 74%. Overall, the combination of hyper-CVAD plus ofatumumab was highly effective. Ofatumumab is our preferred anti-CD20 monoclonal antibody in ALL, particularly for patients with CD20 expression less than 20%.[81]

T-Cell Acute Lymphoblastic Leukemia

Treatment of adults with T-ALL and T-cell lymphoblastic lymphoma (T-LL) results in long-term survival rates of 40% to 60%; the outcome is strongly associated with the T-cell phenotype.[18,82] Nelarabine, a T-cell-specific purine nucleoside analog, is approved for the treatment of patients with relapsed and refractory T-ALL, leading to CR rates of 31% to 36% in phase II trials,[83,84] allowing some patients to undergo AHSCT with long-term survival. In the pediatric experience, the addition of nelarabine to frontline aBFM chemotherapy in patients with T-ALL up to 31 years of age improved the 4-year DFS rate from 83% with aBFM alone to 89% ($P = .0332$).[85] However, these results have not yet been replicated in adult patients. A single-arm phase II study from MDACC of nelarabine combined with frontline hyper-CVAD regimen in 67 patients failed to improve CR duration or OS rates compared with historical control participants treated with hyper-CVAD alone.[86] This study has now been amended to include the incorporation of nelarabine, peg-asparaginase, and venetoclax into the hyper-CVAD regimen.

Recent insights into the biology of ETP-ALL have revealed BCL-2 dependence, which perhaps explains the sensitivity to BCL-2 antagonism.[87] The addition of venetoclax to lower-intensity chemotherapy in older adults with newly diagnosed ALL has yielded encouraging early results in interim reports of 10 patients treated (three with T-ALL, including two with ETP-ALL), with 90% CR/CR with incomplete hematologic recovery (CRi) rate and 90% MRD negativity.[88] The combination of venetoclax and navitoclax may also be particularly promising in this subgroup. Clinical trials evaluating the efficacy and safety of venetoclax with navitoclax (NCT03181126) and in combination with chemotherapy (NCT03808610; NCT03504644; NCT03576547; NCT03319901) in patients with relapsed and refractory ALL are currently ongoing. Studies evaluating the biology of near ETP-ALL are ongoing at our institution to better tailor the treatment and thus improve the outcome of this poor-risk subgroup.

Adolescent and Young Adult Acute Lymphoblastic Leukemia

The AYA population consists of patients 15 to 39 years of age. The biology of ALL differs between children, AYAs, and older adults, which is the rationale behind tailoring ALL therapy to the different treated populations. Such differences include (1) a higher T-cell phenotype in patients aged 10 to 40 years old; (2) a near absence of the two favorable subgroups of ALL (hyperdiploidy and t(12;21)/*ETV6-RUNX1*) during the second decade of life compared with a 60% prevalence in children; and (3) an increasing prevalence of high-risk Ph-positive ALL with age, from 3% in children to almost 50% in older adults.[89] In the US intergroup trial C10403 of 295 AYA patients (17–39 years of age) treated with a pediatric regimen, the 3-year OS rate was 73%.[90] At MDACC, a nonrandomized study including AYA patients showed no difference between the pediatric asparaginase-containing aBFM regimen and the non-asparaginase-containing hyper-CVAD regimen. The 5-year CR duration rate was 53% with hyper-CVAD, compared with 55% with aBFM. The 5-year OS rates were 60% in both groups. The aBFM regimen had a higher incidence of asparaginase adverse effects, such as hepatotoxicity (41%), pancreatitis (11%), and thrombosis (19%), and myelosuppression-related complications were more common with hyper-CVAD.[91] More recently, the hyper-CVAD and ofatumumab combination reported a 4-year OS rate of 74% in the AYA population.[81]

In summary, pediatric regimens and the hyper-CVAD regimen showed similar CR, remission duration, and survival outcomes. In the absence of a randomized study comparing both regimens in the AYA population, our practice is to use the hyper-CVAD regimen as a backbone for clinical trial development because this regimen has less organ-specific toxicity than asparaginase-based regimens and is thus more conducive to combination with investigational agents.

Acute Lymphoblastic Leukemia in Older Patients

In older patients with ALL (generally defined as those older than 55–60 years), intensive chemotherapy results in CR rates of 80% but with unacceptable toxicities.[92] One-third of patients achieving CR may die of myelosuppression-associated complications. The historical long-term cure rate is 15% to 20%.[93] Among 727 older adult patients (older than 65 years; 2007–2012) treated under Medicare, the majority of patients did not receive chemotherapy; in those who received chemotherapy, the median OS period was only 10 months.[94] In the National Cancer Institute Surveillance, Epidemiology, and End Results database, among 1675 adults (age 60 years or older) with ALL (1980–2011), the median survival time was 4 months, and the 3-year survival rate was 12.8%.[95]

Strategies to de-intensify treatment regimens have been thus investigated in this population. Inotuzumab ozogamicin with mini hyper-CVD (i.e., a lower

intensity version of the hyper-CVAD regimen without anthracycline), with or without blinatumomab, is one such strategy and appears to be promising in the older adult population. Among 64 patients treated with this regimen, the median age was 68 years (range, 60–81 years), and 42% of patients were 70 years of age or older. The CR rate was 98%, and 95% achieved MRD negativity. The 3-year CR duration and OS rates were 76% and 54%, respectively. A propensity-matched analysis showed that this regimen significantly improved survival compared with a historical 3-year OS rate of 32% with hyper-CVAD in this older population (P = .007). No early deaths occurred during induction. However, the rates of death in remission were 33% overall and were significantly higher in those 70 years of age or older compared with those ages 60 to 69 years (50% vs 22%, respectively; P = .02). For the population of patients 70 years of age or older, the protocol has now been amended to decrease the number of mini hyper-CVD and inotuzumab ozogamicin cycles from four to two and to replace POMP maintenance with blinatumomab monotherapy to mitigate toxicity in this population.[96]

Role of Allogeneic Hematopoietic Stem Cell Transplantation

AHSCT has traditionally been reserved for patients with high-risk features, including B lineage with WBC 30 × 109/L or greater; T-lineage with WBC 100 × 109/L of greater; hypodiploid; Ph-positive; or *KMT2A* translocation ALL [e.g., t(4;11)]. However, there has been some debate regarding who should be referred for AHSCT in CR1 because of the emergence of newer promising therapies that have improved outcomes in this disease. As an alternative, many centers have incorporated MRD via Flow cytometry (FCM) or reverse transcription PCR after induction or consolidation to stratify patients based on their response to chemotherapy.[97] In one study, MRD status at various time points after CR was used to guide treatment in adult patients with ALL.[37] Patients who remained MRD positive at the end of consolidation were deemed to be higher risk and underwent AHSCT instead of receiving prolonged maintenance therapy. Patients who achieved MRD-negative status had a significantly improved 5-year OS (75% vs 33%; P = .001). Ph-like ALL and ETP-ALL confer a poor prognosis, and AHSCT should be considered regardless of MRD status.[19,98] The GRAALL (Group for Research in Adult Acute Lymphoblastic Leukemia)-2003/2005 trials showed that postinduction MRD positivity, the presence of *IKZF1* mutations in B-ALL, and the absence of *NOTCH1* or *FBXW7* mutations in T-ALL are the main factors predicting benefits of AHSCT in CR1.[23,69] It is noteworthy that newer agents, such as blinatumomab, are potent in eradicating MRD, as was proved by the BLAST trial, which showed no difference in OS or RFS between patients who received AHSCT during CR1 and those who did not.[99] Hence, the role of AHSCT in the era of new therapeutics is becoming increasingly questionable.

Similarly, in the era of potent TKIs, the role of AHSCT in patients with Ph-positive ALL is also becoming controversial, even though it has been historically shown that AHSCT does improve outcomes in these patients. Although a study showed that AHSCT improved RFS and OS in patients with Ph-positive ALL treated with hyper-CVAD and dasatinib, a subgroup analysis according to molecular responses was not performed.[57] On the other hand, achievement of a 3-month CMR predicted a very good prognosis in patients who received chemotherapy plus TKIs, suggesting that these patients might not need AHSCT.[100,101] An analysis performed on patients treated with hyper-CVAD and ponatinib with censoring at time of transplant showed that the long-term probability of survival is the same, suggesting that most of these patients may be cured without AHSCT.[61,63]

The role of AHSCT in CR1 remains currently valid in certain high-risk circumstances, such as (1) *KMT2A*-rearranged ALL, (2) ETP-ALL, and (3) ALL with complex cytogenetics and hypodiploidy. Patients with Ph-like ALL with negative MRD and those in CR1 who achieve MRD negativity after blinatumomab may not need AHSCT. Patients with Ph-positive ALL with 3-month CMR should not be referred to AHSCT; in contrast, patients with positive MRD should be considered for blinatumomab or other MRD-targeted therapy and eventually AHSCT, particularly in patients who remain positive for MRD. Patients with ALL in CR2 should be referred for AHSCT (Fig. 1–2).

SALVAGE THERAPY

The prognosis of adult patients with relapsed ALL was historically associated with a dismal prognosis, with a cure rate of less than 10%[102,103] and CR rates of 30% to 40% in first relapse and 20% to 25% in second relapse with standard chemotherapy regimens, with an AHSCT rate of only 10% to 30% in adult patients.[102,103] The recent advent of monoclonal antibodies, bispecific antibodies, and chimeric antigen receptor T-cell (CAR T) therapies has revolutionized the treatment of ALL and resulted in a number of Food and Drug Administration approvals for the treatment of ALL in the salvage setting, such as blinatumomab in 2014 and inotuzumab ozogamicin and tisagenlecleucel in 2017.[104–106] These agents are currently the subject of investigation in different schemas and combinations (Table 1–5).

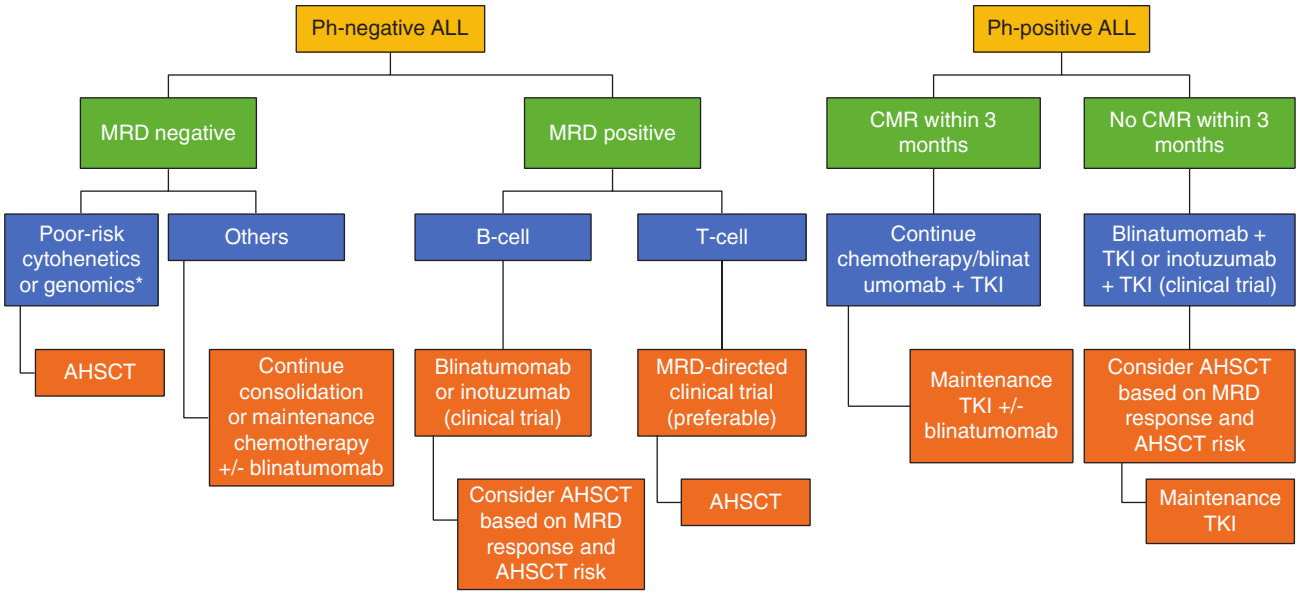


FIGURE 1-2 **MD Anderson Cancer Center algorithm for referring for allogeneic hematopoietic stem cell transplant (AHSCT) in acute lymphoblastic leukemia (ALL).** *Asterisk* **indicates Philadelphia chromosome (Ph)–like, 11q23 rearrangement, early T-cell precursor ALL, low hypodiploidy or near triploidy, or complex cytogenics. CMR, complete molecular response; MRD, measurable residual disease; TKI, tyrosine kinase inhibitor.**

Table 1–5 Seminal Trials for Treatment of Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia

Clinical Trial	Disease Setting	Patients (*n*)	Response	Median Overall Survival Time (months)	MRD Negativity (%)[a]
Blinatumomab					
TOWER[103]	R/R Ph- ALL	271	ORR: 44% CR: 34%	7.7	76
ALCANTARA[109]	R/R Ph+ ALL	45	ORR: 36% CR: 31%	7.1	88[b]
Inotuzumab Ozogamicin					
INO-VATE[105]	R/R ALL	109	ORR: 81% CR: 35.8%	7.7	78
mini-hyper-CVD + inotuzumab ozogamicin ± blinatumomab[115]	R/R ALL	84	ORR: 80% CR: 58%	S1: 25 S2: 6 S3: 7	82
CAR T-Cell Therapy					
ELIANA[105,123]	R/R ALL (age younger than 26 years)	79	ORR: 82% CR/CRi: 62%	NR	98
Anti-CD19 CAR T cells[124]	R/R ALL (adults)	53	CR: 83%	12.9	67

[a]Measured by flow cytometry.
[b]Within two cycles.
ALL, acute lymphoblastic leukemia; CAR, chimeric antigen receptor; CR, complete remission; CRi, complete response with incomplete hematologic recovery; CVD, cyclophosphamide, vincristine, and dexamethasone; MRD, measurable residual disease; NR, not reported; ORR, objective response rate; Ph, Philadelphia; R/R, relapse or refractory; S1, salvage 1; S2, salvage 2; S3, salvage 3.

Blinatumomab

Blinatumomab is an anti-CD19-directed CD3 bispecific T-cell engager constructed using BiTE antibody technology.[107] It consists of a recombinant monoclonal antibody composed of an anti-CD19 fragment antigen-binding (Fab) region joined by a short linker to

an anti-CD3 Fab region.[107] In the confirmatory phase II study of 189 patients with Ph-negative ALL, blinatumomab was associated with an objective response rate (ORR) of 43%. The median response duration was 9 months, and the median OS period was 6 months.[108]

Following these results, a phase III trial (TOWER study) was conducted in more than 400 patients with relapsed or refractory Ph-negative ALL randomized (2:1) to blinatumomab (n = 271) or standard of care (n = 134). The rate of CR with full, partial, or incomplete hematologic recovery was significantly higher in the blinatumomab group than in the chemotherapy group (44% and 25%, respectively; P <.001). Molecular remission rates among responders, defined as MRD less than 10^{-4} in the first 12 weeks, were 76% and 48%, respectively. Blinatumomab prolonged survival, the primary study endpoint; the median OS was 7.7 months versus 4.0 months (P = .01). A total of 24% of the patients in each group underwent AHSCT.[104]

A recent report from a phase III study with 1:1 randomization of 208 children and AYAs in first salvage to blinatumomab or standard of care showed that blinatumomab induced a higher rate of MRD negativity (79% with blinatumomab compared to 21% with standard of care; P <.001) and a better 2-year OS rate (79% with blinatumomab compared with 59% with standard of care; P = .005).[109]

In patients with relapsed or refractory Ph-positive ALL, blinatumomab also demonstrated a positive effect. In the phase II ALCANTARA trial, 45 patients with relapsed or refractory Ph-positive ALL were treated. Thirty-six percent achieved a response. The median RFS and OS periods were 6.7 months and 7.1 months, respectively; 44% of patients received AHSCT.[110]

Inotuzumab Ozogamicin

Inotuzumab ozogamicin is a novel anti-CD22 monoclonal antibody conjugated to the toxin calicheamicin.[111] In a single-institution phase II study in patients with relapsed or refractory ALL, inotuzumab ozogamicin was administered at a starting dose of 1.3 to 1.8 mg/m^2 intravenously (IV) every 3 to 4 weeks. Forty-nine patients were treated. The ORR was 57%, and the median survival period was 5.1 months. Nearly half of the patients treated with inotuzumab ozogamicin proceeded to AHSCT.[112] To minimize toxicities and based on pharmacokinetic and pharmacodynamic data, inotuzumab ozogamicin was administered on a weekly basis at 0.8 mg/m^2 IV on day 1 followed by 0.5 mg/m^2 IV on days 8 and 15 every 3 to 4 weeks in 40 patients. The study yielded a similar response rate as inotuzumab ozogamicin given every 3 to 4 weeks (59% vs 57%), with a median survival period of 9.5 months. Weekly administration of inotuzumab ozogamicin resulted in fewer adverse events, including lower rates of veno-occlusive disease (VOD).[113] In a separate, multicenter phase II trial in heavily pretreated patients with relapsed or refractory ALL, inotuzumab ozogamicin therapy resulted in a remission rate of 66%, with 78% of patients who achieved CR becoming MRD negative. The median survival period was 7.4 months.[114]

These results led to a randomized trial comparing inotuzumab ozogamicin with physician's choice of chemotherapy in patients with relapsed ALL. The CR rates were 81% with inotuzumab ozogamicin and 29% with standard of care (P <.0001). Among responders, the MRD negativity rates were 78% and 28% (P <.0001), respectively. The median survival period was 7.7 versus 6.7 months (P = 0.02; HR, 0.77). The 2-year survival rates were 23% and 10%, respectively. Serious toxicities included VOD after AHSCT, mainly in patients who received double alkylators in pretransplant conditioning. Age was also a risk factor for VOD.[105]

Recently, inotuzumab ozogamicin was assessed in 48 children and AYAs (median age, 9 years).[1–21] The ORR and MRD negativity rates were 62% and 65%, respectively. The 12-month OS rate was 40%.[115]

Combination Immunotherapies

Given the encouraging results achieved with these novel antibody constructs in ALL, they were further evaluated in combination with lower-intensity chemotherapy backbone with the goal of further improving outcomes.

Inotuzumab ozogamicin was evaluated with mini hyper-CVD in relapsed or refractory B-cell Ph-negative ALL (details described earlier). Among the initial 59 patients with relapsed or refractory ALL treated, the response rate was 78%, with 82% of responders achieving MRD negativity. The 1-year RFS and OS rates were 46% and 41%, respectively. The median OS and RFS were 11 months and 8 months, respectively. Almost half of the patients were able to receive subsequent AHSCT, with an estimated 1-year survival rate of 63% among these patients. The rate of VOD was 15%, mainly in patients with prior or subsequent AHSCT (23%). When compared with a historical cohort of patients treated with inotuzumab ozogamicin monotherapy in the salvage setting, the results of the combination were significantly better (median survival 9.3 months vs 5.6 months, P = .02). To further improve these outcomes, the study was amended to investigate the addition of four cycles of blinatumomab following four cycles of the combination of weekly lower doses of inotuzumab ozogamicin and mini hyper-CVD. The hypothesis is that the

addition of blinatumomab may allow for the use of less chemotherapy and lower doses of weekly inotuzumab ozogamicin, the eradication of MRD, and the distancing of AHSCT from the last dose of inotuzumab ozogamicin, thereby leading to less treatment-related morbidity, less VOD, and less mortality. In fact, the incidence of VOD was significantly reduced (from 15% to 5%) by using lower and fractionated doses of inotuzumab ozogamicin (first dose of 0.6 mg/m^2; then 0.3 mg/m^2 for each subsequent dose) and by spacing out the last dose of inotuzumab ozogamicin from AHSCT by 3 to 6 months. In the overall cohort of patients treated with mini hyper-CVD with inotuzumab ozogamicin (n = 59) alone and those treated with sequential combination with blinatumomab (n = 30), the 2-year survival rate was 39%, and the median survival period was 14 months. In 62 patients treated in first salvage with mini hyper-CVD and inotuzumab ozogamicin with or without blinatumomab, the CR/CRi rate was 92%, the MRD negativity rate was 86%, the median survival time was 25 months, and the 3-year OS rate was 42%. The 60-day mortality rate was 3%.[116] These results compare favorably with the results obtained with single-agent inotuzumab ozogamicin and blinatumomab and historical salvage chemotherapy with median survival period of only 6 to 12 months. Longer follow-up is needed to assess the relative contribution of blinatumomab to the regimen.

The SWOG 1312 study is a phase I trial of inotuzumab ozogamicin and CVP (cyclophosphamide, vincristine, and prednisone) for relapsed or refractory ALL. Fifty patients (median age, 43 years) were enrolled, among whom five patients were identified as having a Ph-like signature. The CR/CRi rate was 61% in the 23 evaluable patients treated at the maximal tolerated dose (MTD), and 60% (three of five) in patients with the Ph-like signature. The median OS periods were 7.7 months for all patients and 10.9 months for patients treated at the MTD.[117]

BH3 Mimetics

The BH3 mimetics venetoclax and navitoclax have demonstrated promising preclinical activity in cell lines of B-TALL and T-ALL.[118–120] Navitoclax is a BH3 mimetic that inhibits BCL-2, BCL-xL, and BCL-W with encouraging antileukemic activity in ALL cells.[120] A particularly strong activity was seen in *KMT2A*-rearranged B-ALL, and both single-agent activity as well as synergistic killing in combination with chemotherapy were observed because of the upregulation of *BCL-2* in these cell lines.[118,119] In a phase I trial, 36 patients with relapsed or refractory ALL (median age, 27 years; range, 6–72 years) were treated with venetoclax and navitoclax in combination with chemotherapy. The ORR was 56%, and the 6-month duration of response rate was 43%.[121]

Chimeric Antigen Receptor T-Cell Therapies

CAR T cells are autologous T cells that are genetically engineered to express a chimeric antigen receptor that is composed of different structural parts, including a binding site of a specific antibody and a signal transduction part with or without additional costimulatory domains.[122] CAR T cells are powerful therapeutic innovations that combine the antigen specificity of antibodies and the cytotoxic activity of T-cells and hence harness the power of targeted therapy and immunotherapy. Although first-generation CAR T cells expressing anti-CD20 or -CD19 CAR T cells failed to expand in vivo and produce significant antitumor effects,[122] second- and third-generation CAR T cells, incorporating one or more co-stimulatory domains, respectively, demonstrated strong expansion and persistence in vivo and powerful antitumor activity. In fourth-generation CAR T cells, cytokines are added to further increase the expansion and survival of CAR T cells.

A multicenter phase I/II study was conducted in 25 centers around the world and treated 79 children and young adults (median age, 11 years) with relapsed or refractory CD19-positive B-ALL with a single infusion of tisagenlecleucel, anti-CD19 CAR T cells produced by Novartis. Among the 65 patients with CR/CRi, 64 (98%) were MRD negative within 3 months. The median duration of response was not reached. The estimated 18-month RFS rate was 66%. Median OS was not reached, and the estimated 18-month OS rate was 70%.[106,123] Tisagenlecleucel is now approved for patients up to age 25 years with B-ALL that is refractory to frontline therapy or with two or more relapses.

Anti-CD19 CAR-T cells were also studied in 53 adult patients at Memorial Sloan Kettering Cancer Center and showed a CR rate of 83%. The median EFS and OS were 6.1 months and 12.9 months, respectively. The median EFS in patients with low (<5% bone marrow blasts) and high disease burden (≥5% bone marrow blasts or extramedullary disease) were 10.6 months and 5.3 months, respectively. The median OS periods were 20.1 and 12.4 months, respectively. Patients with a higher burden of disease had a greater incidence of cytokine release syndrome (CRS) and neurotoxic events as well.[124] ZUMA-3 is a phase I trial that investigated the autologous anti-CD19 KTE-X19 in adults with relapsed or refractory ALL and successfully refined the dosing and the safety of the product,[125] leading to a pivotal phase II trial that is currently ongoing (NCT02614066).

There are two main safety concerns with CAR T-cell therapy: CRS and neurotoxicity, occurring in 77% to

Table 1–6 Ongoing Trials at MD Anderson Cancer Center Available for Patients with Acute Lymphoblastic Leukemia (Frontline and Salvage Settings)

	Trial Characteristics	
ALL Subgroup	**Frontline Setting**	**Salvage Setting**
Pre-B-cell ALL	1. Hyper-CVAD + inotuzumab ozogamicin + blinatumomab 2. Hyper-CVD + inotuzumab ozogamicin + blinatumomab	1. Hyper-CVD + inotuzumab ozogamicin + blinatumomab 2. Hyper-CVD + venetoclax 3. ADCT-602 4. CAR T cells (UCART19, UCART22, KTE-C19) 5. CAR-NK cells
Pre-B-cell ALL, MRD+	1. Blinatumomab 2. Inotuzumab ozogamicin	
T-cell ALL	1. Hyper-CVAD + nelarabine + peg asparaginase + venetoclax 2. Hyper-CVD + venetoclax	1. Hyper-CVD + venetoclax
Ph-positive ALL	1. Hyper-CVD + ponatinib + blinatumomab 2. Blinatumomab + ponatinib	1. Blinatumomab + ponatinib 2. Venetoclax + ponatinib

ALL, acute lymphoblastic leukemia; CAR, chimeric antigen receptor; CVAD, cyclophosphamide, vincristine, doxorubicin, and dexamethasone; CVD, cyclophosphamide, vincristine, and dexamethasone; MRD, measurable residual disease; NK, natural killer; Ph, Philadelphia chromosome.

83% and 40% to 43% of patients, respectively, and being more common in patients with a higher disease burden at baseline.[126] Grade 3 or greater CRS, including one death, was observed in 26% of patients and grade 3 or greater neurotoxicity in 42% of patients, and most of them required treatment with the anti–interleukin-6 monoclonal antibody tocilizumab.[124]

Strategies to improve the safety of CAR T cells while preserving their efficacy are an active area of basic and translational research. A novel anti-CD19 CAR T cell product with a lower affinity to CD19 and fast-off rate has been evaluated and showed improved in vitro proliferation and cytotoxic activity and enhanced proliferation and in vivo antitumor effect.[127] To circumvent CD19 antigen escape as a mechanism of resistance, CD22-targeted CAR T cells and dual CD19 and CD22 CAR T cells have also been developed.

Tremendous efforts have also been made to develop new platforms of "off-the-shelf" CAR-based therapies to decrease the high cost and manufacturing complexity and delay associated with currently approved CAR T cells. Allogeneic CAR T cells manufactured from healthy donors have been investigated. For example, UCART19 is an allogeneic, genetically modified second-generation CAR T cell product manufactured from healthy donor T-cells, in which *TRAC* and *CD52* genes have been knocked out to allow its administration to non–human leukocyte antigen–matched patients without increasing the risk of graft-versus-host disease. "Off-the-shelf" NK cells derived from umbilical cord blood and modified to express CAR (CAR-NK cells) are being developed at our institution with promising results in B-lymphoid malignancies.[128]

EMERGING THERAPIES: MD ANDERSON APPROACH

A number of innovative therapies for various stages of disease, tailored to risk-adapted strategies, are transforming the treatment of adult ALL and resulting in significant improvements in long-term outcomes. Several ongoing trials are available for patients with ALL at our institution and elsewhere in the frontline and salvage settings (Table 1–6).

Our preferred approach to newly diagnosed Ph-negative B-ALL is the addition of blinatumomab to hyper-CVAD in the frontline setting. In this ongoing protocol, only four cycles of chemotherapy are given instead of the standard eight cycles followed by four cycles of blinatumomab incorporated into an 18-month maintenance regimen (half the duration of standard POMP maintenance). With the addition of blinatumomab, the goal is to both decrease the amount of intensive chemotherapy received and deepen responses. This protocol was recently amended to add the CD22 antibody–drug conjugate inotuzumab ozogamicin, thereby incorporating all of the most active agents in B-ALL into our frontline regimen.

Because older adult patients often cannot tolerate intensive chemotherapy, our preferred regimen consists of low-intensity chemotherapy (hyper-CVD) combined with both inotuzumab ozogamicin (given at a lower fractionated dose to decrease the rate of VOD) and blinatumomab to deepen the level of response. We also use this regimen in the relapsed or refractory setting at any age. We also have protocols for low-intensity chemotherapy with venetoclax in older patients

with Ph-negative ALL and for patients with relapsed or refractory ALL (mainly T-ALL).

In patients with Ph-positive ALL, there is a rationale to combine ponatinib with a less intensive chemotherapy backbone (mini hyper-CVD). Given its activity in patients with Ph-positive ALL, blinatumomab is also added to this regimen. The goal is that by reducing toxicity from intensive chemotherapy and incorporating the most active agents in Ph-positive ALL (blinatumomab and ponatinib), we will reduce treatment-related morbidity and mortality and further increase the cure rate. This regimen is open to patients of all ages with newly diagnosed Ph-positive ALL. In older patients (60 years and older) with newly diagnosed Ph-positive ALL or younger patients who are unfit for intensive chemotherapy, we are also evaluating a chemotherapy-free combination of ponatinib and blinatumomab, which is also available for patients with relapsed or refractory Ph-positive ALL at any age.

In the salvage setting, we designed a phase I/II study of the combination of hyper-CVD plus venetoclax for patients with relapsed or refractory ALL. This regimen is particularly promising for patients with T-ALL. Another phase I/II trial available at our institution is investigating ADCT-602, which is an antibody drug conjugate composed of a humanized monoclonal antibody directed against CD22, conjugated to the cross-linking cytotoxic agent tesirine (SG3249). The hope is that this agent will be a potent anti-CD22 therapy, without the hepatic toxicity associated with inotuzumab ozogamicin. Moreover, we have a number of CAR-based therapies being investigated in clinical trials, including those targeting both CD19 and CD22 as well as both autologous (KTE-C19) and allogeneic approaches (UCART19, UCART22, and CAR NK-cell therapies).

Finally, for relapsed or refractory Ph-positive ALL, besides the chemotherapy-free combination of ponatinib and blinatumomab being investigated, we have an ongoing phase I/II trial of the oral, chemotherapy-free regimen, consisting of the combination of venetoclax and ponatinib, for patients of all ages with relapsed or refractory Ph-positive ALL. There is a significant preclinical rationale for the combination of venetoclax and ponatinib, showing synergistic activity. Ponatinib may also help to prevent venetoclax resistance by preventing upregulation of Mcl-1, an established resistance mechanism of venetoclax-based regimens.

CONCLUSION

Therapeutic capabilities in adult ALL have rapidly reached new heights over the past decade with the introduction of highly promising monoclonal antibodies, immune conjugates, CAR T cells, and new-generation TKIs. Genomic profiling has identified new prognostic markers (e.g., *IKZF1*) as well as new therapeutic targets (e.g., *ABL*, *JAK1/2*, *ETV6-NTRK3*) to improve the adverse prognosis of some ALL subsets, such as Ph-like ALL. As many of the newer agents advance through the final stages of development, we will seek to determine the optimal combination and order of delivery and the role of cytotoxic chemotherapy in the safest achievement of durable cure rates. Moreover, the frontline introduction of these effective therapies can be expected to increase the rate of MRD negativity, optimize responses, and close the outcome gap separating pediatric from adult ALL. Harnessing the full potential of the immune system with the durable presence of autologous or allogeneic T-cell constructs may ultimately lead to obviation of AHSCT in search of better cure rates in adult ALL.

MD ANDERSON PRACTICE TIPS

- There are several ongoing clinical trials at MDACC for patients with ALL. The treatment follows a risk-tailored strategy. Our preferred approach to patients with newly diagnosed Ph-negative B-ALL is the addition of blinatumomab to hyper-CVAD in the frontline setting.
- Our preferred regimen in older adult patients consists of low-intensity chemotherapy (hyper-CVD) combined with both inotuzumab ozogamicin (given at a lower fractionated dose to decrease the rate of VOD) and blinatumomab to deepen the level of response. We also use this regimen in the relapsed or refractory setting at any age. We also have protocols for low-intensity chemotherapy with venetoclax in older patients with Ph-negative ALL and for patients with relapsed or refractory ALL (mainly T-ALL).
- In patients with Ph-positive ALL, we combine ponatinib with a less intensive chemotherapy backbone (mini hyper-CVD). Given its activity in Ph-positive ALL, blinatumomab is also added to this regimen. In older patients (60 years or older) with newly diagnosed Ph-positive ALL or younger patients who are unfit for intensive chemotherapy, we are also evaluating a chemotherapy-free combination of ponatinib and blinatumomab, which is also available for patients with relapsed or refractory Ph-positive ALL at any age.
- In the salvage setting, we have a number of trials including the combination of hyper-CVD with venetoclax and antibody drug conjugates as well as CAR-based therapies with T-cells as well as NK cells.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(1):7-30.
2. Lightfoot TJ, Roman E. Causes of childhood leukaemia and lymphoma. *Toxicol Appl Pharmacol*. 2004;199(2):104-117.
3. Richardson RB. Promotional etiology for common childhood acute lymphoblastic leukemia: the infective lymphoid recovery hypothesis. *Leuk Res*. 2011;35(11):1425-1431.
4. Chevalier SA, Durand S, Dasgupta A, et al. The transcription profile of Tax-3 is more similar to Tax-1 than Tax-2: insights into HTLV-3 potential leukemogenic properties. *PLoS One*. 2012;7(7):e41003.
5. Lombardi L, Newcomb EW, Dalla-Favera R. Pathogenesis of Burkitt lymphoma: expression of an activated c-*myc* oncogene causes the tumorigenic conversion of EBV-infected human B lymphoblasts. *Cell*. 1987;49(2):161-170.
6. Vianna NJ, Polan AK. Childhood lymphatic leukemia: prenatal seasonality and possible association with congenital varicella. *Am J Epidemiol*. 1976;103(3):321-332.
7. Cortes J. Central nervous system involvement in adult acute lymphocytic leukemia. *Hematol Oncol Clin North Am*. 2001;15(1):145-162.
8. Faderl S, O'Brien S, Pui CH, et al. Adult acute lymphoblastic leukemia: concepts and strategies. *Cancer*. 2010;116(5):1165-1176.
9. Swerdlow SH. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. International Agency for Research on Cancer; 2017.
10. Murphy SB. Childhood non-Hodgkin's lymphoma. *N Engl J Med*. 1978;299(26):1446-1448.
11. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the acute leukaemias. French-American-British (FAB) co-operative group. *Br J Haematol*. 1976;33(4):451-458.
12. Matutes E, Morilla R, Farahat N, et al. Definition of acute biphenotypic leukemia. *Haematologica*. 1997;82(1):64-66.
13. Preti HA, Huh YO, O'Brien SM, et al. Myeloid markers in adult acute lymphocytic leukemia. Correlations with patient and disease characteristics and with prognosis. *Cancer*. 1995;76(9):1564-1570.
14. Putti MC, Rondelli R, Cocito MG, et al. Expression of myeloid markers lacks prognostic impact in children treated for acute lymphoblastic leukemia: Italian experience in AIEOP-ALL 88-91 studies. *Blood*. 1998;92(3):795-801.
15. Pui CH, Rubnitz JE, Hancock ML, et al. Reappraisal of the clinical and biologic significance of myeloid-associated antigen expression in childhood acute lymphoblastic leukemia. *J Clin Oncol*. 1998;16(12):3768-3773.
16. Serrano J, Román J, Sánchez J, Torres A. Myeloperoxidase gene expression in acute lymphoblastic leukaemia. *Br J Haematol*. 1997;97(4):841-843.
17. Bene MC, Castoldi G, Knapp W, et al. Proposals for the immunological classification of acute leukemias. European Group for the Immunological Characterization of Leukemias (EGIL). *Leukemia*. 1995;9(10):1783-1786.
18. Coustan-Smith E, Mullighan CG, Onciu M, et al. Early T-cell precursor leukaemia: a subtype of very high-risk acute lymphoblastic leukaemia. *Lancet Oncol*. 2009;10(2):147-156.
19. Jain N, Lamb AV, O'Brien S, et al. Early T-cell precursor acute lymphoblastic leukemia/lymphoma (ETP-ALL/LBL) in adolescents and adults: a high-risk subtype. *Blood*. 2016;127(15):1863-1869.
20. Van Vlierberghe P, Ambesi-Impiombato A, Perez-Garcia A, et al. ETV6 mutations in early immature human T cell leukemias. *J Exp Med*. 2011;208(13):2571-2579.
21. Freud AG, Caligiuri MA. Human natural killer cell development. *Immunol Rev*. 2006;214:56-72.
22. Mancini M, Scappaticci D, Cimino G, et al. A comprehensive genetic classification of adult acute lymphoblastic leukemia (ALL): analysis of the GIMEMA 0496 protocol. *Blood*. 2005;105(9):3434-3441.
23. Trinquand A, Tanguy-Schmidt A, Ben Abdelali R, et al. Toward a NOTCH1/FBXW7/RAS/PTEN-based oncogenetic risk classification of adult T-cell acute lymphoblastic leukemia: a Group for Research in Adult Acute Lymphoblastic Leukemia study. *J Clin Oncol*. 2013;31(34):4333-4342.
24. Beldjord K, Chevret S, Asnafi V, et al. Oncogenetics and minimal residual disease are independent outcome predictors in adult patients with acute lymphoblastic leukemia. *Blood*. 2014;123(24):3739-3749.
25. Kohlmann A, Schoch C, Schnittger S, et al. Pediatric acute lymphoblastic leukemia (ALL) gene expression signatures classify an independent cohort of adult ALL patients. *Leukemia*. 2004;18(1):63-71.
26. Ferrando AA, Neuberg DS, Staunton J, et al. Gene expression signatures define novel oncogenic pathways in T cell acute lymphoblastic leukemia. *Cancer Cell*. 2002;1(1):75-87.
27. Yeoh EJ, Ross ME, Shurtleff SA, et al. Classification, subtype discovery, and prediction of outcome in pediatric acute lymphoblastic leukemia by gene expression profiling. *Cancer Cell*. 2002;1(2):133-143.
28. Den Boer ML, van Slegtenhorst M, De Menezes RX, et al. A subtype of childhood acute lymphoblastic leukaemia with poor treatment outcome: a genome-wide classification study. *Lancet Oncol*. 2009;10(2):125-134.
29. Roberts KG, Li Y, Payne-Turner D, et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. *N Engl J Med*. 2014;371(11):1005-1015.
30. Harvey RC, Mullighan CG, Chen IM, et al. Rearrangement of CRLF2 is associated with mutation of JAK kinases, alteration of IKZF1, Hispanic/Latino ethnicity, and a poor outcome in pediatric B-progenitor acute lymphoblastic leukemia. *Blood*. 2010;115(26):5312-5321.
31. Konoplev S, Lu X, Konopleva M, et al. CRLF2-positive B-cell acute lymphoblastic leukemia in adult patients: a single-institution experience. *Am J Clin Pathol*. 2017;147(4):357-363.
32. Yilmaz M, Kantarjian H, Wang X, et al. The early achievement of measurable residual disease negativity in the treatment of adults with Philadelphia-negative B-Cell acute lymphoblastic leukemia is a strong predictor for survival. *Blood*. 2019;134(suppl 1):1297.
33. Berry DA, Zhou S, Higley H, et al. Association of minimal residual disease with clinical outcome in pediatric and adult acute lymphoblastic leukemia: a meta-analysis. *JAMA Oncol*. 2017;3(7):e170580.
34. Logan AC, Vashi N, Faham M, et al. Immunoglobulin and T cell receptor gene high-throughput sequencing quantifies minimal residual disease in acute lymphoblastic leukemia and predicts post-transplantation relapse and survival. *Biol Blood Marrow Transplant*. 2014;20(9):1307-1313.
35. van Dongen JJ, van der Velden VH, Brüggemann M, et al. Minimal residual disease diagnostics in acute lymphoblastic leukemia: need for sensitive, fast, and standardized technologies. *Blood*. 2015;125(26):3996-4009.
36. van der Velden VH, Jacobs DC, Wijkhuijs AJ, et al. Minimal residual disease levels in bone marrow and peripheral blood are comparable in children with T cell acute lymphoblastic leukemia (ALL), but not in precursor-B-ALL. *Leukemia*. 2002;16(8):1432-1436.
37. Bassan R, Spinelli O, Oldani E, et al. Improved risk classification for risk-specific therapy based on the molecular study of minimal residual disease (MRD) in adult acute lymphoblastic leukemia (ALL). *Blood*. 2009;113(18):4153-4162.

38. Gökbuget N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. *Blood*. 2018;131(14):1522-1531.
39. Gökbuget N, Dombret H, Giebel S, et al. Blinatumomab vs historic standard-of-care treatment for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukaemia. *Eur J Haematol*. 2020;104(4):299-309.
40. Yilmaz M, Kantarjian H, Wang X, et al. The early achievement of measurable residual disease negativity in the treatment of adults with Philadelphia-negative B-cell acute lymphoblastic leukemia is a strong predictor for survival. *Am J Hematol*. 2020;95(2):144-150.
41. Paul S, Kantarjian H, Jabbour EJ. Adult Acute lymphoblastic leukemia. *Mayo Clin Proc*. 2016;91(11):1645-1666.
42. Kantarjian H, Thomas D, O'Brien S, et al. Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. *Cancer*. 2004;101(12):2788-2801.
43. Pui C, Relling MV, Downing JR. Acute lymphoblastic leukemia. *N Engl J Med*. 2004;350(15):1535-1548.
44. Richard-Carpentier G, Kantarjian HM, Short NJ, et al. A phase II study of the hyper-CVAD regimen in sequential combination with blinatumomab as frontline therapy for adults with B-cell acute lymphoblastic leukemia (B-ALL). *Blood*. 2018;132(suppl 1):32.
45. Thomas DA, O'Brien S, Faderl S, et al. Chemoimmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in de novo Philadelphia chromosome-negative precursor B-lineage acute lymphoblastic leukemia. *J Clin Oncol*. 2010;28(24):3880-3889.
46. Benjamini O, Dumlao TL, Kantarjian H, et al. Phase II trial of hyper CVAD and dasatinib in patients with relapsed Philadelphia chromosome positive acute lymphoblastic leukemia or blast phase chronic myeloid leukemia. *Am J Hematol*. 2014;89(3):282-287.
47. Paul S, Sasaki, K, Savoy JM, et al. 12 versus 8 prophylactic intrathecal (IT) chemotherapy administration decrease incidence of central nervous system (CNS) relapse in patients (pts) with newly diagnosed Philadelphia (Ph)-positive acute lymphocytic leukemia (ALL). *Blood*. 2019;134(suppl 1):3810.
48. Jabbour E, O'Brien S, Kantarjian H, et al. Neurologic complications associated with intrathecal liposomal cytarabine given prophylactically in combination with high-dose methotrexate and cytarabine to patients with acute lymphocytic leukemia. *Blood*. 2007;109(8):3214-3218.
49. Daver N, Thomas D, Ravandi F, et al. Final report of a phase II study of imatinib mesylate with hyper-CVAD for the front-line treatment of adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Haematologica*. 2015;100(5):653-661.
50. Bassan R, Rossi G, Pogliani EM, et al. Chemotherapy-phased imatinib pulses improve long-term outcome of adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: Northern Italy Leukemia Group protocol 09/00. *J Clin Oncol*. 2010;28(22):3644-3652.
51. Schultz KR, Bowman WP, Aledo A, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a Children's Oncology Group study. *J Clin Oncol*. 2009;27(31):5175-5181.
52. Wassmann B, Pfeifer H, Goekbuget N, et al. Alternating versus concurrent schedules of imatinib and chemotherapy as front-line therapy for Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL). *Blood*. 2006;108(5):1469-1477.
53. Fielding AK, Rowe JM, Buck G, et al. UKALLXII/ECOG2993: addition of imatinib to a standard treatment regimen enhances long-term outcomes in Philadelphia positive acute lymphoblastic leukemia. *Blood*. 2014;123(6):843-850.
54. Chalandon Y, Thomas X, Hayette S, et al. Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia. *Blood*. 2015;125(24):3711-3719.
55. Ravandi F, O'Brien SM, Cortes JE, et al. Long-term follow-up of a phase 2 study of chemotherapy plus dasatinib for the initial treatment of patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Cancer*. 2015;121(23):4158-4164.
56. Porkka K, Koskenvesa P, Lundán T, et al. Dasatinib crosses the blood-brain barrier and is an efficient therapy for central nervous system Philadelphia chromosome-positive leukemia. *Blood*. 2008;112(4):1005-1012.
57. Ravandi F, Othus M, O'Brien SM, et al. US Intergroup Study of chemotherapy plus dasatinib and allogeneic stem cell transplant in Philadelphia chromosome positive ALL. *Blood Adv*. 2016;1(3):250-259.
58. Rousselot P, Coudé MM, Gokbuget N, et al. Dasatinib and low-intensity chemotherapy in elderly patients with Philadelphia chromosome-positive ALL. *Blood*. 2016;128(6):774-782.
59. Yilmaz M, Jabbour E. Tyrosine kinase inhibitors early in the disease course: lessons from chronic myelogenous leukemia. *Semin Oncol*. 2015;42(6):876-886.
60. Ottmann OG, Pfeifer H, Cayuela J-M, et al. Nilotinib (Tasigna®) and low intensity chemotherapy for first-line treatment of elderly patients with BCR-ABL1-positive acute lymphoblastic leukemia: final results of a prospective multicenter trial (EWALL-PH02). *Blood*. 2018;132(suppl 1):31.
61. Jabbour E, Short NJ, Ravandi F, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: long-term follow-up of a single-centre, phase 2 study. *Lancet Haematol*. 2018;5(12):e618-e627.
62. Short NJ, Kantarjian HM, Ravandi F, et al. Long-term safety and efficacy of hyper-CVAD plus ponatinib as frontline therapy for adults with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood*. 2019;134(suppl 1):283.
63. Short NJ, Kantarjian HM, Ravandi F, et al. Frontline hyper-CVAD plus ponatinib for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: updated results of a phase II study. *J Clin Oncol*. 2017;35(suppl 15):7013.
64. Martinelli G, Piciocchi A, Papayannidis C, et al. First report of the Gimema LAL1811 phase II prospective study of the combination of steroids with ponatinib as frontline therapy of elderly or unfit patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood*. 2017;130(suppl 1):99.
65. Jabbour E, DerSarkissian M, Duh MS, et al. Efficacy of ponatinib versus earlier generation tyrosine kinase inhibitors for front-line treatment of newly diagnosed Philadelphia-positive acute lymphoblastic leukemia. *Clin Lymphoma Myeloma Leuk*. 2018;18(4):257-265.
66. Sasaki K, Jabbour EJ, Ravandi F, et al. Hyper-CVAD plus ponatinib versus hyper-CVAD plus dasatinib as frontline therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: a propensity score analysis. *Cancer*. 2016;122(23):3650-3656.
67. Assi R, Kantarjian H, Short NJ, et al. Safety and efficacy of blinatumomab in combination with a tyrosine kinase inhibitor for the treatment of relapsed Philadelphia chromosome-positive leukemia. *Clin Lymphoma Myeloma Leuk*. 2017;17(12):897-901.
68. Chiaretti S, Bassan R, Vitale A, et al. Dasatinib-blinatumomab combination for the front-line treatment of adult Ph+ ALL patients. Updated results of the Gimema LAL2116 D-Alba trial. *Blood*. 2019;134(suppl 1):740.
69. Jain N, Roberts KG, Jabbour E, et al. Ph-like acute lymphoblastic leukemia: a high-risk subtype in adults. *Blood*. 2017;129(5):572-581.

70. Tanasi I, Ba I, Sirvent N, et al. Efficacy of tyrosine kinase inhibitors in Ph-like acute lymphoblastic leukemia harboring ABL-class rearrangements. *Blood*. 2019;134(16):1351-1355.
71. Thomas DA, Faderl S, O'Brien S, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. *Cancer*. 2006;106(7):1569-1580.
72. Hoelzer D, Walewski J, Döhner H, et al. Improved outcome of adult Burkitt lymphoma/leukemia with rituximab and chemotherapy: report of a large prospective multicenter trial. *Blood*. 2014;124(26):3870-3879.
73. Rizzieri DA, Johnson JL, Byrd JC, et al. Improved efficacy using rituximab and brief duration, high intensity chemotherapy with filgrastim support for Burkitt or aggressive lymphomas: cancer and Leukemia Group B study 10 002. *Br J Haematol*. 2014;165(1):102-111.
74. Ribrag V, Koscielny S, Bosq J, et al. Rituximab and dose-dense chemotherapy for adults with Burkitt's lymphoma: a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2016;387(10036):2402-2411.
75. Dunleavy K, Pittaluga S, Shovlin M, et al. Low-intensity therapy in adults with Burkitt's lymphoma. *N Engl J Med*. 2013;369(20):1915-1925.
76. Zayac A, Evens AM, Stadnik A, et al. Outcomes of patients with newly-diagnosed Burkitt lymphoma (BL) and central nervous system (CNS) Involvement treated in the modern era: a multi-institutional real-world analysis. *Blood*. 2019;134 (suppl 1):402.
77. Thomas DA, O'Brien S, Jorgensen JL, et al. Prognostic significance of CD20 expression in adults with de novo precursor B-lineage acute lymphoblastic leukemia. *Blood*. 2009;113(25):6330-6337.
78. Gökbuget N, Hoelzer D. Rituximab in the treatment of adult ALL. *Ann Hematol.* 2006;85:117–119.
79. Maury S, Chevret S, Thomas X, et al. Rituximab in B-lineage adult acute lymphoblastic leukemia. *N Engl J Med*. 2016;375(11):1044-1053.
80. Arzerra (ofatumumab). Package insert. GlaxoSmithKline; 2011.
81. Richard-Carpentier G, Kantarjian HM, Konopleva MY, et al. Phase II study of the hyper-CVAD regimen in combination with ofatumumab (HCVAD-O) as frontline therapy for adult patients (pts) with CD20-positive B-cell acute lymphoblastic leukemia (B-ALL). *Blood*. 2019;134(suppl 1):2577.
82. Zhang J, Ding L, Holmfeldt L, et al. The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. *Nature*. 2012;481(7380):157-163.
83. DeAngelo DJ, Yu D, Johnson JL, et al. Nelarabine induces complete remissions in adults with relapsed or refractory T-lineage acute lymphoblastic leukemia or lymphoblastic lymphoma: Cancer and Leukemia Group B study 19801. *Blood*. 2007;109(12):5136-5142.
84. Gökbuget N, Basara N, Baurmann H, et al. High single-drug activity of nelarabine in relapsed T-lymphoblastic leukemia/lymphoma offers curative option with subsequent stem cell transplantation. *Blood*. 2011;118(13):3504-3511.
85. Dunsmore KP, Winter SS, Devidas M, et al. Children's Oncology Group AALL0434: a randomized trial testing nelarabine in newly diagnosed T-cell malignancy. *J Clin Oncol*. 2018;36(suppl 15):10500.
86. Abaza Y, Kantarjian HM, Faderl S, et al. Hyper-CVAD plus nelarabine in newly diagnosed adult T-cell acute lymphoblastic leukemia and T-lymphoblastic lymphoma. *Am J Hematol*. 2018;93(1):91-99.
87. Chonghaile TN, Roderick JE, Glenfield C, et al. Maturation stage of T-cell acute lymphoblastic leukemia determines BCL-2 versus BCL-XL dependence and sensitivity to ABT-199. *Cancer Discov*. 2014;4(9):1074-1087.
88. Jain N, Stevenson KE, Winer ES, et al. A multicenter phase I study combining venetoclax with mini-hyper-CVD in older adults with untreated and relapsed/refractory acute lymphoblastic leukemia. *Blood*. 2019;134(suppl 1):3867.
89. Boissel N. How should we treat the AYA patient with newly diagnosed ALL? *Best Pract Res Clin Haematol*. 2017;30(3):175-183.
90. Stock W, Luger SM, Advani AS, et al. A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403. *Blood*. 2019;133(14):1548-1559.
91. Rytting ME, Jabbour EJ, Jorgensen JL, et al. Final results of a single institution experience with a pediatric-based regimen, the augmented Berlin-Frankfurt-Munster, in adolescents and young adults with acute lymphoblastic leukemia, and comparison to the hyper-CVAD regimen. *Am J Hematol*. 2016;91(8):819-823.
92. Gökbuget N. Treatment of older patients with acute lymphoblastic leukemia. *Hematology Am Soc Hematol Educ Program*. 2016;2016(1):573-579.
93. Yilmaz M, Kantarjian H, Jabbour E. Treatment of acute lymphoblastic leukemia in older adults: now and the future. *Clin Adv Hematol Oncol*. 2017;15(4):266-274.
94. Li S, Molony JT, Chia V, et al. Patient characteristics and treatment patterns in elderly patients newly diagnosed with acute lymphoblastic leukemia (ALL) using 100% Medicare ALL data. *Blood*. 2016;128(22):3981.
95. Geyer MB, Hsu M, Devlin SM, et al. Overall survival among older US adults with ALL remains low despite modest improvement since 1980: SEER analysis. *Blood*. 2017;129(13):1878-1881.
96. Short NJ, Kantarjian HM, Ravandi F, et al. Updated results of a phase II study of reduced-intensity chemotherapy with mini-hyper-CVD in combination with inotuzumab ozogamicin, with or without blinatumomab, in older adults with newly diagnosed Philadelphia chromosome-negative acute lymphoblastic leukemia. *Blood*. 2019;134(suppl 1):823.
97. Campana D. Minimal residual disease in acute lymphoblastic leukemia. *Hematology Am Soc Hematol Educ Program*. 2010;2010:7-12.
98. Moorman AV, Harrison CJ, Buck GA, et al. Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. *Blood*. 2007;109(8):3189-3197.
99. Ravandi F, Jorgensen JL, Thomas DA, et al. Detection of MRD may predict the outcome of patients with Philadelphia chromosome-positive ALL treated with tyrosine kinase inhibitors plus chemotherapy. *Blood*. 2013;122(7):1214-1221.
100. Gökbuget N, Dombret H, Bonifacio M, et al. Long-term outcomes after blinatumomab treatment: follow-up of a phase 2 study in patients (Pts) with minimal residual disease (MRD) positive B-Cell precursor acute lymphoblastic leukemia (ALL). *Blood*. 2015;126(23):680.
101. Short NJ, Jabbour E, Sasaki K, et al. Impact of complete molecular response on survival in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood*. 2016;128(4):504-507.
102. Fielding AK, Richards SM, Chopra R, et al. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. *Blood*. 2007;109(3):944-950.
103. Gökbuget N, Dombret H, Ribera JM, et al. International reference analysis of outcomes in adults with B-precursor Ph-negative relapsed/refractory acute lymphoblastic leukemia. *Haematologica*. 2016;101(12):1524-1533.
104. Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. *N Engl J Med*. 2017;376(9):836-847.

105. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. *N Engl J Med*. 2016;375(8):740-753.
106. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med*. 2018;378(5):439-448.
107. Buie LW, Pecoraro JJ, Horvat TZ, et al. Blinatumomab: a first-in-class bispecific T-cell engager for precursor B-cell acute lymphoblastic leukemia. *Ann Pharmacother*. 2015;49(9):1057-1067.
108. Topp MS, Gökbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. *Lancet Oncol*. 2015;16(1):57-66.
109. Brown PA, Ji L, Xu X, et al. A randomized phase 3 trial of blinatumomab vs. chemotherapy as post-reinduction therapy in high and intermediate risk (HR/IR) first relapse of B-acute lymphoblastic leukemia (B-ALL) in children and adolescents/young adults (AYAs) demonstrates superior efficacy and tolerability of blinatumomab: a report from Children's Oncology Group Study AALL1331. *Blood*. 2019;134(suppl 2):LBA-1.
110. Martinelli G, Boissel N, Chevallier P, et al. Complete hematologic and molecular response in adult patients with relapsed/refractory Philadelphia chromosome-positive B-precursor acute lymphoblastic leukemia following treatment with blinatumomab: results from a phase II, single-arm, multicenter study. *J Clin Oncol*. 2017;35(16):1795-1802.
111. de Vries JF, Zwaan CM, De Bie M, et al. The novel calicheamicin-conjugated CD22 antibody inotuzumab ozogamicin (CMC-544) effectively kills primary pediatric acute lymphoblastic leukemia cells. *Leukemia*. 2012;26(2):255-264.
112. Kantarjian H, Thomas D, Jorgensen J, et al. Inotuzumab ozogamicin, an anti-CD22-calecheamicin conjugate, for refractory and relapsed acute lymphocytic leukaemia: a phase 2 study. *Lancet Oncol*. 2012;13(4):403-411.
113. Kantarjian H, Thomas D, Jorgensen J, et al. Results of inotuzumab ozogamicin, a CD22 monoclonal antibody, in refractory and relapsed acute lymphocytic leukemia. *Cancer*. 2013;119(15):2728-2736.
114. Advani AS, Stein AS, Kantarjian HM, et al. A phase II study of weekly inotuzumab ozogamicin (InO) in adult patients with CD22-positive acute lymphoblastic leukemia (ALL) in second or later salvage. *Blood*. 2014;124(21):2255.
115. O'Brien MM, Ji L, Shah NN, et al. A phase 2 trial of inotuzumab ozogamicin (InO) in children and young adults with relapsed or refractory (R/R) CD22+ B-acute lymphoblastic leukemia (B-ALL): results from Children's Oncology Group protocol AALL1621. *Blood*. 2019;134(suppl 1):741.
116. Sasaki K, Kantarjian HM, Ravandi F, et al. Sequential combination of inotuzumab ozogamicin (InO) with low-intensity chemotherapy (mini-hyper-CVD) with or without blinatumomab is highly effective in patients (pts) with Philadelphia chromosome-negative acute lymphoblastic leukemia (ALL) in first relapse. *Blood*. 2019;134(suppl 1):3806.
117. Advani AS, Moseley A, Liedtke M, et al. SWOG 1312 final results: a phase 1 trial of inotuzumab in combination with CVP (cyclophosphamide, vincristine, prednisone) for relapsed/refractory CD22+ acute leukemia. *Blood*. 2019;134(suppl 1):227.
118. Benito JM, Godfrey L, Kojima K, et al. MLL-rearranged acute lymphoblastic leukemias activate BCL-2 through H3K79 methylation and are sensitive to the BCL-2-specific antagonist ABT-199. *Cell Rep*. 2015;13(12):2715-2727.
119. Khaw SL, Suryani S, Evans K, et al. Venetoclax responses of pediatric ALL xenografts reveal sensitivity of MLL-rearranged leukemia. *Blood*. 2016;128(10):1382-1395.
120. Frismantas V, Dobay MP, Rinaldi A, et al. Ex vivo drug response profiling detects recurrent sensitivity patterns in drug-resistant acute lymphoblastic leukemia. *Blood*. 2017;129(11):e26-e37.
121. Lacayo NJ, Pullarkat VA, Stock W, et al. Safety and efficacy of venetoclax in combination with navitoclax in adult and pediatric relapsed/refractory acute lymphoblastic leukemia and lymphoblastic lymphoma. *Blood*. 2019;134(suppl 1):285.
122. Batlevi CL, Matsuki E, Brentjens RJ, et al. Novel immunotherapies in lymphoid malignancies. *Nat Rev Clin Oncol*. 2016;13(1):25-40.
123. Grupp SA, Maude SL, Rives S, et al. Updated analysis of the efficacy and safety of tisagenlecleucel in pediatric and young adult patients with relapsed/refractory (r/r) acute lymphoblastic leukemia. *Blood*. 2018;132(suppl 1):895.
124. Park JH, Rivière I, Gonen M, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. *N Engl J Med*. 2018;378(5):449-459.
125. Shah BD, Bishop MR, Oluwole OO, et al. End of phase I results of ZUMA-3, a phase 1/2 study of KTE-X19, anti-CD19 chimeric antigen receptor (CAR) T cell therapy, in adult patients (pts) with relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL). *J Clin Oncol*. 2019;37(suppl 15):7006.
126. Frey NV, Porter DL. Cytokine release syndrome with novel therapeutics for acute lymphoblastic leukemia. *Hematology Am Soc Hematol Educ Program*. 2016;2016(1):567-572.
127. Ghorashian S, Kramer AM, Onuoha S, et al. Enhanced CAR T cell expansion and prolonged persistence in pediatric patients with ALL treated with a low-affinity CD19 CAR. *Nat Med*. 2019;25(9):1408-1414.
128. Liu E, Marin D, Banerjee P, et al. Use of CAR-transduced natural killer cells in CD19-positive lymphoid tumors. *N Engl J Med*. 2020;382(6):545-553.

2 Adult Acute Myeloid Leukemia

Tapan M. Kadia
Joseph D. Khoury
Farhad Ravandi

KEY CONCEPTS

- Newer techniques and wider applicability of genomic sequencing have identified numerous recurrent somatic mutations and patterns of mutation that reveal the extensive heterogeneity of acute myeloid leukemia (AML). Better understanding of the biology behind the genomic aberrations has led to more accurate disease prognostication as well as development of specific therapies for genomically defined subgroups. The most recent European LeukemiaNet (ELN) 2017 classification system incorporates several of these mutations for risk classification. Therefore, pretreatment assessment of these mutations (*FLT3, NPM1, CEBPA, TP53, RUNX1, ASXL1*) along with conventional karyotyping is becoming a part of standard practice.
- Since 2017 and as of 2020, several new therapies have been approved or reintroduced for the treatment of patients with AML. These include the FLT3 (fms-like tyrosine kinase 3) inhibitors midostaurin and gilteritinib, the IDH1 inhibitor ivosidenib, the IDH2 inhibitor enasidenib, the BCL2 inhibitor venetoclax, the hedgehog inhibitor glasdegib, the CD33 antibody–drug conjugate gemtuzumab ozogamicin (GO), the liposomal formulation CPX-351, and oral azacytidine.
- The CD33 antibody–drug conjugate GO has been shown to provide significant survival benefit in patients with favorable or intermediate-risk disease and should be incorporated into the frontline treatment of core-binding factor AML when appropriate. GO also has an important role in the treatment of patients with acute promyelocytic leukemia.
- Chemotherapy combined with an FLT3 inhibitor such as midostaurin or others on clinical trial are now part of the standard of care for patients with newly diagnosed *FLT3*-mutated AML.
- The BCL2 inhibitor venetoclax has significantly improved outcomes for older and unfit patients with newly diagnosed AML, having demonstrated a significant survival benefit in combination with hypomethylating agents (HMAs) compared with HMAs alone.
- Monitoring of minimal residual disease (MRD) by multiparameter flow cytometry or molecular methods at the time of remission after induction and after consolidation is a powerful tool to help predict the risk of relapse and guide risk stratification, including postremission strategies such as stem cell transplant (SCT). Complete remission with or without MRD positivity is being incorporated into response criteria.
- Maintenance therapy with oral azacytidine (CC486) has become the standard of care for patients not eligible for postremission SCT after demonstrating improvement in survival compared with placebo. Maintenance strategies with targeted therapies after achieving remission and even after SCT are being investigated.
- Repeat molecular testing for mutations at the time of relapse should be strongly considered to allow incorporation of specific targeted therapies that are indicated in genomically defined subgroups (eg, enasidenib, ivosidenib, gilteritinib).

Acute myeloid leukemia (AML) consists of a heterogeneous group of hematologic neoplasms characterized by clonal proliferation of myeloid blasts involving peripheral blood and bone marrow, with occasional tumor formation in extramedullary tissues. Despite advances in our understanding of the molecular biology of AML, its treatment remains challenging, and outcomes vary greatly depending on a constellation of cytogenetic and molecular features as well as age and comorbidities.

AML is thought to be the culmination of genetic mutations and chromosomal aberrations within myeloid precursors resulting in disrupted differentiation, excessive proliferation, and suppressed apoptosis of neoplastic cells referred to as *blasts*.

Over the past several decades, improvements in chemotherapeutic regimens, supportive care, and improved understanding of underlying biology have resulted in significant progress in treating patients with AML. Knowledge of the biological underpinnings and heterogeneity of AML has resulted in the identification of new therapeutic targets and rationally designed inhibitors for a number of these targets. Despite these advances, the majority of patients with AML have an incurable disease and succumb from relapses or complications of their disease. With better definition of molecular abnormalities and elucidation of the pathogenic events in various AML subtypes and with the development of novel targeted agents, a better outcome for patients with AML may be achievable in the near future.

EPIDEMIOLOGY, ETIOLOGY, AND RISK FACTORS

Approximately 19,000 individuals are diagnosed with leukemia annually in the United States. The incidence of AML is 4.3 per 100,000. The median age at presentation is 68 years. The incidence of AML, as well as myelodysplastic syndrome (MDS), rises with age, with the majority of AML patients being older than 60 years old.[1] The incidence of AML is slightly higher in males and in populations of European descent. Acute promyelocytic leukemia (APL), a distinct subtype of AML, has been reported to be more common among populations of Hispanic background.[2]

An increased incidence of AML is seen in patients with disorders associated with increased chromatin fragility such as Bloom syndrome, Fanconi anemia, Kostmann syndrome, Wiskott-Aldrich syndrome, and ataxia-telangiectasia. Other syndromes, such as Down (trisomy of chromosome 21), Klinefelter (XXY and variants), and Patau (trisomy of chromosome 13) syndromes, have also been associated with a higher incidence of AML.[3]

Exposure to cytotoxic therapies increases AML risk. Two categories of therapy-related AML have been described. Patients exposed to alkylating agents (eg, cyclophosphamide, melphalan, nitrogen mustard) or radiation therapy can develop AML after a latency period of 4 to 8 years, which is often associated with abnormalities of chromosomes 5 and/or 7 and/or complex karyotype but may also present without characteristic chromosome abnormalities.[4,5] Recent analysis of next-generation sequencing (NGS) data also suggests an enrichment of *TP53* mutations among patients with therapy-related AML.[6,7] Exposure to agents that inhibit the DNA repair enzyme topoisomerase II (eg, etoposide) is also associated with secondary AML with a typically shorter latency period, usually 1 to 3 years.[8] Benzene, smoking, dyes, herbicides, and pesticides have been implicated as potential risk factors for development of AML.[9]

AML may also be secondary to transformation of an antecedent myeloid disorder, such as MDS, myeloproliferative neoplasm (MPN), or MDS/MPN, or other bone marrow disorders, such as aplastic anemia.

CLINICAL PRESENTATION

Fatigue, bruising or bleeding, fever, and infection, reflecting a state of bone marrow failure, are common in patients with AML. Only 10% of patients present with white blood cell (WBC) count greater than $100 \times 10^9/L$[1]; these patients are at higher risk of tumor lysis syndrome, central nervous system involvement, and leukostasis. Leukostasis may manifest as dyspnea, chest pain, headaches, altered mental status, cranial nerve palsies, or priapism. Leukostasis and tumor lysis syndrome are oncologic emergencies and require prompt recognition and management.

Physical findings other than bleeding and infection may include organomegaly, lymphadenopathy, sternal tenderness, retinal hemorrhages, and infiltration of gingivae, skin, soft tissues, lungs, or meninges (more common in AML with monocytic differentiation). Disseminated intravascular coagulopathy (DIC) with bleeding diathesis is a common presentation in APL.

DIAGNOSIS AND CLASSIFICATION

The diagnosis of AML is typically defined as the presence of 20% or more myeloid blasts in the bone marrow or peripheral blood in accordance with World Health Organization (WHO) classification criteria (Table 2–1).[10] AML subtypes in the WHO classification are defined on the basis of morphology, immunophenotype, and molecular or genetic features. In some patients, AML presents as a mass in extramedullary tissues (myeloid sarcoma). Patients who have the "AML-defining" cytogenetic abnormalities t(8;21)(q22;q22), inv(16)(p13q22) or t(16;16)(p13;q22), and t(15;17)(q22;q12) are diagnosed with AML regardless of the blast percentage.

Bone marrow sampling is essential for the initial workup of a patient with suspected acute leukemia. Sampling should include a core (trephine) biopsy as well as aspiration material. The core biopsy is used to perform touch preparations, which are invaluable in

Table 2–1 Acute Myeloid Leukemia and Related Precursor Neoplasms and Acute Leukemias of Ambiguous Lineage

Myeloproliferative neoplasms (MPN)
- Chronic myeloid leukemia (CML), BCR-ABL11
- Chronic neutrophilic leukemia (CNL)
- Polycythemia vera (PV)
- Primary myelofibrosis (PMF)
- PMF, prefibrotic/early stage
- PMF, overt fibrotic stage
- Essential thrombocythemia (ET)
- Chronic eosinophilic leukemia, not otherwise specified (NOS)
- MPN, unclassifiable

Mastocytosis

Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of
- PDGFRA, PDGFRB, or FGFR1, or with PCM1-JAK2
- Myeloid/lymphoid neoplasms with PDGFRA rearrangement
- Myeloid/lymphoid neoplasms with PDGFRB rearrangement
- Myeloid/lymphoid neoplasms with FGFR1 rearrangement
- Provisional entity: Myeloid/lymphoid neoplasms with PCM1-JAK2

Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)
- Chronic myelomonocytic leukemia (CMML)
- Atypical chronic myeloid leukemia (aCML), BCR-ABL12
- Juvenile myelomonocytic leukemia (JMML)
- MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
- MDS/MPN, unclassifiable

Myelodysplastic syndromes (MDS)
- MDS with single lineage dysplasia
- MDS with ring sideroblasts (MDS-RS)
- MDS-RS and single lineage dysplasia
- MDS-RS and multilineage dysplasia
- MDS with multilineage dysplasia
- MDS with excess blasts
- MDS with isolated del(5q)
- MDS, unclassifiable
- Provisional entity: Refractory cytopenia of childhood

Myeloid neoplasms with germ line predisposition

Acute myeloid leukemia (AML) and related neoplasms

AML with recurrent genetic abnormalities
- AML with t(8;21)(q22;q22.1);RUNX1-RUNX1T1
- AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);CBFB-MYH11
- APL with PML-RARA
- AML with t(9;11)(p21.3;q23.3);MLLT3-KMT2A
- AML with t(6;9)(p23;q34.1);DEK-NUP214
- AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM
- AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);RBM15-MKL1
- Provisional entity: AML with BCR-ABL1
- AML with mutated NPM1
- AML with biallelic mutations of CEBPA
- Provisional entity: AML with mutated RUNX1

AML with myelodysplasia-related changes

Therapy-related myeloid neoplasms

AML, NOS
- AML with minimal differentiation
- AML without maturation
- AML with maturation
- Acute myelomonocytic leukemia
- Acute monoblastic/monocytic leukemia
- Pure erythroid leukemia
- Acute megakaryoblastic leukemia
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis

Myeloid sarcoma

Myeloid proliferations related to Down syndrome
- Transient abnormal myelopoiesis (TAM)
- Myeloid leukemia associated with Down syndrome

Blastic plasmacytoid dendritic cell neoplasm

Acute leukemias of ambiguous lineage
- Acute undifferentiated leukemia
- Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); BCR-ABL1
- MPAL with t(v;11q23.3); KMT2A rearranged
- MPAL, B/myeloid, NOS
- MPAL, T/myeloid, NOS

B-lymphoblastic leukemia/lymphoma
- B-lymphoblastic leukemia/lymphoma, NOS
- B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
- B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);BCR-ABL1
- B-lymphoblastic leukemia/lymphoma with t(v;11q23.3);KMT2A rearranged
- B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); ETV6-RUNX1
- B-lymphoblastic leukemia/lymphoma with hyperdiploidy
- B-lymphoblastic leukemia/lymphoma with hypodiploidy
- B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) IL3-IGH
- B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);TCF3-PBX1
- Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like
- Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21

T-lymphoblastic leukemia/lymphoma
- Provisional entity: Early T cell precursor lymphoblastic leukemia
- Provisional entity: NK cell lymphoblastic leukemia/lymphoma

NK, natural killer.

Reproduced with permission from Arber DA, Orazi A, Hasserjian R, et al: The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia, *Blood* 2016 May 19;127(20):2391-2405.

TABLE 2–2 Immunophenotypic Markers of Hematopoietic Lineage Differentiation Commonly Used in Routine Flow Cytometry Analysis

Myeloid				Lymphoid	
Granulocytic	**Monocytic**	**Erythroid**	**Megakaryocytic**	**B Cell**	**T Cell**
MPO	CD4	CD36	CD41	CD19	CD2
CD13	CD14	CD71	CD42b	CD20	cCD3
CD15	CD64	CD235a	CD61	CD22	CD5
CD33				cCD79a	CD7
CD117				cIgM	

TABLE 2–3 Next-Generation Sequencing–Based Mutation Analysis Panel for Myeloid Neoplasms Currently Used for Frontline Assessment at the MD Anderson Cancer Center

ANKRD26	*CBLB*	*EED*	*GFI1*	*JAK1*	*NF1*	*PTEN*	*SH283*	*SUZ12*
ASXL1	*CBLC*	*ELANE*	*GNAS*	*JAK2*	*NOTCH1*	*PTPN11*	*SMC1A*	*TERC*
ASXL2	*CEBPA*	*ETNK1*	*HNRNPK*	*JAK3*	*NPM1*	*RAD21*	*SMC3*	*TERT*
BCOR	*CREBBP*	*ETV6*	*HRAS*	*KDM6A*	*NRAS*	*RARA*	***SRSF2***	***TET2***
BCORL1	*CRLF2*	*EZH2*	*IDH1*	*KIT*	*PAX5*	***RUNX1***	*STAG1*	*TP53*
BRAF	*CSF3R*	*FBXW7*	*IDH2*	*KMT2A*	*PHF6*	*SETBP1*	***STAG2***	*U2AF1*
BRINP3	*CUX1*	*FLT3*	*IKZF1*	*KRAS*	*PIGA*	*SF1*	*STAT3*	*U2AF2*
CALR	*DDX41*	*GATA1*	*IL2RG*	*MAP2K1*	*PML*	*SF3A1*	*STAT5A*	*WT1*
CBL	*DNMT3A*	*GATA2*	*IL7R*	*MPL*	*PRPF40B*	*SF3B1*	*STAT5B*	*ZRSR2*

case of a dry tap. The aspiration material is typically used to prepare a clot and aspirate smears, in addition to having portions submitted for flow cytometry, cytogenetics, and molecular diagnostics. Wright-Giemsa–stained aspirate smears or touch preparations are evaluated, and the percentage of blasts is determined through a 500-cell manual differential count.

Confirmation of myeloid lineage is commonly accomplished using flow cytometry immunophenotyping. In most AML cases, blasts express one or more markers of immature hematopoietic precursors such as CD34, CD117, and HLA-DR, in addition to dim CD45 (common leukocyte antigen). Myeloid lineage is predicated on the expression of antigens associated with granulocytic, monocytic, erythroid, and/or megakaryocytic differentiation by blasts (Table 2–2). Expression of myeloperoxidase (MPO) is considered specific for myeloid differentiation, although AML blasts may lack MPO expression. Although aberrant expression of lymphoid antigens is commonly seen in some cases with a bona fide AML phenotype, such expression is generally limited to one or a few lymphoid antigens. Acute leukemia with ambiguous lineage is beyond the scope of this discussion; briefly, it refers to acute leukemia with overlapping expression of myeloid and lymphoid antigens or lack of both.

Molecular diagnostics play a critical role in the laboratory workup of AML. Whereas the scope of known molecular alterations in AML was limited until a few years ago, the advent of NGS has dramatically increased our understanding of the molecular landscape of AML. As a result, the limited number of polymerase chain reaction (PCR)–based assays that used to be performed during AML workup have now been largely replaced by NGS-based panels that simultaneously assess the mutation status of tens to hundreds of genes. The current NGS mutation panel for new and relapsed myeloid malignancies used at our institution assesses the coding sequences of the 81 genes listed in Table 2–3.

RISK STRATIFICATION OF ACUTE MYELOID LEUKEMIA

After a diagnosis of AML has been made, risk stratification is the critical next step to determine therapy, prognosis, and longer-term management. Several variables are predictive of outcome, including patient-related variables, such age and performance status, as well as disease-related predictors, such as cytogenetic and molecular characteristics.

TABLE 2–4 Risk Stratification of Acute Myeloid Leukemia European LeukemiaNet Criteria, 2017

ELN	Genetic Abnormality
Favorable	t(8;21)(q22;q22), inv(16)/t(16;16)(p13;q22), *NPM1*-mutated and *FLT3*-ITD-wild type (normal karyotype) or *FLT3*-ITD mutated (low allelic ratio), mutated *CEBPα* (normal karyotype)
Intermediate	*NPM1*-mutated and *FLT3*-ITD mutated (high allelic ratio[a]) *NPM1*-wild type and *FLT3*-ITD mutated (low allelic ratio) *NPM1*-wild type and *FLT3*-ITD wild type Cytogenetics that are neither favorable nor adverse t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*
Adverse	inv(3)/t(3;3)(q21;q26); t(6;9)(p23,q34); t(v;11q23.3), *KMT2A* rearranged; t(9;22) BCR-ABL; -5 or del(5q); -7; abnl(17p); complex karyotype; monosomal karyotype; NPM1-wildtype and FLT3-ITD (high allelic ratio); RUNX1, ASXL1, TP53 mutations

[a]Low allelic ratio is <0.5; high allelic ratio is ≥0.5.
Abn, abnormal; ELN, European LeukemiaNet; inv, inversion

The karyotype remains one of the best predictors of outcome in patients with AML. The European LeukemiaNet (ELN) guidelines have proposed a risk-stratification system based on cytogenetics and molecular analysis.[1] As listed in Table 2–4, patients are classified as having favorable-, intermediate-, or unfavorable-risk disease. A limitation of the current ELN classification system is that it takes into account only a few of the commonly mutated genes for prognostication. As more validated data on other mutations and co-mutations become available, a more expansive prognostication system may help refine risk stratification. For example, it is known that the favorable prognosis attributed to mutant *CEBPA* is true in cases of biallelic *CEBPA* mutation rather than the monoallelic mutation.[11] In patients with *FLT3*-wild-type/*NPM1*-mutated AML, *DNMT3A* assessment is of importance. Loghavi et al[12] showed that in patients with karyotypically normal AML with *NPM1* mutations, the presence of concurrent *DNMT3A* mutation has an adverse effect on outcomes, with the effect being more detrimental than either *FLT3-ITD* or *FLT3-TKD* mutations. This analysis demonstrated that in patients with de novo karyotypically normal AML, particularly those younger than 60 years old, patients with AML$^{DNMT3A/FLT3/NPM1}$ (sometimes referred to as triple-positive) seem to have the worst clinical outcomes followed by those with AML$^{FLT3/DNMT3A}$ and then those with AML$^{NPM1/DNMT3A}$.[12] Currently, normal karyotype AML patients with *NPM1*-mutated/*FLT3*-wild-type disease are considered favorable risk according to the ELN guidelines.

The presence of *TP53* mutations is associated with a poor outcome.[13] A recent report by German and Austrian investigators indicated that the outcome of patients with *TP53* mutations is worse than that of patients with the monosomal karyotype known to be an adverse prognostic indicator.[14] In this study, the analysis showed that the *TP53* mutation was commonly associated with older patients and a monosomal karyotype and correlated with a low complete remission (CR) rate and shorter relapse-free survival (RFS), event-free survival (EFS), and overall survival (OS). On multivariate analysis, *TP53* mutations were associated with the worst prognosis.[14] We recently reported the importance of *TP53* variant allelic frequency in determining outcome to various intensities of therapy.[15]

Several novel molecular aberrations, including mutations of the *DNMT3A*, *TET2*, *MLL*, and *PHF6* genes, have been described, particularly in patients with a normal karyotype.[16] However, their utility in current clinical practice remains limited, and they have limited value in determining best treatment strategies for patients. However, the presence of other mutations such as *RUNX1* and *ASXL1* has been recognized to have an adverse prognostic impact as reported in the revised version of ELN classification.

TREATMENT OF ACUTE MYELOID LEUKEMIA

In the 1960s, Freireich et al[17] demonstrated the significance of achieving a CR to improve survival. Since then, the objective of therapy has been to produce and maintain CR, the only currently accepted approach to AML cure. Criteria for CR have been defined by the International Working Group and are followed in the clinic and in clinical trials for response assessment.[1,18] After 3 years in CR, the probability of AML recurrence declines sharply to less than 10%,[19] and patients in continuous CR for 3 or more years can be considered "potentially cured." However, the definition of CR is an arbitrary one, signaling control of the disease burden and recovery of spontaneous hematopoiesis; with improved technology,

the precision for detection of residual disease after the initial therapy has increased prompting the addition of minimal residual disease (MRD) status to the definition of CR (ie, CR with or without detectable MRD). The persistence of MRD after remission induction and consolidation has important implications on risk of relapse as well as indications for and success of allogeneic stem cell transplant (allo-SCT).[20] Whether the improved detection and application of novel strategies to eradicate the residual leukemia will translate to improved cure rates is the subject of ongoing and future trials.

After AML is diagnosed, the need for emergency therapy must be assessed. Emergency treatment is required (1) in cases of APL, (2) in cases of circulating blast count greater than 50 to 100 × 10^9/L or rapid rate of proliferation, and (3) in the presence of DIC or organ dysfunction (especially pulmonary) attributed to leukemic infiltration (mostly seen in patients with >10 × 10^9/L circulating blasts and/or M4 or M5 French-American-British [FAB] morphology). In the latter situation, it is important to initiate immediate chemotherapy. Leukapheresis for severe leukocytosis and/or leukostasis should also be considered,[21] although a number of studies have suggested that this has limited value on long-term outcome. In patients presenting with low WBC counts, several studies have demonstrated that initiation of therapy can be delayed for several days until all the necessary diagnostic information is available,[22] however, this delay should be as short as possible.

At the University of Texas MD Anderson Cancer Center (MDACC), most patients are enrolled in clinical trials, if eligible. Urgent cytoreductive therapy is given when needed, with clinical trials designed to accommodate and expressly allow emergent chemotherapy before enrollment. The therapy is tailored to the individual patients' characteristics, including their pretreatment cytogenetic and molecular profiles. We discuss here the therapies for the various patient groups with AML.

INDUCTION THERAPY IN ACUTE MYELOID LEUKEMIA

Conventional treatment for AML with intensive chemotherapy, divided into remission induction and postremission therapy, has been with combinations of anthracyclines and cytarabine (ara-C).

Anthracyclines and Cytarabine

At MDACC, young patients (younger than 60 years old) with AML are treated with a core backbone of idarubicin (IDA) plus cytarabine-based regimens. The dosage of IDA is 10 to 12 mg/m^2 for 3 days, and ara-C is given at a dosage ranging from 1 to 2 g/m^2 for 4 to 5 days (IA). An alternative used by many cooperative groups and in the community is the "3 + 7 regimen," in which the anthracycline (ie, IDA or daunorubicin [DNR]) is usually given daily for 3 days and ara-C is given at a lower dosage of 100 to 200 mg/m^2 daily for 7 days by continuous infusion. Based on evidence of synergy, a second nucleoside analogue such as fludarabine, clofarabine, or cladribine has been added to the IA backbone (discussed in detail later).

In clinical practice, a bone marrow aspirate is usually obtained 2 to 3 weeks after beginning therapy. A biopsy is needed only if the quality of the aspirate does not permit determination of cellularity. If the day 21 marrow is hypoplastic, therapy is usually delayed until count recovery (in the case of remission) or until it is clear that there is persistence of leukemia, at which time the second course begins. A second repeated course of induction therapy can produce remissions in a subset of patients, but these are usually of shorter duration than remissions produced after one course of therapy. The timing of a second course with persistent AML is controversial. Several cooperative groups advocate starting a second course if there is persistent AML on days 10 to 15 of chemotherapy. With high-dose ara-C (HDAC), a delay of a second course with persistent disease on days 21 to 28 may be indicated if the blasts are decreasing because most (90%) CRs are obtained after the first course and response to a second course is poor. It is important to recognize that the initial marrow obtained after a period of hypoplasia may occasionally demonstrate a higher percentage of blasts, sometimes as high as 30% to 40%, as a reflection of the regeneration of normal, not "leukemic," marrow elements while peripheral blood counts are recovering. In this circumstance, follow-up (eg, at 1- to 2-week intervals) marrows may show sequential reduction in blast percentages concomitant with a rise in neutrophils and platelets.[23] Detection of persistent cytogenetic or pretreatment clonal abnormalities in the blasts can help distinguish disease-related versus healthy regenerating blasts. Such a distinction can also be achieved using flow cytometry immunophenotyping in specialized centers.

Typically, when in remission after treatment with the induction course, patients receive postremission consolidation therapy, with the same drugs administered at approximately monthly intervals for 4 to 6 months. After sufficient consolidation therapy, patients may be referred for allo-SCT or be offered long-term maintenance therapy.

Choice of Anthracyclines

Randomized trials have attempted to identify the superior anthracycline (eg, IDA, DNR, mitoxantrone [MTZ], aclarubicin).[24] In a three-arm randomized

study comparing DNR, IDA, and MTZ as part of the induction regimen for older patients, there was no advantage for any one arm.[25] In contrast, in a three-arm randomized trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) and Italian Group for Hematological Diseases in Adults (GIMEMA) comparing the same three agents, the 5-year disease-free survival (DFS) and OS were significantly better for patients receiving IDA and MTZ (P = .03 and .02, respectively). The recovery time was longer with IDA and MTZ (P <.0001).[26] A study by Pautas and colleagues[27] randomized 468 patients to either DNR 80 mg/m^2 daily for 3 days versus IDA 12 mg/m^2 daily for 3 or 4 days combined with standard-dose cytarabine. Three days of IDA resulted in a higher CR rate (83% vs 70%; P = .007) and a trend for better 4-year EFS (21% vs 12%) and survival (32% vs 23%) rates, with no additional benefit seen with 4 days of IDA. Gardin et al[28] analyzed pooled data from trials conducted in patients with AML who were age 50 years of age or older. These trials compared the efficacy of IDA versus DNR in induction and consolidation. They assessed the outcomes of these patients and showed that IDA resulted in a higher CR rate of 69% (vs 61% with DNR; P = .02) but did not lead to superior OS (median OS, 14.2 months; P = .13).[28]

Different doses of DNR have been evaluated in several trials, combined with standard-dose ara-C (SDAC; 100 or 200 mg/m^2 daily for 7 days). Two studies showed that using DNR 90 mg/m^2 had better outcomes than DNR 45 mg/m^2 regardless of age. Both studies showed higher CR rates and OS in patients receiving a higher dose of DNR, without any additional toxicity. The beneficial effect was mostly seen in patients younger than 50 years old and with more favorable cytogenetics.[29,30] More recently, a French group also showed that DNR 60 mg/m^2 had similar relapse rate, RFS, and OS compared with DNR 90 mg/m^2.[31]

Although there is not a clear survival advantage with IDA over DNR, CR rates and RFS favor the use of IDA, with a trend for OS advantage. Based on these data, at MDACC, IDA is the preferred anthracycline of for intensive induction therapy.

CPX-351

CPX-351 is a liposomal formulation for delivery of ara-C and DNR preferentially to leukemic cells. In this formulation, ara-C and DNR are encapsulated in a 5:1 fixed molar ratio that was found to be consistently synergistic in vitro. A multicenter, open-label, phase II study was conducted across 18 centers in the United States in the first-line setting. Patients older than 60 years old with de novo AML were randomized to receive the CPX-351 versus the 7 + 3 regimen. Higher response rates were noted with CPX-351, with an overall response rate (ORR) of 66.7% (vs 57.6%; P = .06). Improvements in the median OS (14.7 months vs 12.9 months) and EFS (6.5 months vs 2 months) were noted in the CPX-351 cohort.[32] Based on these data and a significant signal of efficacy in secondary AML, a randomized phase 3 trial was conducted in patients with newly diagnosed secondary AML. Among 309 patients randomized to CPX-351 versus the 3 + 7 regimen, CPX-351 was associated with a significantly improved OS compared with the 7 + 3 regimen(9.56 vs 5.95 months; hazard ratio [HR], 0.69;P = .005). The CR rate was 38% with CPX-351 versus 26% with the 3 + 7 regimen(P = .035), and the CR + complete response with incomplete hematologic recovery (CRi) rate was 48% versus 33% (P = .016).[33] CPX-351 was well tolerated and associated with lower induction morality but was associated with more prolonged myelosuppression compared with the 7 + 3 regimen. More of the patients achieving CR after CPX-351 were able to undergo later allo-SCT (20% vs 12%); their survival was also longer after SCT. This pivotal study was the basis for Food and Drug Administration (FDA) approval of CPX-351 as frontline therapy for patients with secondary AML. Combinations using CPX-351 as a new backbone for AML therapy, including gemtuzumab, venetoclax, IDH inhibitors, and FLT3 (fms-like tyrosine kinase 3) inhibitors are being investigated.

High-Dose Cytarabine

Several randomized trials have assessed the efficacy of HDAC (1–3 g/m^2) versus SDAC (100–200 mg/m^2) for induction therapy. The Cancer and Leukemia Group B (CALGB) and the Eastern Cooperative Oncology Group (ECOG) restricted their analysis to patients in CR, whereas the SWOG compared HDAC with SDAC during induction and randomized SDAC patients to SDAC or HDAC when the patients were in CR.[34] Finally, the Australian Leukemia Study Group (ALSG) randomized patients to HDAC or SDAC during induction only (Table 2–5).[35] These trials concluded that (1) the toxicity of HDAC (eg, cerebellar) outweighs the anti-AML effect in patients older than 65 years; (2) patients older than 60 years benefit from HDAC given during induction (SWOG, ALSG), in CR (CALGB, ECOG), and perhaps both (SWOG); and (3) HDAC potentially increases the cure rates to 70% to 80% in patients with inversion 16 or t(8;21) and to 30% to 40% in patients with normal karyotype, but little, if at all, in patients with adverse karyotypes. In a meta-analysis of three trials in 1691 patients, induction with HDAC was compared with SDAC. Although there was no difference in CR rates, the 4-year RFS (P = .03), 4-year OS (P <= .0005), and 5-year EFS (P <.0001) were better with HDAC.[36]

TABLE 2–5 Standard versus High-Dose Cytarabine (HDAC) in Patients with Newly Diagnosed Acute Myeloid Leukemia

Study	HDAC During:	Patients (*n*)	Beneficial Effect of HDAC
ALSG	Induction	279	CR duration
SWOG	Induction, consolidation, or both	723	EFS
ECOG	Consolidation	170	If age younger than 60 years
CALGB	Consolidation	596	If age younger than 60 years

ALSG, Australian Leukemia Study Group; CALGB, Cancer and Leukemia Group B; CR, complete response; EFS, event-free survival; ECOG, Eastern Cooperative Oncology Group.

A group of more recent randomized studies, in the era of modern supportive care, looked to reexamine the utility of higher dose cytarabine during AML induction and reported some nuanced results. Lowenberg et al[37] randomized 858 patients with a median age of 49 years to induction therapy with IDA combined with either high-dose cytarabine 1g/m^2 every 12 hours for 10 versus standard-dose cytarabine given at 200 mg/m^2 daily for 7 days. The study found no difference in rate CR, EFS, or OS between the two arms. Further examination of the treatment plan design reveals that all patients in both arms received high-dose cytarabine during cycle 2 of therapy, confounding the results and failing to have a clear comparison between higher or standard-dose cytarabine. The EORTC-GIMEMA cooperative group compared HDAC with standard-dose cytarabine in a backbone combining DNR and etoposide.[38] Among 1942 patients aged 60 years or younger, they found significantly higher rates of CR (82% vs 76%), rates of 6-year EFS (44% vs 35%), and OS (52% vs 43%) in patients receiving HDAC-based induction. These benefits were seen primarily and significantly in patients younger than 46 years of age, but there was only a trend for OS improvement in those aged 46 to 60 years.[38] Finally, Bassan et al[39] randomized 574 patients with a median age of 52 years to IDA + etoposide + standard-dose cytarabine or IDA plus sequential high-dose cytarabine. The sequential high-dose cytarabine arm was associated a higher CR rate after one course (81% vs 69%; $P = .0007$) and a significantly improved the 5-year survival rate (49vs versus 39%; $P = .045$). Our current approach at MDACC, therefore, is the incorporation of higher dose cytarabine during induction and consolidation for intensive regimens.

Gemtuzumab Ozogamicin

Gemtuzumab ozogamicin (GO) is a CD33-targeted immunoconjugate linking an anti-CD33 antibody to calicheamicin. It received an accelerated approval by the FDA for use in older adults with relapsed or refractory AML but was withdrawn voluntarily by the manufacturer from the market in 2010 because of toxicity concerns. However, in a trial by the French Leukemia Association, patients aged 50 to 70 years with previously untreated de novo AML were randomized to receive standard chemotherapy with the 7 + 3 regimen (DNR, ara-C) with or without GO. Gemtuzumab was administered in fractionated doses. The ORR was 81%. The OS (34 months vs 19 months; $P = .036$), EFS (15.6 months vs 9.7 months; $P = .0003$), and RFS (28 months vs 11 months; $P = .0003$) were significantly better in the GO group.[40] Another study by the Medical Research Council (MRC) in the United Kingdom showed a benefit for the addition of GO to ara-C and anthracycline-based induction regimen.[41] A recent meta-analysis examined five randomized trials in untreated patients with AML demonstrated that the addition of GO to frontline therapy of AML led to a significantly reduced risk of relapse and improved 5-year OS.[42] This was most evident in patients with favorable- and intermediate-risk cytogenetics but not in those with adverse karyotype. These data suggest utility of GO in patients with AML, supporting the recent re-approval of GO by the FDA.

TREATMENT OF YOUNGER PATIENTS WITH ACUTE MYELOID LEUKEMIA

Purine Analogues

The addition of the purine analogues clofarabine, cladribine, and fludarabine to cytarabine and anthracyclines has been associated with improved outcomes in a number of studies. Based on work by Plunkett and Gandhi,[43–48] the addition of a second nucleoside analogue such as fludarabine, cladribine, or clofarabine functioned as a potent inhibitor of ribonucleotide reductase, increased intracellular cytarabine concentration, and led to synergistic activity against leukemic blasts. Our frontline intensive induction therapy has evolved to incorporate a second nucleoside analogue (fludarabine, clofarabine, or cladribine) along with a lower dose of cytarabine (1–2 g/m^2) to optimize the balance of synergy and reduced extramedullary toxicity.[49]

Fludarabine, Idarubicin, and Cytarabine

The first translation of this preclinical work into the clinic was the combination of fludarabine, high-dose cytarabine, and IDA (FLAG-IDA or FIA), developed at MDACC for patients with AML.[43,50] The regimen has since been used internationally and forms a standard backbone for patients with newly diagnosed as well as relapsed AML. The MRC of the United Kingdom has published several analyses of the AML 15 randomized trial studying FLAG-IDA in younger patients with AML compared with 3 + 7 regimens without or with etoposide.[41,51,52] The FLAG-IDA regimen (cytarabine 2 g/m^2 on days 1–5, fludarabine 30 mg/m^2 on days 1–5, and IDA 8–10 mg/m^2 on days 1–5), among patients who were able to receive four courses, was associated with an improved 8-year survival rate of 66% compared with 47% in the standard arm.

Clofarabine, Idarubicin, and Cytarabine

Clofarabine is a second-generation nucleoside analogue that has activity in adult patients with AML. A phase I trial of clofarabine conducted at MDACC, in combination with IDA alone versus IDA and ara-C (CIA) in patients with relapsed, refractory AML showed a CR rate of 13% versus 48%, respectively. The median duration of remission was also longer with the CIA combination (15 months) compared with clofarabine and IDA (4.5 months).[53] This was followed by a phase II trial that investigated the CIA regimen in patients 60 years old or younger with newly diagnosed AML. Patients who achieved a response (CR or CRp) went on to receive up to six cycles of consolidation therapy. The cycles were administered every 4 to 6 weeks. All patients received prophylactic antibiotics, antifungals, and antivirals. The median age of the patients was 48 years (range, 19–60 years), 66% had intermediate-risk cytogenetics, and 36% had diploid and 34% adverse karyotype. The ORR was 79%, with 74% CR and 3% CRp. Eighteen percent of patients received two induction cycles to achieve a CR or CRp, and 42% went on to receive an allo-SCT in first CR. The median OS and RFS were not reached, whereas the median EFS was 13.5 months. A subset analysis showed better OS (P = .04) and EFS (P = .04) in patients 40 years old or younger compared with those older than 40 years.[54]

Cladribine

Holowiecki et al[55] conducted a randomized phase III trial evaluating the addition of cladribine or fludarabine to DNR/ara-C in younger patients with untreated AML. A total of 652 patients, with a median age of 47 years (range, 17–60 years), were randomized to receive DNR plus ara-C (DA), DA plus cladribine (DAC), and DA plus fludarabine (DAF). The consolidation regimen was the same for all arms and included two consecutive courses of ara-C (1.5 g/m^2 intravenously [IV] days 1–3) plus MTZ (10 mg/m^2 IV days 3–5) and HDAC (2 g/m^2 IV twice a day on days 1, 3, and5). The overall CR rate was 61%, with 56% achieving a CR after one cycle of induction and 5% after two cycles. The CR rate was higher in the DAC arm compared with the DA arm (62% vs 51%; P = .02). The CR rates were similar in the DA and DAF arms. The median OS was significantly higher in the DAC arm (24 months) compared with the DA arm (14 months; P = .02). There was no significant difference in the median OS between the DAF and DA arms.[55]

Based on these data, we designed a higher-dose cytarabine-based combination of cladribine (5 mg/m^2 IV on days 1–5), IDA (10 mg/m^2 IV on days 1–3), and cytarabine (1 g/m^2 IV on days 1–5) (CLIA) for patients with AML. In a recent update of our data with CLIA in 73 fit patients with newly diagnosed AML, we observed a CR/CRi rate of 76% with 58% of patients having undetectable MRD at the time of response.[56] The median OS and DFS were 21.9 months and none reached, respectively. Based on these promising results and tolerability, CLIA currently forms our frontline backbone for younger and fit patients with AML.

TREATMENT OF PATIENTS 60 YEARS OF AGE OR OLDER

AML in older adults (60 years or older) is considered a biologically and clinically distinct entity. The outcomes of older AML patients are poor with the standard anti-AML therapies. The analysis of the Swedish Acute Leukemia Registry (1976–2005) showed that the early death rates in all patients with AML, regardless of age, were lower with intensive therapy compared with palliative therapy.[57] However, most older patients may not be ideal candidates for intensive chemotherapy because of disease- and patient-related factors. Newer, lower intensity therapies with less toxicity and preserved efficacy are being developed to help address this challenging subset.

AML in older adults has adverse biologic features such as higher frequency of stem cell–like phenotype of leukemic blasts, higher frequency of multilineage involvement with dysplastic features, higher frequency of antecedent hematologic disorders, and higher frequency of *MDR-1* gene expression, which leads to higher potential for cytotoxic drug extrusion by the leukemic blasts, causing resistance to chemotherapeutic agents.[58] AML in older patients is more frequently associated with poor-risk cytogenetics (≤50% vs 10%–15% in younger patients).[59] Given the poor outcomes associated with standard therapy in these high-risk

subgroups, most older patients with newly diagnosed AML should be considered for investigational clinical trials. Other factors contributing to worse outcomes in older patients include poor performance status, organ dysfunction, and a higher incidence of an antecedent hematologic disorders. In general, patients with three or more of these factors have expected CR rates of less than 20%, 8-week mortality rates greater than 50%, and 1-year survival rates of less than 10% using conventional regimens. These patients constitute 25% to 30% of older adult patients with AML. Approximately 20% of older adult patients have none or one of these adverse factors and have a reasonable outcome with expected CR rates above 60%, 8-week mortality rates of 10%, and 1-year survival rates of 50% or greater.[60] Several groups have proposed predictive models for geriatrics assessment before determining what therapy to assign older patients.[61,62] These models look at several prognostic factors, including functional status, cytogenetics, age, and molecular status, to predict mortality and survival with therapy. This suggests that a careful assessment of the patient and disease characteristics is needed before assigning therapy to older patients.

Low-Dose Cytarabine

Low-dose ara-C (LDAC) was superior to hydroxyurea in a randomized trial enrolling 204 older adult patients with AML considered unfit for chemotherapy.[63] The CR rates were 15% with LDAC and 1% with hydroxyurea (P = .0003); the 1-year survival rates were 27% versus 3% (P = .0004). Although the responses were modest and not widely used in clinical practice as a single-agent, this trial confirmed the benefit of *treating* older patients with newly diagnosed AML rather than considering only supportive care.

Clofarabine

A randomized phase II study compared clofarabine (30 mg/m^2 IV × 5 days) versus clofarabine and ara-C (20 mg/m^2 subcutaneously daily × 14 days) in 70 older adult patients with AML.[64] Combination therapy achieved a better CR (63% vs 31%; P = .025) and better EFS (7.1 months vs 1.7 months; P = .04) but did not improve OS (11.4 months vs 5.8 months; P = .1).

Hypomethylating Agents

Building on their activity in myelodysplastic syndrome, hypomethylating agents (HMAs) such as decitabine (DAC) and 5-azacitidine (5-AZA) have been studied in and become the de facto lower intensity therapy for older and unfit patients with newly diagnosed AML. Kantarjian et al[65] conducted a randomized phase III trial comparing DAC 20 mg/m^2 for 10 days with physician's choice in 485 patients. This study showed that DAC improved CR/CRp rates compared with physician's choice (18% vs 8%; P = .001). DAC was well tolerated with a good safety profile. The primary analysis showed a nonsignificant improvement in the OS, but an unplanned analysis 2 years later demonstrated an improvement in the OS AML who are older than 65 years old have an ORR of 47% (CR rate, 42%) with intensive chemotherapy and an ORR of 29% (CR rate, 28%) with epigenetic therapy (azacitidine, DAC) (P ≤.001).[40] The median OS was similar in both the groups (0.5 months; P = .413).[66] These studies show that hypomethylating agents have similar survival outcomes in older patients with AML compared with intensive chemotherapy.

In the AML-AZA 001 trial, patients 65 years of age or older with newly diagnosed de novo or secondary AML who were deemed ineligible for transplant and with intermediate- or poor-risk cytogenetics were enrolled. Patients were randomized to receive either azacitidine or a conventional care regimen. Azacitidine was administered at 75 mg/m^2/day for 7 days subcutaneously. A prolongation in the median OS was observed in the azacitidine arm (6.4 months vs 3.2 months; P = .0185). The conventional care regimen included best supportive care in 18%, LDAC in 64%, and intensive chemotherapy in 18%.[67] Several groups have consistently shown a CR rate of 31% to 47% with DAC 20 mg/m^2 administered daily for 10 days, with a median OS of 9 to 12 months. However, the associated increased myelosuppression leads to increased rates of hospitalization for infections.[68]

Venetoclax

One of the most important advances in the treatment of AML in older and unfit patients has been the development of the BCL-2 inhibitor venetoclax in this disease. Based on the observation of modest single-agent activity in AML,[69] venetoclax was studied in combination with lower intensity (HMA or LDAC) in older and unfit patients with newly diagnosed AML. Single-arm phase Ib/II studies of venetoclax in combination with either HMA or LDAC demonstrated ORRs of 54% to 68% and median OS ranging from 10.1 to 17.5 months, leading to the accelerated FDA approval of these combinations in November 2018. The recently reported phase III randomized VIALE-A study confirmed the OS benefit of the combination of AZA + venetoclax in older or unfit patients with newly diagnosed AML, establishing it as standard frontline therapy in this population. Among 431 patients with a median age of 76 years, AZA + venetoclax demonstrated a significant improvement in OS of 14.7 months versus 9.6 months (HR, 0.66; P <.001) compared with AZA alone.[70]

Ongoing studies in this population of patients continues to build on the backbone of HMA + venetoclax to optimize efficacy among subsets.

Cladribine + Low-Dose Cytarabine

Although HMAs have been safe and well tolerated in older patients with newly diagnosed AML, newer backbones and combinations may be developed to maintain safety and tolerability while augmenting efficacy. Based on the synergy of cladribine and cytarabine, we developed a lower intensity regimen combining cladribine (5 mg/m^2 IV on days 1–5) with LDAC (20 mg subcutaneously twice a day on days 1–10) alternating with two cycles of DAC (20 mg/m^2 IV on days 1–5). Among 118 patients with a median age of 69 years, we observed a CR/CRi rate of 68%, including a CR rate of 58%. The 4- and 8-week mortality rates were 1% and 7% , respectively.[71] With a median follow-up period of 37 months, the median OS was 13.8 months with a median DFS of 10.8 months. Although these data compare favorably with single-agent HMAs in this population, it is very similar to outcomes seen with HMA + venetoclax. Ongoing studies are evaluating the safety and efficacy of venetoclax and other targeted therapies added to the cladribine–LDAC backbone.

Targeted Therapy in Acute Myeloid Leukemia

The wider application of newer techniques in DNA NGS and a better understanding AML biology have demonstrated deep heterogeneity in AML and led to a surge in targeted therapy development for genomically defined subsets. Early detection of recurrent genetic abnormalities in newly diagnosed AML now not only help delineate prognosis but also provide opportunities for targeted therapy. Specific inhibitors have been developed and FDA approved for patients with AML.

FLT3-Mutated Acute Myeloid Leukemia

FLT3 is a member of the class III receptor tyrosine kinase family that plays an important role in the survival, proliferation, and differentiation of hematopoietic progenitor cells. *FLT3* is overexpressed in most patients with AML, and activating mutations of *FLT3* are among the most prevalent molecular abnormalities in AML, with internal tandem duplication (ITD) occurring in 25% to 35% of patients with normal karyotypes.[72] In addition, 5% to 7% of patients may have point mutations within the activation loop of the kinase domain or in the juxtamembrane domain. Patients with *FLT3* activating mutations have an inferior outcome with a shorter RFS and OS. In addition, after exposure to *FLT3* inhibitors, nearly one quarter of patients with *FLT3-ITD* develop mutations in the kinase domain as a mechanism of resistance.

Incorporation of FLT3 inhibitors into the treatment of AML is now the standard of care. Stone and colleagues conducted a randomized phase III RATIFY trial (CALGB 10603) in 717 patients younger than 60 years of age with newly diagnosed *FLT3*-mutated AML (*FLT3-ITD* and/or *FLT3-TKD*; median age, 48 years; range, 18–60 years) with the 7 + 3 regimen with or without the FLT3 inhibitor midostaurin.[73] The addition of midostaurin improved the CR rate (59% vs 54%, P = .045) and survival (median survival, 74.7 vs 25.6 months; P = .009). At MDACC, we have incorporated FLT3 inhibitors as our standard on clinical trials. In a matched-cohort analysis we similarly showed the benefit of adding the multikinase FLT3 inhibitor sorafenib to an IDA cytarabine backbone in *FLT3*-mutated AML.[74] More recently, our analysis with CLIA + FLT3 inhibitor (sorafenib–midostaurin) demonstrated a CR rate of 86% and a 1-year OS of 70%.[56] The second-generation FLT3 inhibitor gilteritinib has also been FDA approved for use in patients with relapsed or refractory FLT3-mutated AML. In the ADMIRAL study, patients with relapsed or refractory AML were randomized to either gilteritinib or one of four salvage chemotherapy regimens chosen by their doctor. Gilteritinib was associated with a higher CR rate (21.1% vs 10.5%) and a significant improvement in OS (9.3 vs 5.6 months; P = .007).[75] Studies in the frontline setting with gilteritinib and other FLT3 inhibitors in combination with intensive and lower intensity therapy are ongoing. Several new *FLT3* inhibitors currently under development.

IDH-Mutated Acute Myeloid Leukemia

Isocitrate dehydrogenase enzymes (IDH1, IDH2) play a critical role in cellular metabolism and are ubiquitously expressed. Recurrent point mutations in the *IDH1* and *IDH2* genes each occur in about 10% to 12% of AML cases, resulting in neomorphic enzyme activity and the aberrant production of the onco-metabolite 2-hydroxyglutarate (2-HG). The 2-HG competitively inhibits α-ketoglutarate and leads to dysregulated epigenetic function, a hypermethylated phenotype, and a block in maturation, contributing to AML leukemogenesis. Enasidenib is an orally bioavailable small molecule inhibitor of mutant *IDH2* that is FDA approved for the treatment of relapsed or refractory IDH2-mutated AML. A phase I/II trial of patients with relapsed or refractory IDH2-mutated AML treated with enasidenib demonstrated an ORR of 39%, a CR/CRh rate of 23%, a median response duration of 8.2 months, and a median survival period of 8.8 months.[76] Ivosidenib is a selective small molecule inhibitor of *IDH1* that is FDA approved for the treatment of relapsed or

refractory IDH2-mutated AML and recently was also approved in the frontline for patients ineligible for intensive therapy. A phase I/II clinical trial evaluating 179 patients with relapsed or refractory *IDH1* mutated reported an ORR of 42%, a CR/CRh of 30%, a CR of 22%, and a median survival period of 12 months.[77] In a phase 1 dose escalation or expansion study among older patients with newly diagnosed *IDH1*-mutated AML with a median age of 76.5 years, treatment with ivosidenib produced a CR rate of 30% and an ORR of 55%, allowing expansion of the indication to older, unfit patients with untreated disease.[78] Combinations of IDH inhibitors in the frontline and relapsed or refractory settings with chemotherapy and other targeted therapies are ongoing.

TP53-Mutated Acute Myeloid Leukemia

Mutations in *TP53* are present in 15% to 20% of patients with AML, particularly enriched among patients with therapy-related AML and complex karyotypes, and have been associated with an exceptionally adverse prognosis and poor response to intensive chemotherapy.[13] Lower intensity approaches with HMAs and other backbones have produced similar outcomes to intensive chemotherapy, with less toxicity and lower rates of early mortality.[79,80] Recent data suggest that the quantified variant allelic frequency (VAF) of mutated *TP53*, reflecting its clonal dominance within a bulk AML sample, may help predict whether intensive chemotherapy may benefit a subset of *TP53*-mutated patients. A TP53 VAF of less than 40%, for example, was associated with better outcomes when using intensive chemotherapy compared with those with a higher VAF.[15] This latter subgroup represents a challenging subset, in which there is a strong need for newer, more effective therapy. Our approach and recommendation for this subset of patients has been enrollment in clinical trials.

TREATMENT OF CORE-BINDING FACTOR ACUTE MYELOID LEUKEMIA

Core-binding factor (CBF) AML is a distinct entity. It is considered a favorable karyotype. It includes patients with a pericentric inversion of chromosome 16 (inversion 16; associated with FAB subtype M4EO) and translocation (16;16) or a translocation between chromosomes 8 and 21 (t[8;21]; associated with FAB subtype M2). Each of these abnormalities disrupts the function of a transcription factor, regulating the expression of genes important in hematopoietic differentiation: inv(16) and t(16;16) lead to the formation of the *CBF-MYH11* fusion gene, and $t^{8;21}$ leads to the formation of the *RUNX1-RUNXT1* fusion gene. The *CBF-MYH11*– and *RUNX1-RUNXT1*–related leukemias represent CBF-AML. These leukemias are chemo-sensitive to intensive induction and consolidation and are characterized by high rates of CR. About 10% of unselected newly diagnosed patients (typically younger patients) have CBF-AML. At MDACC, all newly diagnosed patients with CBF-AML are treated with fludarabine (30 mg/m^2/day on days 1–5) and HDAC (2 g/m^2/day on days 1–5) regimens with or without the addition of granulocyte colony-stimulating factor (G-CSF). This is followed by up to six courses of an HDAC-containing consolidation regimen. A CR rate of 93% and an EFS of 20 months in 114 newly diagnosed patients with CBF-AML were previously reported[52]. A frontline regimen of fludarabine, ara-C, and G-CSF (FLAG)-GO was evaluated at MDACC and showed a remission rate of 95% and a 3-year OS and RFS of 78% and 85%, respectively.[81] In the UK MRC-AML15 trial, 1113 patients with AML were randomized to receive or not receive a small dose of GO (3 mg/m^2) with their induction therapy. A benefit of adding GO to the induction regimen was seen in patients with CBF-AML.[28] In a meta-analysis of five clinical trials in which addition of GO to induction chemotherapy was evaluated, a significant improvement in OS was noted in patients with favorable- and intermediate-risk cytogenetics ($P = .01$). The improvement in survival was attributed to reduced relapse ($P = .00006$).[42] All of these studies strongly support the use of FLAG-based regimens for CBF-AML and advocate the addition of GO to the induction to improve survival and RFS in these patients.

Approximately 25% of patients with CBF-AML carry a gain-of-function mutation in the *KIT* gene, which results in a constitutively activated tyrosine kinase and an inferior outcome when using standard 7 + 3–based chemotherapy. Hence, the CALGB 10801 alliance and a group in Germany are evaluating the addition of a *KIT* inhibitor, dasatinib, to the standard induction therapy. The initial results showed a 92% CR rate and 1-year DFS and OS rates of 90% and 87%, respectively.[82] Further analysis of this data and confirmatory studies will help to better define the role of inhibiting KIT in CBF-AML.

MAINTENANCE THERAPY IN ACUTE MYELOID LEUKEMIA

Although dose intensification, novel drug combinations, and improvements in support care for have led to high response rates in newly diagnosed AML, disease relapse remains a major cause of treatment failure and mortality. Post remission consolidation with allo-SCT has been shown to improve remission duration and survival in patients with higher risk disease, but this is

not available to many patients, particularly for the older and unfit patients that make a up a large proportion of patients. Postconsolidation maintenance strategies in patients with AML have been investigated for decades, with no consistent evidence of survival benefit. Most of those strategies involved using the same or similar agents in maintenance that were used during induction and consolidation. With the discovery of new therapies with newer schedules of delivery, there has been a renewed focus to develop maintenance therapies in AML. The availability of low-dose and well-tolerated HMAs such as DAC or AZA has prompted investigation of these agents for maintenance in AML. The HOVON group conducted a randomized phase III study comparing maintenance with 5-AZA at a dosage of 50 mg/m^2 IV or subcutaneous on days 1 to 5 every 4 weeks with placebo among patients 60 years of age or older with AML in remission after two cycles of intensive chemotherapy. Among 116 patients, maintenance therapy with parenteral 5-AZA demonstrated a significant improvement in 12-month DFS compared with placebo (64% vs 42%; $P = .04$), but there was no OS benefit.[83] In the ECOG-ACRIN E2906 randomized study evaluating consolidation with clofarabine or high-dose cytarabine, a second randomization studied the utility of postconsolidation maintenance with IV DAC given at a dosage of 20 mg/m^2 IV on days 1 to 3 of a 4-week cycle. A total of 120 AML patients with a median age of 69 years who had received induction and two cycles of consolidation were randomized 1:1 to DAC or placebo. DAC maintenance was associated with an improved median OS of 25.8 versus 19.5 months (HR, 0.69 [0.43–1.09]; $P = .06$). Recently, an oral formulation of AZA, CC-486, demonstrated an OS benefit, leading to its FDA approval as maintenance therapy in AML. The international, multicenter QUAZAR AML-001 trial randomized 472 patients55 years of age or older in first CR after intensive chemotherapy, with or without consolidation to receive either CC-486 or placebo on days 1 to 14 of a 28-day cycle. CC-486 was associated with a significant improvement on median OS compared with placebo (24.7 months vs 14.8 months; $P < .001$), with 1- and 2-year OS rates of 73% and 51%, respectively.[84] Similarly, CC-486 was associated with an improvement in median RFS compared with placebo (10.2 vs 4.8 months; $P < .001$). Recent advances in the development of targeted drugs in AML has created the possibility of long-term remission maintenance with chronic dosing of small molecule targeted drugs in specific genetically determined subgroups. Demonstration of their long-term safety and tolerability has made these drugs ideal candidates for long-term ambulatory maintenance strategies. For example, the multikinase inhibitor sorafenib has been used successfully as an FLT3 inhibitor in patients with FLT3-mutated AML. The SORMAIN trial was a randomized double-blind placebo-controlled trial investigating the use of post-transplant sorafenib in patients with FLT3-mutated AML.[85] Among 83 patients randomized, with a median age of 54 years, sorafenib was associated with a significant improvement in 2-year PFS and OS in favor of sorafenib, effectively establishing this as a standard of care in the post-SCT setting in this subgroup. Similarly, the phase III ADMIRAL trial of the type I FLT3 inhibitor gilteritinib evaluated post-SCT maintenance in a nonrandomized observational manner. Among 35 patients who received post-SCT gilteritinib, there was an observed improvement in median OS of 16.2 versus 8.4 compared with patients who did not receive gilteritinib (HR, 0.39 [0.16–0.92]; $P = .024$).[75] Studies are ongoing evaluating FLT3 inhibitors, including gilteritinib, in the postconsolidation maintenance setting for FLT3-mutated AML. IDH inhibitors, including enasidenib (IDH2) and ivosidenib (IDH1), are currently approved as single agents in patients with relapsed AML with IDH2 or IDH1 mutated AML, respectively. As part of the approved treatment label, these patients are treated indefinitely with single-agent IDH inhibitor as part of the initial "induction" as well as ongoing, indefinite therapy to maintain response. They have thus demonstrated feasibility and excellent long-term tolerability in this setting. At MDACC, our approach is to design appropriate risk-adapted and genomically individualized postremission maintenance strategies for patients, including post-SCT–based maintenance in patients at high risk for relapse.

The treatment for newly diagnosed AML is summarized in Figures 2–1 and 2–2.

RELAPSED OR REFRACTORY ACUTE MYELOID LEUKEMIA

Although the outcome of patients with AML has improved, relapse remains frequent and constitutes the leading cause of death. Relapsed AML remains a major challenge with few therapies providing meaningful durable responses or cures. Breems et al[86] defined a prognostic score for patients with AML in first relapse based on the following variables: (1) relapse-free interval from first CR, (2) cytogenetics at diagnosis, (3) age at first relapse, and (4) SCT before first relapse. In an analysis of 818 patients who underwent one or more lines of salvage therapy at MDACC between 2002 and 2016, rates of CR decreased from 14% after first salvage to 9% and 3% after second and third salvage, respectively.[87] The median OS periods were 6.3, 4.07, and 2.98 months after first, second, and third salvage therapies, respectively.[87] In an updated analysis, we specifically patients treated at MDACC in the second salvage setting from 2000 to 2018 to determine factors predicting factors associated with OS and nonresponse to salvage

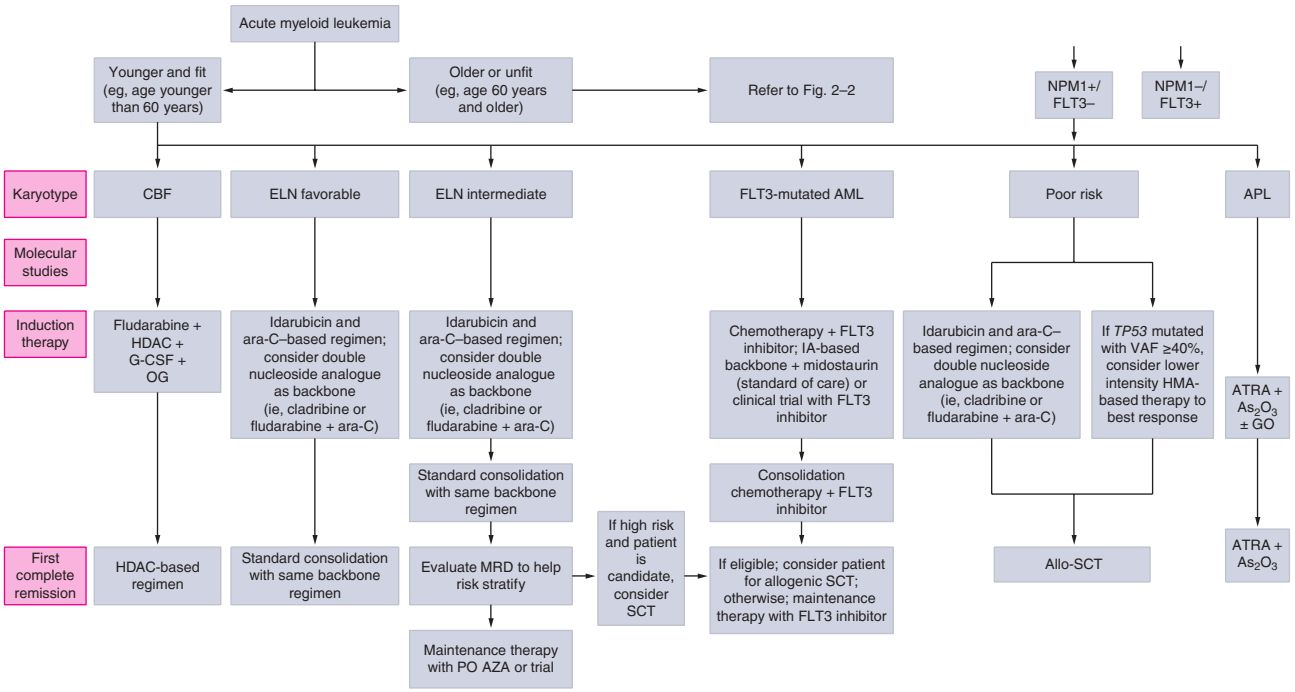


FIGURE 2–1 A proposed approach to the management of patients with newly diagnosed adult acute myeloid leukemia. allo-SCT, allogeneic stem cell transplantation; APL, acute promyelocytic leukemia; As_2O_3, arsenic trioxide; ATRA, all-*trans*-retinoic acid; CBF, core-binding factor leukemias (including inv[16], t[8;21]); FLT3, fms-like tyrosine kinase 3; G-CSF, granulocyte colony-stimulating factor; GO, gemtuzumab ozogamicin; HDAC, high-dose cytarabine; IA, idarubicin and cytarabine; MRD, minimal residual disease; NPM1, nucleophosmin; PO, oral.

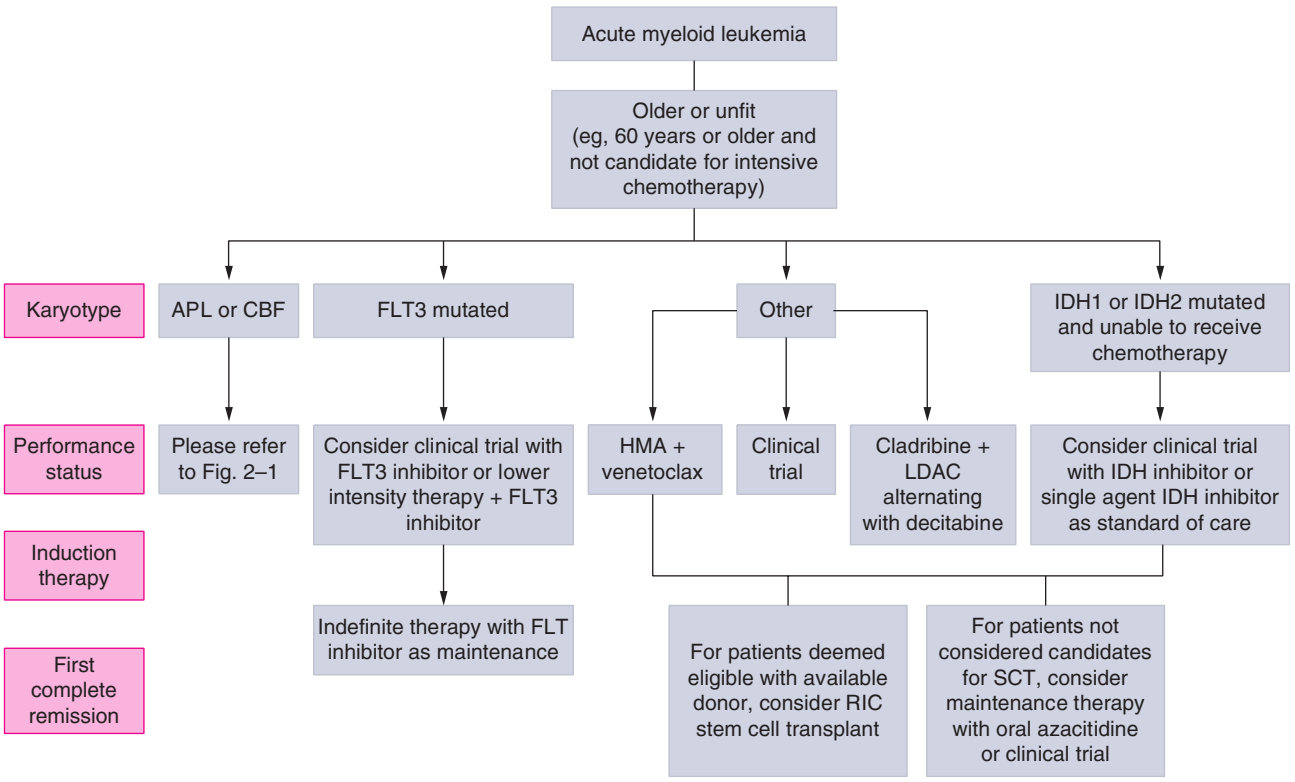


FIGURE 2–2 A proposed approach to the management of newly diagnosed adult acute myeloid leukemia in patients 60 years of age or older. APL, acute promyelocytic leukemia; CBF, core-binding factor leukemias (including inv[16], t[8;21]); PS, performance status according to the Eastern Cooperative Oncology Group; RIC transplant, reduced-intensity conditioning transplant.

therapy. By multivariate analysis, independent factors associated with worse survival were age 60 years or older, platelets less than 50, peripheral blasts 20% or greater, albumin 3 g/dL or less, and complex karyotype (three or more abnormalities). Independent factors associated with nonresponse (CR-CRp) in the second salvage setting were platelets less than 50, complex karyotype, treatment with regimens that did not include cytarabine or HMAs, and no prior CR for 12 months or longer (Fig. 2–3).[88] Recent identification and approval of targeted therapies such as FLT3 inhibitors and IDH inhibitors for specific populations in the relapsed setting have started to provide the framework for a path of how we may divide and overcome the enormous challenge of treating patients with relapsed disease.

STEM CELL TRANSPLANTATION

High-dose chemotherapy with or without radiation followed by SCT is increasingly used as therapy for AML patients in first CR. In prospective, nonrandomized trials in Europe and the United States, patients younger than age 55 years in first CR with a human leukocyte antigen (HLA)–matched sibling were assigned to allogeneic transplantation or, if no donor, to autologous transplantation or one further course of HDAC (with DNR in the European study) (Table 2–6).[89–92]

In a meta-analysis of 24 prospective clinical trials involving more than 6000 patients with AML in first CR, Koreth et al[93] showed that allo-SCT has significant

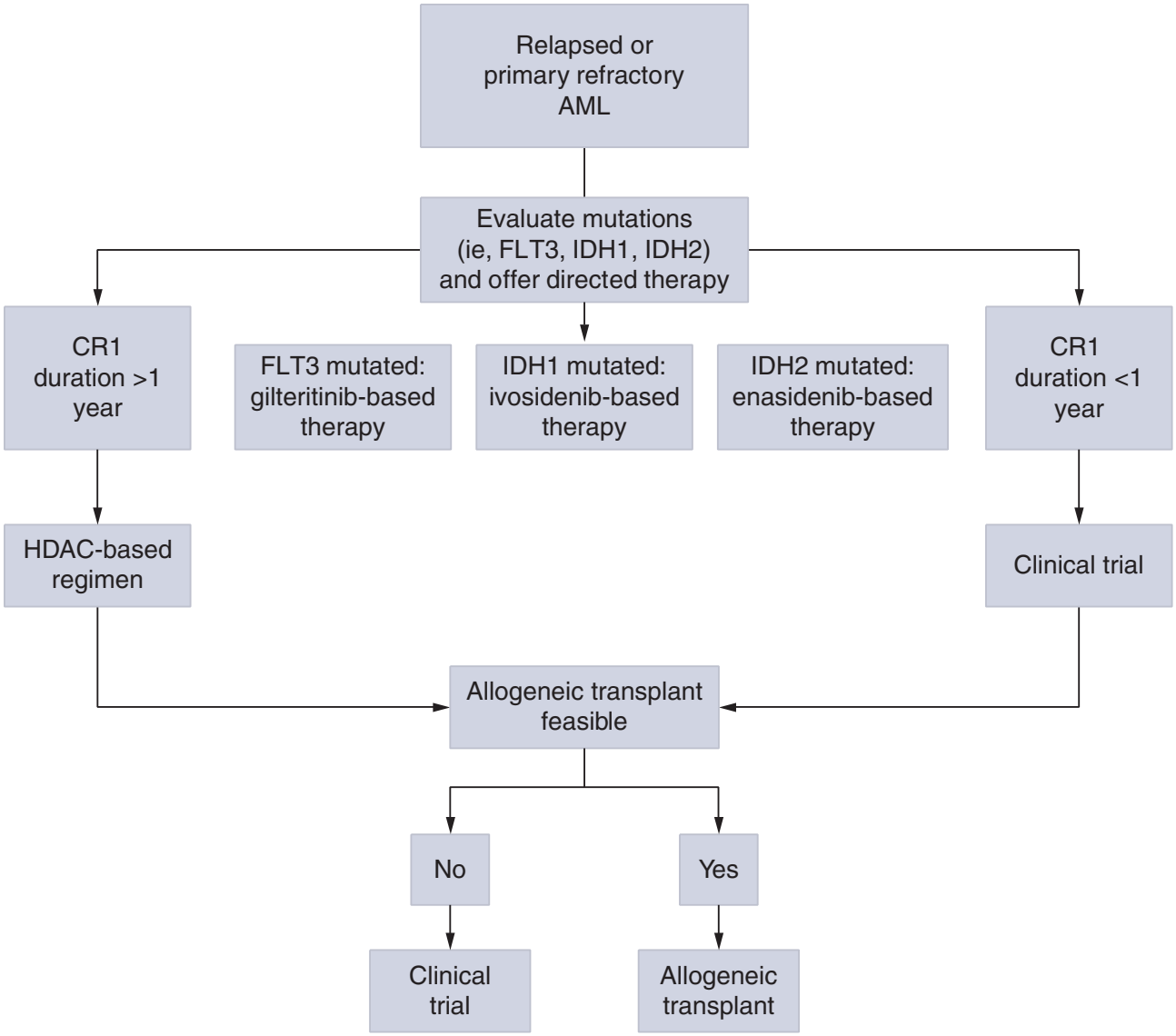


FIGURE 2–3 A proposed algorithm for management of relapsed or refractory acute myeloid leukemia (AML). CR1, first complete remission; HDAC, high-dose cytarabine.

survival benefit in patients with intermediate- and poor-risk AML but not with good-risk AML. This finding contrasts with the retrospective review of 999 patients by Ferrant et al[94] that observed similar benefit with allogeneic and autologous transplantation for patients with poor-risk karyotype and a benefit with allo-SCT only in patients with good- and intermediate-risk cytogenetics. However, further stratification of risk groups based on molecular markers within individual karyotypes suggests that only specific subsets of patients may benefit from allo-SCT . Schlenk et al[95] demonstrated superior OS with allo-SCT compared with intensive chemotherapy in only the following groups of patients with normal-karyotype de novo AML: (1) *FLT3-ITD* positive and (2) *NPM1*/*CEBPA*/*FLT3-ITD* negative. Patients with inversion 16 or t(8;21) do better with chemotherapy.[96] Patients with AML who are younger than 20 years old have a relatively low transplant-related mortality rate and may do better with allo-SCT.

New concepts in both transplantation and chemotherapy have emerged. These include the use of peripheral blood rather than marrow as the source of SCT,[97] the use of nonmyeloablative regimens to allow engraftment and take advantage of the graft-versus-leukemia effect, and the use of IV busulfan to overcome the erratic pharmacology of the oral form.[98] In particular, nonmyeloablative regimens (reduced-intensity conditioning or "mini-transplant") have gained particular traction in older adult patients, who have traditionally experienced high treatment-related mortality rates with conventional myeloablative regimens. The principles of this approach include reduction of regimen-related toxicities and shifting the burden of tumor cell kill from high-dose cytotoxic therapy to graft-versus-leukemia effects. A number of recent studies have reported 2- to 5-year survival rates of 25% to 64% after nonmyeloablative allo-SCT for older patients with high-risk MDS and AML. Survival was similar for recipients of related and unrelated HLA-matched grafts. The nonrelapse mortality rate was 16% to 39%, resulting mainly from complications of graft-versus-host disease and comorbidities preceding SCT. Relapse rates ranged from 16% to 53% and were influenced both by disease burden and cytogenetics at the time of SCT.[99] Further details on this subject are beyond the scope of this chapter.

SUPPORTIVE CARE

Adequate and close supportive care is extremely important in the care of patients with acute leukemia. Both G-CSF and granulocyte-macrophage colony-stimulating factor have reduced the median time to neutrophil recovery by an average of 5 to 7 days.[100] Antileukemic therapeutic efficacy is not compromised by these agents. Therapy of acute leukemia often results in rapid reduction of elevated WBC counts. This is often associated with the development of tumor lysis, characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, acidosis, and renal failure. Prevention of tumor lysis syndrome requires administration of IV fluids and allopurinol (or rasburicase) if the blast count is above 10×10^9/L. Saline or steroid eye drops daily should be given to patients undergoing HDAC therapy until 24 hours after completion of chemotherapy. In these patients, neurologic assessments for cerebellar neurotoxicity should be performed before each dose of HDAC.

Acute pulmonary failure during induction therapy for AML is a serious complication. Predictive factors identified at diagnosis include male sex, diagnosis of APL, poor ECOG performance status, lung infiltrates at diagnosis, and an increased serum creatinine. Fluid restriction, high-dose steroids, and continuous veno-venous hemofiltration have been shown to be effective strategies in treating acute pulmonary failure.

Infectious complications are a major cause of morbidity and death. Prophylactic administration of antibiotics in the absence of fever is usually offered. The development of fever (>101°F), unrelated to administration of chemotherapy, calls for administration of broad-spectrum antibiotics, such as carbapenem or a third- (eg, ceftazidime) or fourth-generation cephalosporin (eg, cefepime). Antibiotic selection should be prompt, individualized, and in accordance with the updated antibiotic susceptibility profile of each institution. If infection

TABLE 2–6 Allogeneic Stem Cell Transplantation (Allo-SCT) versus Chemotherapy in Patients with Acute Myeloid Leukemia in First Complete Remission (CR)

Study	Patients (*n*)	Match %	Allo-SCT in CR (%)	Significant Difference Favoring Allo-SCT
Archimbaud et al[89]	58	74	34	No
Zittoun et al[92]	294	63	23	LFS
Cassileth et al[91]	238	88	23	No
Burnett et al[90]	656	58	23	No

LFS, leukemia-free survival.

persists, G-CSF should be started, and if indicated, granulocyte transfusions, using G-CSF to increase the donors' granulocyte counts, should be given. Close fluid balance is critical because fluid retention is common, can radiologically mimic pneumonia, and may increase the risk of diffuse alveolar hemorrhage during induction.

Another controversial area is whether adherence to a neutropenic diet (avoidance of fresh fruits and vegetables) during induction chemotherapy decreases the risk of infection. A total of 153 patients with AML diagnosed at MDACC were admitted to a high-efficiency particulate air-filtered room for induction chemotherapy.[101] They were randomized to receive a diet containing no raw fruits or vegetables (cooked diet) or to a diet containing fresh fruits and vegetables (raw diet). Twenty-nine percent of patients in the cooked group and 35% of patients in the raw group developed a major infection ($P = .60$). Time to major infection and survival time were similar in the two groups, suggesting that a neutropenic diet did not prevent major infection or death.

ACUTE PROMYELOCYTIC LEUKEMIA

APL is a distinct subtype of AML, accounting for 5% to 15% of cases, with unique clinical, morphologic, and cytogenetic features. It results from a translocation between the retinoic acid receptor α (RARα) locus on chromosome 17 and the promyelocytic leukemia protein (PML) locus located on chromosome 15.[102] This *PML-RARα* fusion is demonstrable in 95% to 100% of cases. Independent risk factors for a diagnosis of APL in a patient with AML are younger age, Hispanic ethnicity, and obesity.[2] The main clinical presentation is bleeding diathesis resulting both from plasmin-dependent primary fibrinolysis and DIC.[103] Cytogenetic analysis detects the distinctive t(15;17). In the rare case in which such analysis does not show the t(15;17) but the clinical or morphologic picture is suggestive, molecular test for *PML-RARα* can be confirmatory. The POD test, an immunohistochemical test that can be performed in few hours, can detect the characteristic disruption of PML in virtually all cases and is a rapid and reliable quick test for APL. Recognition of APL is crucial because appropriate treatment with all-*trans*-retinoic acid (ATRA) and arsenic trioxide (ATO) is different than for other types of AML and is curative in most patients.[104] A stratification system has been developed that distinguishes newly diagnosed patients with APL as low, intermediate, or high risk. Low-risk patients present with WBC count less than 10×10^9/L and platelet count above 40×10^9/L; a WBC count above 10×10^9/L identifies high-risk patients. Others are at intermediate risk. At MDACC, we only use the WBC cut-off of 10×10^9/L to distinguish low- or high-risk patients. Anticipated cure rates are close to 100%, 90%, and 70% in low-, intermediate-, and high-risk patients, respectively (Table 2–9).[105]

Several findings have contributed recently to the increased cure rates in APL. Anthracyclines were historically the first effective treatment, inducing a cure rate of 30% to 40% in patients with APL. The role of ara-C is questionable and probably beneficial only in the setting of suboptimal anthracycline therapy. Addition of ATRA 45 mg/m^2 twice daily to chemotherapy (eg, IDA 12 mg/m^2 on days 2, 4, 6, and 8) increases the CR rate and, more dramatically, increases the cure rate from 40% to 70%. The major toxicity of ATRA is a potentially fatal APL differentiation syndrome characterized by fever and leakage of fluid into the extravascular space producing fluid retention, effusions, dyspnea, and hypotension; it is effectively treated with dexamethasone (10 mg IV twice a day for 35 days, with a rapid taper).[106] A molecular test (*PML-RARA*α fusion transcript by PCR) that detects molecular evidence of the t(15;17) provides a relatively sensitive and highly specific means to document MRD negativity and detect impending relapse.[107]

When a diagnosis of APL is suspected, it is imperative that the patient be given ATRA, even before the diagnosis is confirmed. ATRA is given at a dosage of 45 mg/m^2/day in divided doses. It serves to prevent coagulopathy and start induction therapy.[108]

ATO plus ATRA was shown to be at least noninferior, and possibly superior, to ATRA and chemotherapy in low- and intermediate-risk APL. In the Italian-German APL 0406 trial, Lo-Coco et al[109] showed that the CR rate was 100% in the ATRA + ATO arm versus 95% in the ATRA plus chemotherapy (IDA) arm, with a superior

TABLE 2–7 Risk Stratification of Acute Promyelocytic Leukemia

Risk Group	WBC Count (10^9/L)	Platelet Count (10^9/L)	RFS (%)
Low	≤10	>40	98
Intermediate	≤10	≤40	89
High	>10		70

RFS, relapse-free survival; WBC, white blood cell.

OS of 98.7% versus 91.1% (P = .02). This regimen is now considered the best option for patients with standard-risk APL. Patients with high-risk disease require the addition of either GO or chemotherapy such as IDA.

The regimens generally used for treatment of patients with APL, according to risk category, are summarized in Tables 2–8 to 2–10.

Ravandi et al[110] evaluated outcomes of newly diagnosed APL patients treated with ATRA and ATO with or without GO without traditional cytotoxic chemotherapy. The regimen is summarized in Table 2–13. They reported CR rates of 95% and 81%, respectively, for low- and high-risk patients. The estimated 3-year survival rate was 85%.

Hence, in the modern era of APL treatment, it is possible to have long-term cure for APL without the use of conventional chemotherapy, which is a tremendous achievement for modern-day oncology.

MINIMAL OR MEASURABLE RESIDUAL DISEASE

Minimal or measurable residual disease (MRD) is defined as any measurable disease detectable above a certain level of detection, depending on the methodology applied. In AML, this usually refers to the detection of disease that cannot be discerned by morphologic examination alone. MRD evaluation may be done using flow cytometry immunophenotyping assays aimed at identifying leukemic cells with at a sensitivity level of 0.01%. MRD assessment using molecular techniques can often attain deeper sensitivity levels.

MRD predicts a failure to maintain CR, and its detection is critical to assess the quality of response after induction therapy and to outline postremission therapy based on the individual risk of relapse. As mentioned in the section on APL, the detection of

TABLE 2–8 Treatment of Patients with High-Risk Acute Promyelocytic Leukemia (APL)

APL INDUCTION THERAPY	APL CONSOLIDATION THERAPY
Preferred Regimens	
ATRA 45 mg/m^2 (days 1–36, divided) + age-adjusted idarubicin 6–12 mg/m^2 on days 2, 4, 6, and 8 + ATO 0.15 mg/kg (days 9–36 as 2-hour IV infusion)	ATRA 45 mg/m^2 for 28 days + ATO 0.15 mg/kg/day for 28 days for one cycle; then ATRA 45 mg/m^2 for 7 days every 2 weeks × 3 + ATO 0.15 mg/kg/day for 5 days for 5 weeks for one cycle
ATRA 45 mg/m^2 in divided doses + ATO 0.15 mg/kg/day IV + a single dose of GO 9 mg/m^2 may be given on day 1, day 2, day 3, or day 4	ATO 0.15 mg/kg daily 5 days/wk for 4 weeks every 8 weeks for a total of four cycles + ATRA 45 mg/m^2 for 2 weeks every 4 weeks for a total of seven cycles; if ATRA or ATO is discontinued because of toxicity, a single dose of GO 9 mg/m^2 may be given once every 4–5 weeks until 28 weeks from CR
ATRA 45 mg/m^2 in divided doses + ATO 0.3 mg/kg IV on days 1–5 of week 1 and 0.25 mg/kg twice weekly on weeks 2–8 (category 1) + a single dose of GO 6 mg/m^2 may be given on day 1, day 2, day 3, or day 4	ATRA 45 mg/m^2 for 2 weeks every 4 weeks (or for 2 weeks on and 2 weeks off) in consolidation courses 1–4 + ATO 0.3 mg/kg on days 1–5 of week 1 in consolidation courses 1–4 and 0.25 mg/kg twice weekly in weeks 2–4 in consolidation courses 1–4 (category 1); if ATRA or ATO is discontinued because of toxicity, a single dose of GO 9 mg/m^2 may given once every 4–5 weeks until 28 weeks from CR
Other Recommended Regimens	
ATRA 45 mg/m^2 in divided doses + daunorubicin 50 mg/m^2 for 4 days (IV days 3–6) + cytarabine 200 mg/m^2 for 7 days (IV days 3–9)	ATO 0.15 mg/kg/day for 5 days for 5 weeks every 7 weeks for a total of two cycles; then ATRA 45 mg/m^2 × 7 days + daunorubicin 50 mg/m^2 for 3 days for two cycles
ATRA 45 mg/m^2 in divided doses + daunorubicin 60 mg/m^2 for 3 days + cytarabine 200 mg/m^2 for 7 days	Daunorubicin 60 mg/m^2 for 3 days + cytarabine 200 mg/m^2 for 7 days for one cycle; then cytarabine 2 g/m^2 (age younger than 50 years) or 1.5 g/m^2 (age 50–60 years) every 12 hours for 5 days + daunorubicin 45 mg/m^2 for 3 days for one cycle + five doses of IT chemotherapy
ATRA 45 mg/m^2 in divided doses + idarubicin 12 mg/m^2 on days 2, 4, 6, and 8	ATRA 45 mg/m^2 for 15 days + idarubicin 5 mg/m^2 and cytarabine 1 g/m^2 for 4 days for 1 cycle; then ATRA × 15 days + mitoxantrone 10 mg/m^2/day × 5 days for one cycle; then ATRA for 15 days + idarubicin 12 mg/m^2 for 1 day + cytarabine 150 mg/m^2/8 hours for 4 days for one cycle

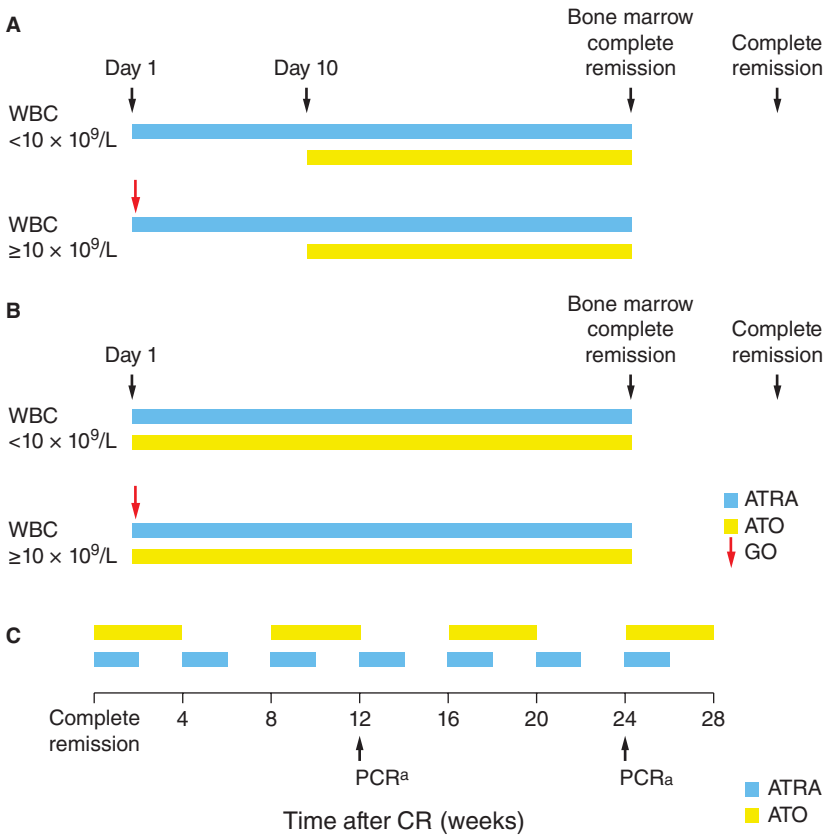
ATO, arsenic trioxide; ATRA, all-*trans*-retinoic acid; CR, complete remission; GO, gemtuzumab ozogamicin; IT, intrathecal; IV, intravenous.
Data from NCCN Guidelines 2021.

TABLE 2–9 Treatment of Patients with Low-Risk Acute Promyelocytic Leukemia (APL)

APL INDUCTION THERAPY	APL CONSOLIDATION THERAPY
Preferred Regimens	
ATRA 45 mg/m^2 in divided doses daily + ATO 0.15 mg/kg IV daily (category 1)	ATO 0.15 mg/kg/day IV 5 day/wk for 4 weeks every 8 weeks for a total of 4 cycles and ATRA 45 mg/m^2/day for 2 weeks every 4 weeks for a total of seven cycles (category 1)
ATRA 45 mg/m^2 in divided doses daily + ATO 0.3 mg/kg IV on days 1–5 of week 1 and 0.25 mg/kg twice weekly during weeks 2–8 (category 1)	**First three consolidation cycles** = 56-day cycles: ATRA 45 mg/m^2/day PO divided into two daily doses on days 1–14 and 29–42 (2 weeks on followed by 2 weeks off) + ATO 0.3 mg/kg on days 1–5 of week 1 followed by 0.25 mg/kg twice during weeks 2–4 **Fourth consolidation cycle** = 28-day cycle: ATRA 45 mg/m^2/day PO divided into 2 daily doses on days 1–14 (2 weeks on followed by 2 weeks off) + ATO 0.3 mg/kg on days 1–5 of week 1 followed by 0.25 mg/kg twice weekly during weeks 2–4
Useful in Certain Circumstances (if arsenic not available or contraindicated)	
ATRA 45 mg/m^2 in divided doses daily + idarubicin 12 mg/m^2 on days 2, 4, 6, and 8	ATRA 45 mg/m^2 for 15 days + idarubicin 5 mg/m^2 for 4 days × 1 cycle; then ATRA for 15 days + mitoxantrone 10 mg/m^2/day for 3 days for one cycle; then ATRA for 15 days + idarubicin 12 mg/m^2 for 1 day for one cycle (category 1)
ATRA 45 mg/m^2 in two divided doses daily + a single dose of GO 9 mg/m^2 on day 5	ATRA 45 mg/m^2 in divided doses daily during weeks 1–2, 5–6, 9–10, 13–14, 17–18, 21–22, and 25–26; a single dose of GO 9 mg/m^2 may be given monthly until 28 weeks from CR

ATO, arsenic trioxide; ATRA, all-*trans*-retinoic acid; CR, complete response; GO, gemtuzumab ozogamicin; IV, intravenous.
Data from NCCN Guidelines 2021.

TABLE 2–10 Treatment of Patients with Acute Promyelocytic Leukemia with All-*Trans*-Retinoic Acid (ATRA) + Arsenic Trioxide (ATO) + Gemtuzumab Ozogamicin (GO)



(*Continued*)

TABLE 2–10 Treatment of Patients with Acute Promyelocytic Leukemia with All-*Trans*-Retinoic Acid (ATRA) + Arsenic Trioxide (ATO) + Gemtuzumab Ozogamicin (GO) *(Continued)*

ATRA + ATO + GO[110]	Low Risk	High Risk
Induction	ATRA 45 mg/m² PO every day until CR + ATO 0.15 mg/kg/day IV from day 10 until there are <5% blasts and no promyelocytes in the bone marrow	ATRA 45 mg/m² PO every day until CR + ATO 0.15 mg/kg/day IV from day 10 + GO 9 mg/m² on day 1 until there are <5% blasts and no promyelocytes in the bone marrow
Consolidation or maintenance	ATO 0.15 mg/kg/day IV × 5 days/wk × 4 wk for four cycles + ATRA 45 mg/m² PO every day × 2 wk every 4 wk for seven cycles	ATO 0.15 mg/kg/day IV × 5 days/wk × 4 wk × 4 cycles + ATRA 45 mg/m² PO every day × 2 wk every 4 wk for seven cycles

ATO, arsenic trioxide; ATRA, all-*trans*-retinoic acid; CR, complete remission; D, day; GO, gemtuzumab ozogamicin; IV, intravenous; PCR, polymerase chain reaction; PO, oral; WBC, white blood cell.

TABLE 2–11 Monitoring of Acute Promyelocytic Leukemia Therapy

- Document MR at end of consolidation
- Monitor PCR (BM or PB) every 3 months for 2 years
  - High risk
  - Age older than 60 years
  - Long treatment delays during consolidation
- If PCR becomes positive from negative, confirm!
- If confirmed, intervene.
- Try to use the same laboratory for PCR.

BM, bone marrow; MR, molecular response; PB, peripheral blood; PCR, polymerase chain reaction.

*PML-RARA*α fusion transcript after achieving CR and its subsequent monitoring to detect early relapse has become the standard of care for patients with APL. Detection of MRD in non-APL AML is an upcoming field in which guidelines and standard of care need to be defined. Several methods are being assessed to determine the best method for detection of MRD in patients with AML. There are several issues with the detection of MRD, including lack of a standardized methodology to measure MRD, inconsistency in MRD thresholds, and uncertainty of the ideal time for evaluation of MRD.

Konopleva et al[111] reported that in patients with newly diagnosed AML who have abnormal cytogenetics at presentation, determination of cytogenetics in the marrow at day 21 of induction chemotherapy predicts RFS independent of the number of blasts. Chen et al[112] from MDACC demonstrated that persistence of cytogenetic abnormalities at the time of morphologic CR portends a worse outcome. They looked at patients with abnormal cytogenetics at the time of diagnosis who achieved a morphologic CR after induction. Twenty-eight percent of patients in CR had abnormal karyotype (ACCR), and the remaining 72% had normal cytogenetic CR (NCCR). Patients with ACCR had a shorted RFS and OS compared with patients with NCCR (6 months vs 21 months; $P < .001$; and 11 months vs 46 months; $P < .001$, respectively). The RFS and OS for patients with unfavorable cytogenetics at diagnosis who were NCCR were similar to those in patients with favorable or intermediate risk at diagnosis who were ACCR. The ACCR patients who underwent an allo-SCT had a significantly longer 3-year RFS (33% vs 9%; $P = .04$) and a 3-year OS (33% vs 8%; $P = .06$) than the patients who did not undergo an SCT. Interestingly, the RFS and OS achieved by patients with ACCR, who underwent an allo-SCT, were similar to the NCCR patients who did not undergo an SCT. This suggests a role for individualizing AML therapy based on cytogenetic MRD status.

Another method of quantitative detection of MRD in AML is real-time PCR (RT-PCR) (Table 2–14). RT-PCR rapidly quantifies PCR products by reverse transcriptase fluorescent signals during exponential amplification. The sensitivity of molecular detection of fusion transcripts ranges from 1 leukemic cell in 1000 to 100,000 normal cells, that is, 0.1% to 0.001% The fusion transcripts most extensively used to monitor MRD in AML (in addition to *PML-RAR*α for APL) are *AML1-ETO*, *CBF*β*-MYH11*, and *MLL-AF9*, which are present in approximately one third of non-APL AML cases.[113] Various mutations, such as *FLT3, NPM1*, and c-*KIT*, can also be assessed by RT-PCR to determine the residual disease status. PCR analysis of *NPM1* mutations after therapy is prognostic and can be used to predict relapse. *NPM1* mutations are present in 30% of all patients with AML and in 50% of patients with normal-karyotype AML. Chou et al[114] looked at the role of MRD analysis of *NPM1* mutations by PCR and the impact on outcomes. A total of 194 samples from 38 patients with de novo AML and *NPM1* mutations were analyzed over 10 years. The samples were taken 1 month after induction and 3 months after consolidation. Any rise in the

TABLE 2–12 Advantages and Disadvantages of Real-Time Reverse Transcriptase Polymerase Chain Reaction

Advantages	Disadvantages
Very sensitive reactions	Applicable to a limited number of molecular targets • *PML-RARα* • CBF leukemias • *NPM1*
Mutations and translocations are commonly found in AML	CBF-AML may have persistence of qualitative assay positivity for years
	Can miss therapy-related AML
	Expensive
	Longer turnaround time

AML, acute myeloid leukemia; CBF, core-binding factor.

mutant signals during follow-up was associated with a 3.2 times increased risk of relapse. Of the relapsed patients, the rise in the mutation levels predicted a relapse at a median of 4.9 months (range, 1–12.3 months) before a clinical relapse being seen. This analysis also showed that the degree of reduction in mutation levels affects outcomes and that there is a co-relation between MRD after consolidation and OS and RFS (but not after induction). The Wilms tumor 1 gene (*WT1*) is highly expressed in most acute leukemias, and its detection in bone marrow has been associated with the presence, persistence, or relapse of leukemia. Recently, investigators from Turin, Italy, systematically applied their best-performing *WT1* RT-PCR assay on 620 patient samples and demonstrated that application of a standardized *WT1* assay can indeed provide independent prognostic information in patients with AML.[115] Studies are ongoing to further elucidate the role of the *WT1* gene assay to risk stratify patients who might benefit from intensification of therapy to improve outcomes.

Leukemic cells express abnormal patterns of cellular markers, and these aberrant immunophenotypes can be identified by multiparameter flow cytometry. To yield a sensitivity of 0.01% (10^{-4}), at least 200,000 cells are needed per tube (at least 200,000 events are required to detect 20 aberrant blasts), and three to four tubes are run per patient; 0.1% is the commonly used threshold in most studies in the literature. An advantage of flow cytometry–based studies of MRD is that they can accurately quantify residual leukemic cells and can also distinguish aberrant blasts from normal myeloid precursors. An immunophenotypic fingerprint of the AML can be established for MRD analysis for follow-up. However, there are several advantages and disadvantages with this technique (Table 2–15).

Rubnitz et al[116] reported outcomes with MRD-directed therapy in childhood AML. In this study, patients were randomized to receive HDAC-based induction versus LDAC-based induction. MRD levels, on day 22 after induction, were used to allocate GO to determine the timing of the second induction. MRD was determined, and GO was given to patients with poor early response; high-risk patients were allocated to allo-SCT. This study showed that MRD was no different with high-dose chemotherapy versus low-dose chemotherapy at day 22 of induction 1. MRD greater than 1% on day 22 was a significant prognostic factor influencing OS and EFS in the high-risk patients but not in the standard- or favorable-risk patients. Patients with low-level MRD (0.1% to <1%) did as well as the MRD-negative cohort. An Italian group analyzed the outcomes of adult AML patients based on MRD levels after induction and consolidation and reported that the MRD status at the end of consolidation was the most important predictor of prognosis. In the MRD-positive group, patients who underwent an allo-SCT had improved outcomes.[117]

In general, a lack of standardization among different laboratories, identification of thresholds, and time points during follow-up represent the major subjects of controversy for the routine implementation of MRD detection in non-APL AML at this time.

CONCLUSION

After a period of paucity in discoveries and approvals, new strategies are finally evolving, and since 2017,

TABLE 2–13 Advantages and Disadvantages of Flow Cytometry for Minimal Residual Disease Assessment

Advantages	Disadvantages
Widely applicable (90%–95% of cases)	Interpretation often challenging; requires experience
	Can be expensive
	Lack of standardization
Relatively rapid turnaround time	LAIPs may not cover all leukemic blasts; partial overlap with normal
	Antigen shift resulting from selection or emergence of subclones: a complete change in LAIPs in ~20% of AML cases, with 80% having at least one LAIP similar to the original
	Posttherapy sample is hypocellular; not enough cells or events
	Use of a comprehensive panel of antibodies to establish baseline

AML, acute myeloid leukemia; LAIP, leukemia-associated immunophenotype.

new drugs have been approved to improve outcomes in patients with AML. The biology of the disease is now better understood, and development of targeted therapy is now catching up with the science. Individualized therapy for patients with FLT3, IDH1, and IDH2 mutated AML is now available and part of the standard of care. Safe *and* highly effective therapy is now available for newly diagnosed older and unfit patients with AML with the discovery of venetoclax. Careful genomic annotation of patients at diagnosis followed by subgroup analyses in large cohorts have identified subgroups that may benefit more or less from selected targeted therapies, as is the case of gemtuzumab and CBF-AML. Patients with APL have benefited from newer treatment with ATRA and arsenical derivatives while avoiding classic chemotherapy. Combinations of these newer drugs are being investigated to optimize future treatment. Better definition of the complex process initiating and sustaining the leukemic process will lead to a better definition of targets for therapeutic intervention that may translate into improved cure rates. Specific attention must be given to prognostic factors that identify subsets of AML in which specific tailored therapies will be helpful.

MD ANDERSON PRACTICE TIPS

- In patients with newly diagnosed CBF-AML, at MDACC, we use the combination of FLAG + GO, achieving high rates of CR and long-term survival rates of 70% to 80%. Dose modifications to the FLAG backbone are implemented to offer these patients the potential for cure. Close monitoring of RT-PCR for the CBF transcript is critical for risk stratification, with the goal to achieve at least 3-log reduction from baseline at the end of consolidation.
- Our frontline approach to newly diagnosed, young, fit patients with newly diagnosed AML is to offer double-nucleoside intensive chemotherapy with either cladribine or fludarabine combined with a higher dose of cytarabine (1–2 g/m^2) combined with IDA as the preferred anthracycline. All patients have baseline genomic sequencing and karyotyping. Patients with targetable mutations receive FLT3 inhibitors, IDH inhibitors, or venetoclax in combination with these backbones on clinical trials. Patients with TP53 mutations with high allelic frequency and complex karyotype may be offered less intensive clinical trials in the frontline setting.
- We recommend close, often inpatient monitoring for patients with newly diagnosed AML during the induction cycle of chemotherapy. We routinely use antibacterial, antifungal, and antiviral prophylaxis in all of our patients with AML when appropriate.
- Our frontline approach to newly diagnosed, older, and unfit patients with AML includes lower intensity therapy on clinical trials in combination with targeted therapy (ie, FLT3 inhibitor, IDH inhibitor) when appropriate. Lower intensity regimens include a newer backbone on clinical trial, involving cladribine + low-dose cytarabine + venetoclax or HMA + venetoclax. When in remission, dose and schedule modifications are implemented to minimize toxicity and prolonged myelosuppression that can be observed after repeated cycles.
- Postremission therapy is recommend based on age, fitness, and risk assessment at baseline and during therapy (ie, MRD monitoring). Maintenance therapy with oral azacytidine or targeted therapy combinations on clinical trials are recommended for most higher risk patients who are not candidates for SCT. Studies of post-transplant maintenance therapy are also being conducted.

REFERENCES

1. Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129(4):424-447.
2. Estey E, Thall P, Kantarjian H, et al. Association between increased body mass index and a diagnosis of acute promyelocytic leukemia in patients with acute myeloid leukemia. *Leukemia*. 1997;11:1661-1664.
3. Crane MM, Strom SS, Halabi S, et al. Correlation between selected environmental exposures and karyotype in acute myelocytic leukemia. *Cancer Epidemiol Biomarkers Prev*. 1996;5(8):639-644.
4. Samra B, Richard-Carpentier G, Kadia TM, et al. Characteristics and outcomes of patients with therapy-related acute myeloid leukemia with normal karyotype. *Blood Cancer J*. 2020;10(5):47.
5. Tiruneh T, Enawgaw B, Shiferaw E. Genetic pathway in the pathogenesis of therapy-related myeloid neoplasms: a literature review. *Oncol Ther*. 2020;8(1):45-57.
6. Ok CY, Patel KP, Garcia-Manero G, et al. Mutational profiling of therapy-related myelodysplastic syndromes and acute myeloid leukemia by next generation sequencing, a comparison with de novo diseases. *Leuk Res*. 2015;39(3):348-354.
7. Ok CY, Patel KP, Garcia-Manero G, et al. TP53 mutation characteristics in therapy-related myelodysplastic syndromes and acute myeloid leukemia is similar to de novo diseases. *J Hematol Oncol*. 2015;8:45.
8. Armstrong SA, Staunton JE, Silverman LB, et al. MLL translocations specify a distinct gene expression profile that distinguishes a unique leukemia. *Nat Genet*. 2002;30(1):41-47.
9. West RR, Stafford DA, White AD, et al. Cytogenetic abnormalities in the myelodysplastic syndromes and occupational or environmental exposure. *Blood*. 2000;95:2093-2097.
10. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood*. 2009;114(5):937-951.
11. Taskesen E, Bullinger L, Corbacioglu A, et al. Prognostic impact, concurrent genetic mutations, and gene expression features of AML with CEBPA mutations in a cohort of 1182 cytogenetically normal AML patients: further evidence for CEBPA double mutant AML as a distinctive disease entity. *Blood*. 2011;117(8):2469-2475.
12. Loghavi S, Zuo Z, Ravandi F, et al. Clinical features of de novo acute myeloid leukemia with concurrent DNMT3A, FLT3 and NPM1 mutations. *J Hematol Oncol*. 2014;7:74.
13. Kadia TM, Jain P, Ravandi F, et al. TP53 mutations in newly diagnosed acute myeloid leukemia: Clinicomolecular characteristics, response to therapy, and outcomes. *Cancer*. 2016;122(22):3484-3491.
14. Rucker FG, Schlenk RF, Bullinger L, et al. TP53 alterations in acute myeloid leukemia with complex karyotype correlate with specific copy number alterations, monosomal karyotype, and dismal outcome. *Blood*. 2012;119(9):2114-2121.
15. Short NJ, Montalban-Bravo G, Hwang H, et al. Prognostic and therapeutic impacts of mutant TP53 variant allelic frequency in newly diagnosed acute myeloid leukemia. *Blood Adv*. 2020;4(22):5681-5689.
16. Patel JP, Gonen M, Figueroa ME, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. *N Engl J Med*. 2012;366(12):1079-1089.
17. Freireich EJ, Gehan EA, Sulman D, et al. The effect of chemotherapy on acute leukemia in the human. *J Chronic Dis*. 1961;14:593-608.
18. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for Diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. *J Clin Oncol*. 2003;21(24):4642-4649.
19. de Lima M, Strom SS, Keating M, et al. Implications of potential cure in acute myelogenous leukemia: development of subsequent cancer and return to work. *Blood*. 1997;90(12):4719-4724.
20. Short NJ, Zhou S, Fu C, et al. Association of measurable residual disease with survival outcomes in patients with acute myeloid leukemia: a systematic review and meta-analysis. *JAMA Oncol*. 2020;6(12):1890-1899.
21. Giles FJ, Shen Y, Kantarjian HM, et al. Leukapheresis reduces early mortality in patients with acute myeloid leukemia with high white cell counts but does not improve long-term survival. *Leuk Lymphoma*. 2001;42(1-2):67-73.
22. Sekeres MA, Elson P, Kalaycio ME, et al. Time from diagnosis to treatment initiation predicts survival in younger, but not older, acute myeloid leukemia patients. *Blood*. 2009;113(1):28-36.
23. Parikh SA, Kadia T, Jabbour E. Peripheral blasts on day 21 of induction chemotherapy in a patient with core binding factor acute myeloid leukemia: more than meets the eye. *Clin Lymphoma Myeloma Leuk*. 2010;10(4):301-302.
24. Berman E, Heller G, Santorsa J, et al. Results of a randomized trial comparing idarubicin and cytosine arabinoside with daunorubicin and cytosine arabinoside in adult patients with newly diagnosed acute myelogenous leukemia. *Blood*. 1991;77(8):1666-1674.
25. Rowe JM ND, Friedenberg W. A phase III study of daunorubicin vs idarubicin vs mitoxantrone for older adult patients (>55 yrs) with acute myelogenous leukemia (AML): a study of the Eastern Cooperative Oncology Group (E3993). *Blood*. 1998;92:1284.
26. Mandelli F, Vignetti M, Suciu S, et al. Daunorubicin versus mitoxantrone versus idarubicin as induction and consolidation chemotherapy for adults with acute myeloid leukemia: the EORTC and GIMEMA Groups Study AML-10. *J Clin Oncol*. 2009;27(32):5397-5403.
27. Pautas C, Merabet F, Thomas X, et al. Randomized study of intensified anthracycline doses for induction and recombinant interleukin-2 for maintenance in patients with acute myeloid leukemia age 50 to 70 years: results of the ALFA-9801 study. *J Clin Oncol*. 2010;28(5):808-814.
28. Gardin C, Chevret S, Pautas C, et al. Superior long-term outcome with idarubicin compared with high-dose daunorubicin in patients with acute myeloid leukemia age 50 years and older. *J Clin Oncol*. 2013;31(3):321-327.
29. Fernandez HF, Sun Z, Yao X, et al. Anthracycline dose intensification in acute myeloid leukemia. *N Engl J Med*. 2009;361(13):1249-1259.
30. Lowenberg B, Ossenkoppele GJ, van Putten W, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. *N Engl J Med*. 2009;361(13):1235-1248.
31. Devillier R, Bertoli S, Prebet T, et al. Comparison of 60 or 90 mg/m(2) of daunorubicin in induction therapy for acute myeloid leukemia with intermediate or unfavorable cytogenetics. *Am J Hematol*. 2015;90(2):E29-30.
32. Lancet JE, Cortes JE, Hogge DE, et al. Phase 2 trial of CPX-351, a fixed 5:1 molar ratio of cytarabine/daunorubicin, vs cytarabine/daunorubicin in older adults with untreated AML. *Blood*. 2014;123(21):3239-3246.
33. Lancet JE, Uy GL, Cortes JE, et al. CPX-351 (cytarabine and daunorubicin) Liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. *J Clin Oncol*. 2018;36(26):2684-2692.
34. Mayer RJ, Davis RB, Schiffer CA, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. Cancer and Leukemia Group B. *N Engl J Med*. 1994;331(14):896-903.

35. Bishop JF, Matthews JP, Young GA, et al. Intensified induction chemotherapy with high dose cytarabine and etoposide for acute myeloid leukemia: a review and updated results of the Australian Leukemia Study Group. *Leuk Lymphoma*. 1998;28:315-327.
36. Kern WaE, EH. High-dose cytosine arabinoside in induction treatment of acute myeloid leukemia: meta-analysis of three trials involving 1691 randomized patients [abstract]. *Blood*. 2002;100:155a.
37. Lowenberg B, Pabst T, Vellenga E, et al. Cytarabine dose for acute myeloid leukemia. *N Engl J Med*. 2011;364(11):1027-1036.
38. Willemze R, Suciu S, Meloni G, et al. High-dose cytarabine in induction treatment improves the outcome of adult patients younger than age 46 years with acute myeloid leukemia: results of the EORTC-GIMEMA AML-12 trial. *J Clin Oncol*. 2014;32(3):219-228.
39. Bassan R, Intermesoli T, Masciulli A, et al. Randomized trial comparing standard vs sequential high-dose chemotherapy for inducing early CR in adult AML. *Blood Adv*. 2019;3(7):1103-1117.
40. Castaigne S, Pautas C, Terre C, et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. *Lancet*. 2012;379(9825):1508-1516.
41. Burnett AK, Hills RK, Milligan D, et al. Identification of patients with acute myeloblastic leukemia who benefit from the addition of gemtuzumab ozogamicin: results of the MRC AML15 trial. *J Clin Oncol*. 2011;29(4):369-377.
42. Hills RK, Castaigne S, Appelbaum FR, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials. *Lancet Oncol*. 2014;15(9):986-996.
43. Gandhi V, Estey E, Du M, et al. Modulation of the cellular metabolism of cytarabine and fludarabine by granulocyte-colony-stimulating factor during therapy of acute myelogenous leukemia. *Clin Cancer Res*. 1995;1(2):169-178.
44. Gandhi V, Estey E, Keating MJ, et al. Chlorodeoxyadenosine and arabinosylcytosine in patients with acute myelogenous leukemia: pharmacokinetic, pharmacodynamic, and molecular interactions. *Blood*. 1996;87(1):256-264.
45. Gandhi V, Estey E, Keating MJ, Plunkett W. Fludarabine potentiates metabolism of cytarabine in patients with acute myelogenous leukemia during therapy. *J Clin Oncol*. 1993;11(1):116-124.
46. Gandhi V, Kemena A, Keating MJ, Plunkett W. Cellular pharmacology of fludarabine triphosphate in chronic lymphocytic leukemia cells during fludarabine therapy. *Leuk Lymphoma*. 1993;10(1-2):49-56.
47. Gandhi V, Plunkett W. Modulation of arabinosylnucleoside metabolism by arabinosylnucleotides in human leukemia cells. *Cancer Res*. 1988;48(2):329-334.
48. Seymour JF, Huang P, Plunkett W, Gandhi V. Influence of fludarabine on pharmacokinetics and pharmacodynamics of cytarabine: implications for a continuous infusion schedule. *Clin Cancer Res*. 1996;2(4):653-658.
49. Plunkett W, Liliemark JO, Adams TM, et al. Saturation of 1-beta-D-arabinofuranosylcytosine 5'-triphosphate accumulation in leukemia cells during high-dose 1-beta-D-arabinofuranosylcytosine therapy. *Cancer Res*. 1987;47(11):3005-3011.
50. Estey EH, Thall PF, Pierce S, et al. Randomized phase II study of fludarabine + cytosine arabinoside + idarubicin +/- all-trans retinoic acid +/- granulocyte colony-stimulating factor in poor prognosis newly diagnosed acute myeloid leukemia and myelodysplastic syndrome. *Blood*. 1999;93(8):2478-2484.
51. Burnett AK, Russell NH, Hills RK, et al. Optimization of chemotherapy for younger patients with acute myeloid leukemia: results of the medical research council AML15 trial. *J Clin Oncol*. 2013;31(27):3360-3368.
52. Burnett AK, Russell NH, Hills RK, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy improves survival in older patients with acute myeloid leukemia. *J Clin Oncol*. 2012;30(32):3924-3931.
53. Faderl S, Ferrajoli A, Wierda W, et al. Clofarabine combinations as acute myeloid leukemia salvage therapy. *Cancer*. 2008;113(8):2090-2096.
54. Nazha A, Kantarjian H, Ravandi F, et al. Clofarabine, idarubicin, and cytarabine (CIA) as frontline therapy for patients </=60 years with newly diagnosed acute myeloid leukemia. *Am J Hematol*. 2013;88:961-966.
55. Holowiecki J, Grosicki S, Giebel S, et al. Cladribine, but not fludarabine, added to daunorubicin and cytarabine during induction prolongs survival of patients with acute myeloid leukemia: a multicenter, randomized phase III study. *J Clin Oncol*. 2012;30(20):2441-2448.
56. Boddu P, Kantarjian HM, Ravandi F, et al. Outcomes By treatment setting and genomic profile in patients with aml on cladribine, idarubicin, and cytarabine. *Blood*. 2017;130(suppl 1):3898-3898.
57. Juliusson G, Antunovic P, Derolf A, et al. Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. *Blood*. 2009;113(18):4179-4187.
58. Leith CP, Kopecky KJ, Godwin J, et al. Acute myeloid leukemia in the elderly: assessment of multidrug resistance (MDR1) and cytogenetics distinguishes biologic subgroups with remarkably distinct responses to standard chemotherapy. A Southwest Oncology Group study. *Blood*. 1997;89(9):3323-3329.
59. Appelbaum FR, Gundacker H, Head DR, et al. Age and acute myeloid leukemia. *Blood*. 2006;107(9):3481-3485.
60. Kantarjian H, O'Brien S, Cortes J, et al. Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognostic models for outcome. *Cancer*. 2006;106(5):1090-1098.
61. Kantarjian H, Ravandi F, O'Brien S, et al. Intensive chemotherapy does not benefit most older patients (age 70 years or older) with acute myeloid leukemia. *Blood*. 2010;116(22):4422-4429.
62. Krug U, Rollig C, Koschmieder A, et al. Complete remission and early death after intensive chemotherapy in patients aged 60 years or older with acute myeloid leukaemia: a web-based application for prediction of outcomes. *Lancet*. 2010;376(9757):2000-2008.
63. Burnett AK MD, Prentice AG, et al. . Low dose ara-C versus hydroxyurea with or without retinoid in older patients not considered fit for intensive chemotherapy: the UK NCRI AML 14 trial. *Blood*. 2004(104:Abstract 872).
64. Faderl S, Ravandi F, Huang X, et al. A randomized study of clofarabine versus clofarabine plus low-dose cytarabine as frontline therapy for patients aged 60 years and older with acute myeloid leukemia and high-risk myelodysplastic syndrome. *Blood*. 2008;112(5):1638-1645.
65. Kantarjian HM, Thomas XG, Dmoszynska A, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. *J Clin Oncol*. 2012;30(21):2670-2677.
66. Quintas-Cardama A, Ravandi F, Liu-Dumlao T, et al. Epigenetic therapy is associated with similar survival compared with intensive chemotherapy in older patients with newly diagnosed acute myeloid leukemia. *Blood*. 2012;120(24):4840-4845.
67. Dombret H, Seymour JF, Butrym A, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. *Blood*. 2015;126(3):291-299.

68. Blum W, Garzon R, Klisovic RB, et al. Clinical response and miR-29b predictive significance in older AML patients treated with a 10-day schedule of decitabine. *Proc Natl Acad Sci U S A*. 2010;107(16):7473-7478.
69. Konopleva M, Pollyea DA, Potluri J, et al. Efficacy and biological correlates of response in a phase II study of venetoclax monotherapy in patients with acute myelogenous leukemia. *Cancer Discov*. 2016;6(10):1106-1117.
70. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383(7):617-629.
71. Kadia TM, Cortes J, Ravandi F, et al. Cladribine and low-dose cytarabine alternating with decitabine as front-line therapy for elderly patients with acute myeloid leukaemia: a phase 2 single-arm trial. *Lancet Haematol*. 2018;5(9):e411-e421.
72. Gilliland DG, Griffin JD. The roles of FLT3 in hematopoiesis and leukemia. *Blood*. 2002;100(5):1532-1542.
73. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *N Engl J Med*. 2017;377(5):454-464.
74. Sasaki K, Kantarjian HM, Kadia T, et al. Sorafenib plus intensive chemotherapy improves survival in patients with newly diagnosed, FLT3-internal tandem duplication mutation-positive acute myeloid leukemia. *Cancer*. 2019;125(21):3755-3766.
75. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. *N Engl J Med*. 2019;381(18):1728-1740.
76. Stein EM, DiNardo CD, Fathi AT, et al. Molecular remission and response patterns in patients with mutant-IDH2 acute myeloid leukemia treated with enasidenib. *Blood*. 2019;133(7):676-687.
77. DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. *N Engl J Med*. 2018;378(25):2386-2398.
78. Roboz GJ, DiNardo CD, Stein EM, et al. Ivosidenib induces deep durable remissions in patients with newly diagnosed IDH1-mutant acute myeloid leukemia. *Blood*. 2020;135(7):463-471.
79. Boddu P, Kantarjian H, Ravandi F, et al. Outcomes with lower intensity therapy in TP53-mutated acute myeloid leukemia. *Leuk Lymphoma*. 2018;59(9):2238-2241.
80. Welch JS, Petti AA, Miller CA, et al. TP53 and decitabine in acute myeloid leukemia and myelodysplastic syndromes. *N Engl J Med*. 2016;375(21):2023-2036.
81. Borthakur G, Kantarjian H, Wang X, et al. Treatment of core-binding-factor in acute myelogenous leukemia with fludarabine, cytarabine, and granulocyte colony-stimulating factor results in improved event-free survival. *Cancer*. 2008;113(11):3181-3185.
82. Marcucci G, Geyer S, Laumann K, et al. Combination of dasatinib with chemotherapy in previously untreated core binding factor acute myeloid leukemia: CALGB 10801. *Blood Adv*. 2020;4(4):696-705.
83. Huls G, Chitu DA, Havelange V, et al. Azacitidine maintenance after intensive chemotherapy improves DFS in older AML patients. *Blood*. 2019;133(13):1457-1464.
84. Wei AH, Dohner H, Pocock C, et al. Oral azacitidine maintenance therapy for acute myeloid leukemia in first remission. *N Engl J Med*. 2020;383(26):2526-2537.
85. Burchert A, Bug G, Fritz LV, et al. Sorafenib maintenance after allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia with FLT3-internal tandem duplication mutation (SORMAIN). *J Clin Oncol*. 2020;38(26):2993-3002.
86. Breems DA, Van Putten WL, Huijgens PC, et al. Prognostic index for adult patients with acute myeloid leukemia in first relapse. *J Clin Oncol*. 2005;23(9):1969-1978.
87. Ravandi F, Pierce S, Garcia-Manero G, et al. Salvage therapy outcomes in a historical cohort of patients with relapsed or refractory acute myeloid leukemia. *Clin Lymphoma Myeloma Leuk*. 2020;20(11):e871-e882.
88. Kantarjian HM, DiNardo CD, Nogueras-Gonzalez GM, et al. Results of second salvage therapy in 673 adults with acute myelogenous leukemia treated at a single institution since 2000. *Cancer*. 2018;124(12):2534-2540.
89. Archimbaud E, Thomas X, Michallet M, et al. Prospective genetically randomized comparison between intensive postinduction chemotherapy and bone marrow transplantation in adults with newly diagnosed acute myeloid leukemia. *J Clin Oncol*. 1994;12(2):262-267.
90. Burnett AK, Goldstone AH, Stevens RM, et al. Randomised comparison of addition of autologous bone-marrow transplantation to intensive chemotherapy for acute myeloid leukaemia in first remission: results of MRC AML 10 trial. UK Medical Research Council Adult and Children's Leukaemia Working Parties. *Lancet*. 1998;351(9104):700-708.
91. Cassileth PA, Harrington DP, Appelbaum FR, et al. Chemotherapy compared with autologous or allogeneic bone marrow transplantation in the management of acute myeloid leukemia in first remission. *N Engl J Med*. 1998;339(23):1649-1656.
92. Zittoun RA, Mandelli F, Willemze R, et al. Autologous or allogeneic bone marrow transplantation compared with intensive chemotherapy in acute myelogenous leukemia. European Organization for Research and Treatment of Cancer (EORTC) and the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) Leukemia Cooperative Groups. *N Engl J Med*. 1995;332(4):217-223.
93. Koreth J, Schlenk R, Kopecky KJ, et al. Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: systematic review and meta-analysis of prospective clinical trials. *JAMA*. 2009;301(22):2349-2361.
94. Ferrant A, Labopin M, Frassoni F, et al. Karyotype in acute myeloblastic leukemia: prognostic significance for bone marrow transplantation in first remission: a European Group for Blood and Marrow Transplantation study. Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). *Blood*. 1997;90(8):2931-2938.
95. Schlenk RF, Dohner K, Krauter J, et al. Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. *N Engl J Med*. 2008;358(18):1909-1918.
96. Burnett AK. Transplantation in first remission of acute myeloid leukemia. *N Engl J Med*. 1998;339(23):1698-1700.
97. Anasetti C, Logan BR, Lee SJ, et al. Peripheral-blood stem cells versus bone marrow from unrelated donors. *N Engl J Med*. 2012;367(16):1487-1496.
98. Chen YB, Coughlin E, Kennedy KF, et al. Busulfan dose intensity and outcomes in reduced-intensity allogeneic peripheral blood stem cell transplantation for myelodysplastic syndrome or acute myeloid leukemia. *Biol Blood Marrow Transplant*. 2013;19(6):981-987.
99. Luger S RO, Perez WS, et al. . Similar outcomes using myeloablative versus reduced intensity and non-myeloablative allogeneic transplant preparative regimens for AML or MDS: from the Center for International Blood and Marrow Transplant Research [abstract 348]. *Blood*. 2008;112:136.
100. Godwin JE, Kopecky KJ, Head DR, et al. A double-blind placebo-controlled trial of granulocyte colony-stimulating factor in elderly patients with previously untreated acute myeloid leukemia: a Southwest oncology group study (9031). *Blood*. 1998;91(10):3607-3615.
101. Gardner A, Mattiuzzi G, Faderl S, et al. Randomized comparison of cooked and noncooked diets in patients undergoing remission induction therapy for acute myeloid leukemia. *J Clin Oncol*. 2008;26(35):5684-5688.
102. Lo Coco F, Diverio D, Falini B, et al. Genetic diagnosis and molecular monitoring in the management of acute promyelocytic leukemia. *Blood*. 1999;94:12-22.

103. Tallman MS, Kwaan HC. Reassessing the hemostatic disorder associated with acute promyelocytic leukemia. *Blood*. 1992;79(3):543-553.
104. Dyck JA, Warrell RP Jr, Evans RM, Miller WH Jr. Rapid diagnosis of acute promyelocytic leukemia by immunohistochemical localization of PML/RAR-alpha protein. *Blood*. 1995;86(3):862-867.
105. Sanz MA, Lo Coco F, Martin G, et al. Definition of relapse risk and role of nonanthracycline drugs for consolidation in patients with acute promyelocytic leukemia: a joint study of the PETHEMA and GIMEMA cooperative groups. *Blood*. 2000;96(4):1247-1253.
106. Sanz MA, Montesinos P. How we prevent and treat differentiation syndrome in patients with acute promyelocytic leukemia. *Blood*. 2014;123(18):2777-2782.
107. Grimwade D, Jovanovic JV, Hills RK, et al. Prospective minimal residual disease monitoring to predict relapse of acute promyelocytic leukemia and to direct pre-emptive arsenic trioxide therapy. *J Clin Oncol*. 2009;27(22):3650-3658.
108. Sanz MA, Martin G, Gonzalez M, et al. Risk-adapted treatment of acute promyelocytic leukemia with all-trans-retinoic acid and anthracycline monochemotherapy: a multicenter study by the PETHEMA group. *Blood*. 2004;103(4):1237-1243.
109. Lo-Coco F, Avvisati G, Vignetti M, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. *N Engl J Med*. 2013;369(2):111-121.
110. Ravandi F, Estey E, Jones D, et al. Effective treatment of acute promyelocytic leukemia with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab ozogamicin. *J Clin Oncol*. 2009;27(4):504-510.
111. Konopleva M, Cheng SC, Cortes JE, et al. Independent prognostic significance of day 21 cytogenetic findings in newly-diagnosed acute myeloid leukemia or refractory anemia with excess blasts. *Haematologica*. 2003;88(7):733-736.
112. Chen Y, Cortes J, Estrov Z, et al. Persistence of cytogenetic abnormalities at complete remission after induction in patients with acute myeloid leukemia: prognostic significance and the potential role of allogeneic stem-cell transplantation. *J Clin Oncol*. 2011;29(18):2507-2513.
113. van der Velden VH, Hochhaus A, Cazzaniga G, et al. Detection of minimal residual disease in hematologic malignancies by real-time quantitative PCR: principles, approaches, and laboratory aspects. *Leukemia*. 2003;17:1013-1034.
114. Chou WC, Tang JL, Wu SJ, et al. Clinical implications of minimal residual disease monitoring by quantitative polymerase chain reaction in acute myeloid leukemia patients bearing nucleophosmin (NPM1) mutations. *Leukemia*. 2007;21(5):998-1004.
115. Cilloni D, Renneville A, Hermitte F, et al. Real-time quantitative polymerase chain reaction detection of minimal residual disease by standardized WT1 assay to enhance risk stratification in acute myeloid leukemia: a European LeukemiaNet study. *J Clin Oncol*. 2009;27(31):5195-5201.
116. Rubnitz JE, Inaba H, Dahl G, et al. Minimal residual disease-directed therapy for childhood acute myeloid leukaemia: results of the AML02 multicentre trial. *Lancet Oncol*. 2010;11(6):543-552.
117. Maurillo L, Buccisano F, Del Principe MI, et al. Toward optimization of postremission therapy for residual disease-positive patients with acute myeloid leukemia. *J Clin Oncol*. 2008;26(30):4944-4951.

3 Chronic Lymphocytic Leukemia and Associated Disorders

Nitin Jain
Philip Thompson
Carlos Bueso-Ramos
Susan M. O'Brien
William G. Wierda

KEY CONCEPTS

- Chronic lymphocytic leukemia (CLL) is the most common leukemia in the United States and has a median age of diagnosis of 70 years.
- The diagnosis of CLL can be established by peripheral blood flow cytometry in the majority of the patients.
- Treatment of patients with CLL has evolved from chemoimmunotherapy (CIT) to targeted therapies. Most patients are currently treated with oral targeted therapies. Oral targeted therapies include Bruton tyrosine kinase inhibitors, B-cell lymphoma 2 (BCL2) inhibitors, and phosphoinositide 3-kinase (PI3K) inhibitors. Randomized studies have shown improved progression-free survival (PFS) and overall survival (OS) with oral targeted therapies compared with CIT in CLL.
- Targeted therapies approved for first-line CLL include ibrutinib, acalabrutinib +/- obinutuzumab, and venetoclax + obinutuzumab. Ibrutinib and acalabrutinib are intended to be given daily continuously. Venetoclax and obinutuzumab is a time-limited treatment approach of 1-year duration.
- In relapsed CLL, the combination of venetoclax + rituximab has shown improved PFS and OS compared with bendamustine and rituximab. Additional approved therapies for relapsed CLL include ibrutinib and acalabrutinib. The PI3K inhibitors idelalisib and duvelisib are also approved for patients with relapsed CLL.
- Richter transformation remains an unmet medical need. Outcomes with CIT remains dismal with median survival of less than 1 year. There are emerging data with checkpoint inhibition, use of venetoclax-based combination therapies, and chimeric antigen receptor T-cell therapy

Chronic lymphocytic leukemia (CLL) is a clonal hematopoietic disorder involving expansion of CD5-positive B cells. Chemoimmunotherapy (CIT) has been the standard first-line treatment for patients with CLL.[1] In the past several years, novel oral small-molecule therapies have become available, and these have significantly improved the outcomes of patients with CLL.

EPIDEMIOLOGY

CLL is the most common leukemia in the Western Hemisphere, accounting for about 25% of all leukemias in the United States. The estimated number of new CLL cases for 2020 was 21,040, with 4060 deaths. CLL is uncommon in the Asian population and accounts for only 2.5% of all leukemias in Japan. The incidence is age related, with an increase from 5.2 per 100,000 persons older than 50 years to 30.4 per 100,000 persons older than 80 years. Population studies have not identified specific occupational or environmental risk factors for developing CLL.[2] The risk of CLL is not increased in Asians settled in Western countries, indicating that genetic factors play a part in CLL risk.[3] Up to 15% to 20% of patients with CLL have a family member with CLL or a related lymphoproliferative disorder.[4] Genome-wide association studies identified several single nucleotide polymorphisms associated with an increased risk of CLL.[5,6]

BIOLOGY

Surface Antigen Phenotype

CLL is a clonal B-cell lymphoid leukemia. CLL cells morphologically resemble small mature lymphocytes arrested in an intermediate stage of the B-cell

differentiation pathway. The hallmark of CLL cells is that they are monoclonal and express CD5, an antigen commonly found on T cells. CD5-positive B cells can be found in the mantle zone of lymphoid follicles, but they constitute a minor fraction of the B-cell population. CD19, CD20, and CD23 are B-cell markers expressed on CLL cells. Surface immunoglobulin (Ig), FMC7, CD22, CD11c, and CD79b are either weakly expressed or negative in CLL. Based on the antigen expression profile, CLL appears to arise from an "activated" B cell.

Somatic Hypermutation of Immunoglobulin Heavy-Chain Variable Gene

Normal B-cell development involves an antigen-independent phase and an antigen-dependent phase. During the antigen-independent phase, B cells undergo rearrangement of the variable (V), diversity (D), and joining (J) genes in the bone marrow. Somatic mutation of the heavy- and light-chain variable gene occurs after encounter with antigen in the germinal center. Assessment for somatic hypermutation of immunoglobulin heavy-chain variable gene (*IGHV*) defines two subsets of CLL. Approximately 50% of patients with CLL have somatic hypermutation (>2% deviation from germline sequence) of the *IGHV* gene and thus appear to arise from postgerminal B cells, whereas the subset of CLL lacking *IGHV* gene hypermutation (≤2% deviation from germline sequence) appears to arise from naïve B cells.[7,8] The mutation status of CLL cells is fixed, and mutational status is not gained or lost throughout the course of disease. With the use of CIT, patients with unmutated *IGHV* have worse clinical outcomes than those with mutated IGHV.[9–11]

Because historically, sequencing of the *IGHV* gene to identify the mutational status was labor intensive and not universally available, Damle et al[7] studied the correlation of *IGHV* mutation status with CD38 expression as a surrogate prognostic marker for *IGHV* mutation status. A significant association between CD38 expression and unmutated *IGHV* status was noted. Gene expression profiling of mutated versus unmutated *IGHV* CLL cases showed zeta-associated protein 70 (*ZAP-70*) to be the most differentially expressed gene with higher expression in unmutated *IGHV* cases, providing another surrogate for *IGHV* mutation status.[12,13]

Genomic Alterations

Using conventional chromosome banding techniques, cytogenetic abnormalities can be detected in up to 50% of CLL cases. These techniques are hampered by the low mitotic activity of CLL cells; B-cell mitogens may be used to enhance this activity. In addition, metaphases obtained for karyotyping may also arise from normal T cells in the sample, as indicated by sequential immunotyping followed by karyotypic analysis. Fluorescent in situ hybridization (FISH) performed on interphase cells using genomic DNA probes greatly enhanced the ability to detect molecular abnormalities in malignant cells. FISH demonstrated that molecular abnormalities occur in over 80% of CLL cases. Del(13q) is the most common genetic aberration found in CLL by FISH (55%) followed by del(11q) (18%), trisomy 12 (16%), and del(17p) (7%).[14] When divided into five prognostic categories—del(17p), del(11q), trisomy 12, no observed abnormalities, and del(13q) (as the sole abnormality)—the survival times were 32, 79, 114, 111, and 133 months, respectively. Patients with del(11q) tend to have more prominent lymphadenopathy. Patients with del(17p) and del(11q) tend to have more advanced disease and respond poorly to chemotherapy-based regimens.[9] Clonal evolution can occur over time and with treatment; therefore, FISH assessment should be repeated whenever a therapeutic intervention is being considered.

Whole-exome sequencing of CLL cases has identified genes that are recurrently mutated and may contribute to the pathogenesis of the disease.[15,16] Recurrently mutated genes include *TP53*, *NOTCH1*, *SF3B1*, *MYD88*, *XPO1*, and *ATM*. *TP53* mutations are typically associated with del(17p). *ATM* and *SF3B1* mutations are typically associated with del(11q).

CLINICAL FEATURES

At diagnosis, most patients are older than 60 years, with more than 90% being older than 50 years. The diagnosis of CLL is often incidental; a routine blood count may reveal an elevated absolute lymphocyte count (ALC). In symptomatic patients, fatigue and infections may be presenting features. B symptoms (fever, weight loss, night sweat) can also occur but are uncommon at initial diagnosis. Exaggerated skin reactions to insect bites (Wells syndrome) are frequent in those with CLL. Leptomeningeal involvement is rare. Some patients may present with autoimmune hemolytic anemia or immune thrombocytopenia. Physical examination may reveal cervical, axillary, or inguinal lymphadenopathy. Splenomegaly and hepatomegaly are not uncommon.

LABORATORY FEATURES

Laboratory findings invariably show lymphocytosis. CLL cells resemble mature lymphocytes; they have dense chromatin as well as scant cytoplasm and lack nucleoli (Fig. 3–1). Preparation of the blood smear may damage these fragile lymphocytes and produce "smudge" cells. The bone marrow is typically hypercellular for age, and infiltration varies in terms of the percentage of marrow involved as well as in the pattern of involvement, which may be nodular, interstitial, or diffuse (Fig. 3–2). Erythroid, myeloid,

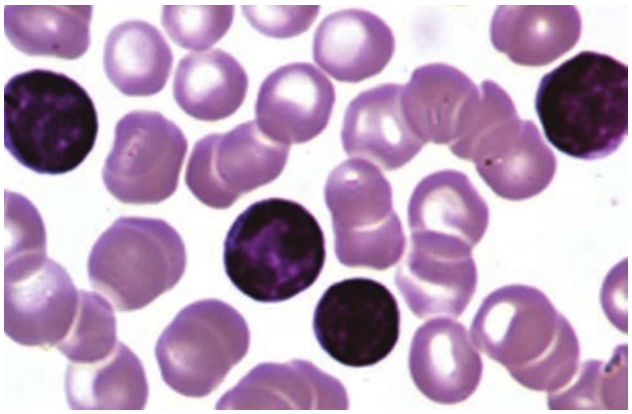


FIGURE 3–1 Chronic lymphocytic leukemia. Peripheral blood smear showing mature-appearing lymphocytes. Note dense chromatin, scant cytoplasm, absence of nucleoli, and smudge cells.

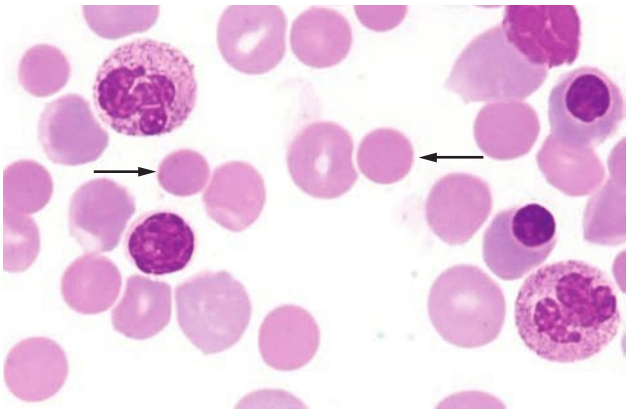
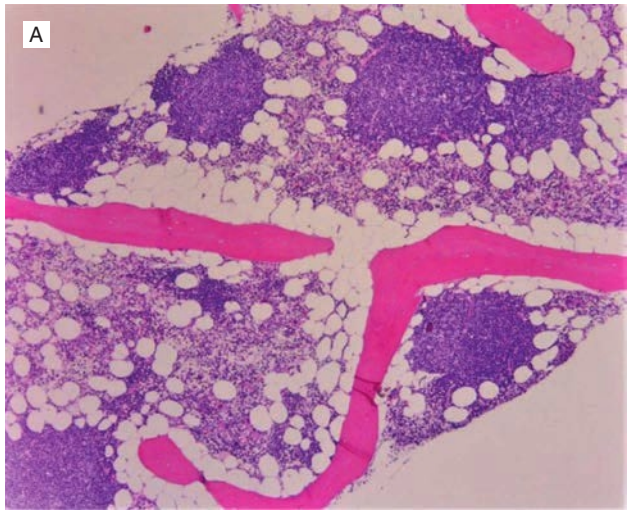


FIGURE 3–3 Immune hemolytic anemia. Presence of microspherocytes (***arrows***) and nucleated red cells indicates immune destruction of red cells. Diagnosis is confirmed by demonstrating the presence of immunoglobulin G (IgG) or complement on red cells.



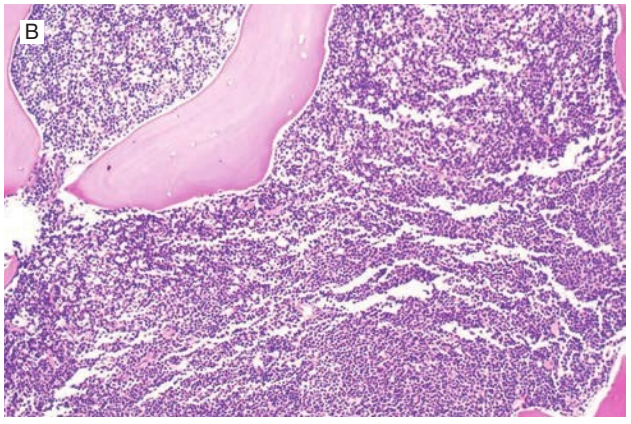


FIGURE 3–2 A and B. Chronic lymphocytic leukemia. Bone marrow biopsies showing nodular, diffuse, and interstitial patterns of involvement.

and megakaryocytic precursors may be normal or decreased. Anemia or thrombocytopenia may result from marrow infiltration or from immune destruction. Findings of microspherocytes in the peripheral blood smear (Fig. 3–3), reticulocytosis, and demonstration of Ig G or complement on red cells support the diagnosis of immune hemolytic anemia. Pure red cell aplasia has been described in 1% to 6% of cases. Patients often develop hypogammaglobulinemia, which can progress in severity with advancing disease. Monoclonal gammopathy may also develop. Other laboratory abnormalities include elevated serum beta-2-microglobulin (B2M); lactate dehydrogenase (LDH) is rarely elevated.

Up to 5% of otherwise normal individuals older than the age 40 years may harbor a population of monoclonal CD5+/CD19+/CD23+ B cells. These individuals are asymptomatic (absence of cytopenia and lymphadenopathy or organomegaly); when the absolute monoclonal lymphocyte count is less than 5000/μL and there is no palpable enlarged lymph node, they are characterized as having monoclonal B lymphocytosis (MBL).[17] It is estimated that the rate of progression from MBL to CLL is 1% to 2% per year.

DIAGNOSIS

In 2018, the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) updated the recommendations on diagnosis and treatment of patients with CLL.[18] The diagnosis of CLL requires 5×10^9 or greater clonal B lymphocytes/L in the peripheral blood, with less than 55% of the cells being prolymphocytes. A monoclonal B-cell count 5×10^9/L or greater was

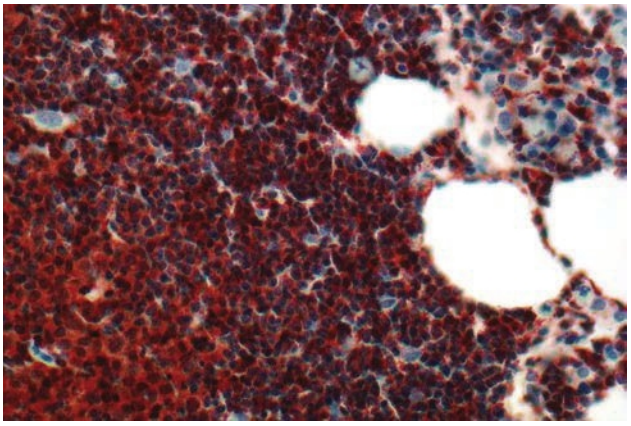


FIGURE 3–4 Zeta-associated protein 70 (ZAP-70) expression in chronic lymphocytic leukemia cells indicates poor prognosis. Immunohistochemistry (*above*) or flow cytometry can be used to detect ZAP-70 expression.

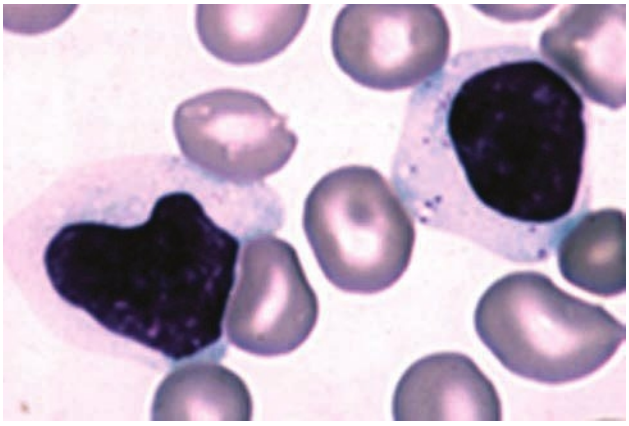
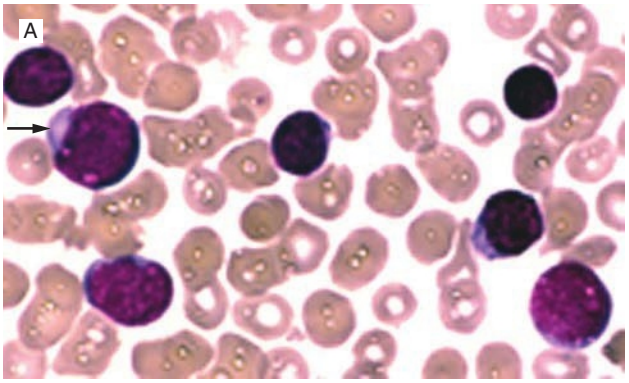


FIGURE 3–6 Large granular lymphocytes with cytoplasmic azurophilic granules.



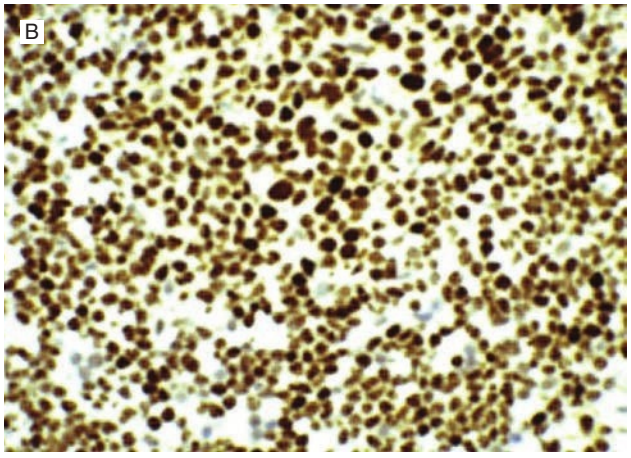


FIGURE 3–5 **A.** Mantle cell lymphoma (MCL) in leukemic phase. MCL cells (*arrow*) are larger than mature lymphocytes (*center*) with speckled chromatin; some show nuclear cleft. **B.** Nuclear cyclin D1 staining in mantle cells.

specified to distinguish CLL from small lymphocytic lymphoma in patients with palpable lymph nodes or splenomegaly. B-lymphocyte clonality should be demonstrated by using flow cytometry, which should also confirm expression of B-cell surface antigens (CD19, CD20, CD23), low-density surface Ig (M or D), CD200, and CD5. ZAP-70 (Fig. 3–4) expression in CLL cells has prognostic implication. Distinguishing CLL from mantle cell lymphoma (MCL); Figs. 3–5A and B) (see "Differential Diagnosis") and large granular leukemia (Fig. 3–6) is of utmost importance.

The presence of more than 55% of prolymphocytes favors a diagnosis of prolymphocytic leukemia (PLL). Prolymphocytes (<55%) can be seen in peripheral blood or bone marrow of patients with CLL (Fig. 3–7).

DIFFERENTIAL DIAGNOSIS

Clinical, morphologic, immunophenotypic, and cytogenetic help to distinguish between CLL and other diseases such as MCL, follicular lymphoma, T-cell PLL (T-PLL), hairy cell leukemia (HCL), marginal zone lymphoma, and Waldenström macroglobulinemia. Table 3–1 summarizes the immunophenotypic features of these disorders. Distinguishing CLL from MCL is important because both can express CD5 (see Fig. 3–5A). Unlike CLL, MCL cells are typically CD23 negative, CD200 negative, and FMC-7 positive and have strong surface Ig staining. Confirmation of MCL can be made by detection of the t(11;14) translocation or positive nuclear cyclin D1 staining (see Fig. 3–5B).

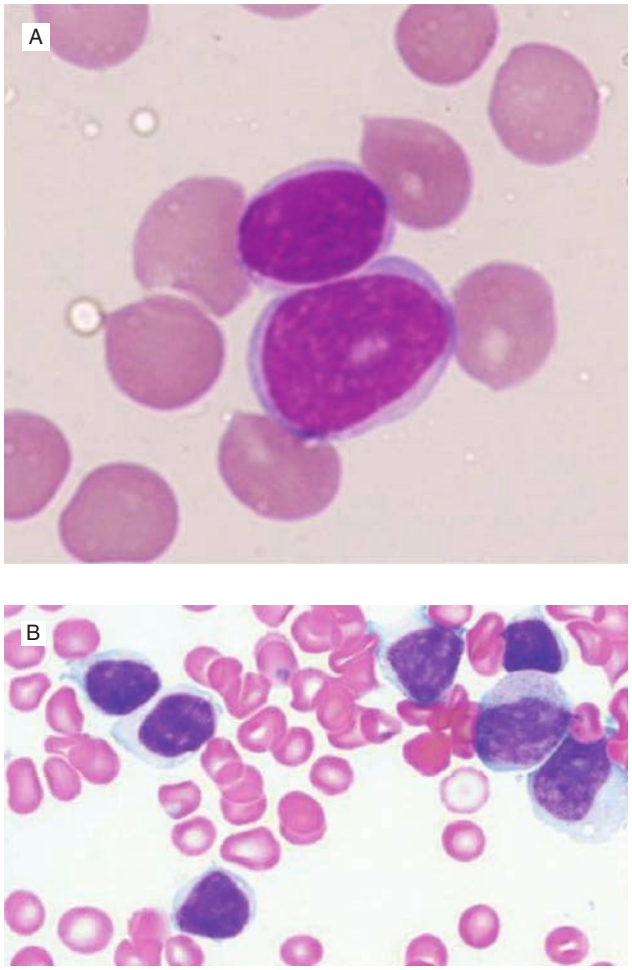


FIGURE 3–7 **A.** High-power view of a prolymphocyte juxtaposed with a mature-appearing lymphocyte. Note larger size, less condensed chromatin, and prominent nucleolus in prolymphocyte. **B.** Bone marrow smear from a 58-year-old man with a 3-year history of untreated chronic lymphocytic leukemia (CLL). There are small lymphocytes and larger prolymphocytoid lymphocytes with abundant lightly basophilic cytoplasm, fine chromatin, and variably prominent nucleoli. **C.** Interphase fluorescent in situ hybridization. Almost all the lymphocytes show deletion of one locus of D13S319 (***white arrow***) (except two lymphocytes on slide 1, left low), and a large subset of CLL cells also showed trisomy 12 (+12). Interestingly, +12 is almost only seen in prolymphocytoid lymphocytes. The small lymphocytes with clumped chromatin and scant cytoplasm usually do not show +12.

TABLE 3–1 Immunophenotypic Analysis in Chronic B-Cell Disorders

Disease	sIg	CD5	CD10	CD20	CD22	CD23	CD79B	CD103	FMC7
CLL	Weak	++	–	+	–/+	++	–/+	–	–/+
B-PLL	Strong	–/+	–/+	++	+	–/+	++	–	++
HCL	Strong	–	–	++	++	–	+	+	++
SLVL	Strong	–/+	–	++	++	–/+	++	–	++
FL	Strong	–/+	++	++	++	–/+	++	–	++
MCL	Strong	++	–	++	++	–	++	–	++

B-PLL, prolymphocytic leukemia; CLL, chronic lymphocytic leukemia; FL, follicular lymphoma; HCL, hairy cell leukemia; MCL, mantle cell lymphoma; sIg, surface immunoglobulin; SLVL, splenic lymphoma with villous lymphocytes.

STAGING

Staging systems for CLL include Rai and Binet staging (Table 3–2).[19,20] The original Rai classification defined five stages from 0 to IV based on the presence or absence of lymphocytosis, lymphadenopathy, organomegaly, and cytopenia; this has been modified to three stages by defining Rai stage 0 as low risk, stages I and II as intermediate risk, and stages III and IV as high risk. Similarly, Binet stages A, B, and C are based on the number of lymph nodal areas involved and the presence or absence of cytopenia. The diagnostic workup that is undertaken in patients with CLL at initial presentation at The University of Texas MD Anderson Cancer Center (MDACC) is listed in Table 3–3.

TABLE 3–2 Staging of Chronic Lymphocytic Leukemia

Rai Stage	Modified Rai Stage	Description	Binet Stage	Description
0	Low risk	Lymphocytosis only	A	Hemoglobin ≥10 g/dL, platelets ≥100 × 10^9/L, and <3 enlarged lymphoid-bearing areas
1	Intermediate risk	Lymphocytosis and lymphadenopathy	B	Hemoglobin ≥10 g/dL, platelets ≥100 × 10^9/L, and ≥3 enlarged lymphoid-bearing areas
2	Intermediate risk	Lymphocytosis and splenomegaly and/or hepatomegaly with/without lymphadenopathy		
3	High risk	Lymphocytosis and anemia (hemoglobin <11 g/dL)	C	Hemoglobin <10 g/dL or platelets <100 × 10^9/L (irrespective of number of lymphoid-bearing areas)
4	High risk	Lymphocytosis and thrombocytopenia (platelets <100 × 10^9/L		

TABLE 3–3 Initial Evaluation of Patients with Chronic Lymphocytic Leukemia at MD Anderson Cancer Center

History and physical (close attention to lymph node areas, liver and spleen size)
Constitutional symptoms (fever, chills, weight loss, night sweats)
Assessment of performance status
CBC, electrolytes, BUN, creatinine, liver function tests, LDH, quantitative immunoglobulins, β_2-microglobulin
Examination of peripheral blood smear
Bone marrow aspiration and biopsy (in patients with cytopenias or those in need of treatment)
Immunophenotyping of peripheral blood or bone marrow lymphocytes to establish diagnosis
Prognostic marker assessment • Interphase FISH (assessment of deletion 17p, deletion 11q, trisomy 12, deletion 13) • *IGHV* mutation status • *TP53* sequencing • Flow cytometry for CD38 • Immunostaining or flow cytometry for ZAP-70
Imaging studies (only if presenting with significant adenopathy or needed treatment); many clinical trials are now incorporating CT scans as per new guidelines, but these are not standard of care outside of a clinical trial. • CT scan or PET scan (PET scan preferred if there is a suspicion of Richter transformation)

BUN, blood urea nitrogen; CBC, complete blood count; CT, computed tomography; FISH, fluorescent in situ hybridization; LDH, lactate dehydrogenase; MDACC, The University of Texas MD Anderson Cancer Center; PET, positron emission tomography; ZAP-70, zeta-associated protein 70.

PROGNOSIS

In the era of CIT, several factors were associated with poor prognosis. These factors included advanced Rai or Binet stage, male gender, older age, lymphocyte doubling time less than 12 months, presence of del(17p) or del(11q), complex karyotype, unmutated IGHV, higher CD38 expression, higher Zap-70 expression, elevated b2-microglobulin, elevated serum thymidine kinase, diffuse marrow involvement, and gene mutations (*TP53, BIRC3, NOTCH1, SF3B1*).[21–24] The CLL-International Prognostic Index (CLL-IPI) evaluated 3472 patients with treatment-naïve CLL and assessed for several demographic and CLL disease-related factors; five prognostic markers for OS were identified, which included *TP53* aberration, *IGHV* status, B2M, clinical stage, and age older than 65 years of age.[25] Based on these five markers, four separate prognostic groups were identified with 5-year overall survival (OS) ranging from 93.2% to 23.3%. It is important to note that the CLL-IPI was developed in patients who received CIT. Given improved outcomes with targeted therapies and overall decline in the use of chemotherapy for patients with CLL, the CLL-IPI will need to be reevaluated with the data from patients treated with targeted therapies. More recently, an international prognostic score to predict time to first treatment (TTFT) in patients with CLL with early, asymptomatic disease (International Prognostic Score for Early-stage CLL [IPS-E]) was developed.[26] A total of 4933 patients were analyzed. Three variables independently correlated with TTFT: unmutated IGHV, ALC greater than 15×10^9/L, and presence of palpable lymph nodes. Each of these variables was given a risk score of 1; patients were categorized into low risk (score of 0), intermediate risk (score of 1), and high risk (score of 2 or 3). The 5-year cumulative risks for treatment were 8.4%, 28.4%, and 61.2% among low-risk, intermediate-risk, and high-risk patients, respectively.

TREATMENT

Indications for Treatment

Unlike most leukemias, an unusual feature of CLL is that making the diagnosis is not necessarily an indication to initiate treatment. Early treatment of asymptomatic CLL with chemotherapy was not shown to prolong survival. In the current era of more effective CIT regimens and targeted therapies, this question is currently being evaluated in clinical trials. The 2018 IWCLL criteria for treatment of CLL are summarized in Table 3–4.

Up until recently, CIT was the standard first-line treatment for patients with CLL. With the significant advances in the field of CLL, targeted therapies have now become standard treatment for most patients with CLL.

Combination CIT such as fludarabine + cyclophosphamide + rituximab (FCR), bendamustine + rituximab (BR), and chlorambucil + CD20 monoclonal antibody (mAB) combination were the standard first-line treatments for patients with CLL.[1,27] In the original FCR study conducted at MDACC, a high overall response rate (ORR) of 95% was noted with a complete remission (CR) rate of 72%.[28] In the long-term follow-up of this trial, a 10-year progression-free survival (PFS) of about 55% was noted in patients with mutated IGHV.[11] The GCLLSG group conducted a phase III trial to evaluate the efficacy of FCR versus FC in first-line treatment of patients with CLL (CLL8 trial).[9] A total of 817 patients were randomized to receive six courses of either FC (409 patients) or

TABLE 3–4 Indications for Treatment in Chronic Lymphocytic Leukemia from the International Workshop on Chronic Lymphocytic Leukemia

Active disease should be confirmed before initiating treatment.
1. Evidence of progressive marrow failure as manifest by the development or worsening of anemia and/or thrombocytopenia
2. Massive (ie, >6 cm below the left costal margin) or progressive or symptomatic splenomegaly
3. Massive nodes (ie, at least 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy
4. Progressive lymphocytosis with an increase of ≥50% over a 2-month period, lymphocyte doubling time of <6 months[a]
5. Autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroid therapy
6. Symptomatic or functional extranodal involvement (eg, skin, kidney, lung, spine)
7. Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs: a. Unintentional weight loss ≥10% within the previous 6 months b. Significant fatigue (ie, ECOG PS 2 or worse; cannot work or unable to perform usual activities) c. Fevers ≥100.5°F or 38.0°C for ≥2 weeks without evidence of infection d. Night sweats for ≥1 month without evidence of infection

<TFN>[a]In patients with a lymphocyte count of $<30 \times 10^9$/L, lymphocyte doubling time should not be used as a single parameter to define treatment indication. Factors contributing to lymphocytosis or lymphadenopathy other than chronic lymphocytic leukemia (ie, infections) should be excluded.
ECOG PS, Eastern Cooperative Oncology Group performance status.

FCR (408 patients). They reported a significantly higher CR rate (44% *vs* 22%; *P* <.0001), ORR (90% *vs* 80%; *P* <.0001), PFS (median PFS, 52 *vs* 33 months; *P* <.0001), and OS (3-year OS, 87% *vs* 83%; *P* =.012) with the addition of rituximab. This trial established the role of anti-CD20 mAB in the first-line therapy of patients with CLL. Bendamustine in combination with rituximab has also been evaluated as first-line treatment for patients with CLL. Fischer et al[29] reported on the outcomes of 117 patients with treatment-naïve CLL who received BR. The ORR was 88% with a CR rate of 23%. The median PFS was 34 months. Notably, one third of the patients had a creatinine clearance of 70 mL/min or less (these patients are typically excluded from the FCR trials), and these patients did equally as well as patients with a creatinine clearance greater than 70 mL/min.

The GCLLSG then conducted a randomized phase III study of FCR versus BR as first-line therapy for patients with CLL (CLL10 trial).[10,30] This trial included patients with CLL with good physical status (Cumulative Illness Rating Scale [CIRS] score ≤6 and creatinine clearance ≥70 mL/min). A total of 282 patients received FCR, and 279 patients received BR. The FCR arm had a significantly higher CR/CR with incomplete count recovery (CRi) rate (39.7 *vs* 30.8; *P* =.03) and significantly improved PFS (median PFS, 55.2 *vs* 41.7 months; *P* <.001). OS was not different between the two groups. Not unexpectedly, patients on the FCR arm experienced more grade 3 or 4 neutropenia (84.2% *vs* 59%; *P* <.001), more thrombocytopenia (21.5% *vs* 14.4%; *P* =.03), and increased risk of grade 3 or 4 infections (39.1% *vs* 26.8%; *P* <.001). However, the treatment-related mortality rate was similar in the two arms. This trial established FCR as a standard first-line CIT regimen for patients with CLL who are 65 years old or younger. Several studies have been conducted with the intent of modifying the FCR regimen by dose-intensifying rituximab,[31] adding mitoxantrone,[32] adding alemtuzumab,[33] adding granulocyte-macrophage colony-stimulating factor,[34] or using lower doses of FCR (FCR-Lite),[35] but these studies have not shown superior results compared with those seen with the standard FCR regimen.

Obinutuzumab is a humanized type II CD20 mAb with a glycoengineered Fc domain that leads to enhanced antibody-dependent cellular cytotoxicity compared with that seen with rituximab. This type II CD20 mAb is more effective at direct induction of CLL cell apoptosis, which leads to more effective B-cell depletion than rituximab. In the GCLLSG CLL11 trial, previously untreated patients with CLL with coexisting conditions (CIRS score >6 and/or creatinine clearance of 30–69 mL/min) were randomly assigned to receive chlorambucil monotherapy, chlorambucil plus rituximab, or chlorambucil plus obinutuzumab.[36,37] A total of 781 patients were enrolled. The median age was 73 years. Treatment with obinutuzumab–chlorambucil, compared to rituximab–chlorambucil, resulted in a higher ORR of 78.4% (CR 20.7% + partial remission (PR) 57.7%) versus 65.1% (CR 7% + PR 58.1%; *P* <.001). PFS was significantly longer with obinutuzumab–chlorambucil compared with that seen with rituximab–chlorambucil (median PFS, 29.2 *vs* 15.4 months; *P* <.001). Both antibody-containing regimens produced better outcomes than that seen with single-agent chlorambucil. This trial established the combination of chlorambucil with a CD20 mAb as a standard of care for first-line therapy in older patients with CLL who have comorbidities.

B-Cell Signaling Pathway Inhibitors

CLL cells receive growth and survival signals from the microenvironment of the bone marrow, lymph nodes, and spleen.[38] Bruton tyrosine kinase (BTK) is a central molecule in signal transduction for the B-cell receptor (BCR) as well as CD19, CD38, CD40, CXCR4 chemokine receptor, tumor necrosis factor receptors, and Toll-like receptors (TLRs). Other important signal transduction molecules include phosphoinositide 3-kinase (PI3K) and Syk.

Bruton Tyrosine Kinase Inhibitors

BTK is a nonreceptor tyrosine kinase of the Tec kinase family that plays a crucial role in BCR signaling. Ibrutinib is an oral, selective, and irreversible inhibitor of BTK. It forms a covalent bond with the cysteine-481 of BTK. Byrd et al[39] reported the outcomes of 85 patients with relapsed or refractory CLL who received ibrutinib monotherapy. This was a heavily pretreated population with a median of four prior therapies. The median age was 66 years (range, 37–82 years). Thirty-three percent of the patients had del(17p). The ORR was 90%, with 7% CR, 65% PR, and 9% PR with lymphocytosis (PR-L). The estimated PFS at 7 years was 34%.[40] In the treatment-naïve cohort of the same trial, 31 patients (65 years or older) with CLL received ibrutinib monotherapy. The estimated 7-year PFS rate was 83%. In a randomized phase III trial (RESONATE trial), patients with relapsed or refractory CLL were randomized to ibrutinib or ofatumumab.[41] The ibrutinib arm had a much higher ORR and superior PFS and OS compared with the ofatumumab arm. In a randomized phase III trial (RESONATE-2), 269 older patients with previously untreated CLL were randomized to ibrutinib versus chlorambucil.[42] The PFS was significantly longer in the ibrutinib arm (5-year PFS 70% vs 12% for chlorambucil; *P* <.001).[43] There was also an OS benefit for the ibrutinib arm (5-year survival rate, 83% vs 68% for chlorambucil arm; *P* <.001) despite crossover that allowed 57% of the patients receiving chlorambucil to receive ibrutinib at the time of disease progression. This trial led to the approval of ibrutinib for previously untreated patients with CLL. Common

adverse events with ibrutinib include diarrhea, arthralgia, hypertension, and atrial fibrillation.

It is important to note that most patients will develop lymphocytosis upon initiating ibrutinib. This is expected with all BCR inhibitors, and it generally resolves over the course of 6 to 9 months with continued treatment. Development of lymphocytosis is not detrimental to the long-term clinical outcomes The mechanism of resistance to ibrutinib include development of a mutation of *BTK* at cysteine-481 (C481S) and gain-of-function mutations in *PLCγ2*, a signaling molecule downstream of BTK.[44]

More recently, the ECOG1912 trial evaluated the activity of ibrutinib + rituximab versus FCR. A total of 519 patients (age 70 years or younger) with previously untreated CLL were randomized.[45] The PFS was significantly better with ibrutinib + rituximab than that seen with FCR (3-year PFS, 89.4% vs 72.9% P <.001). In a subgroup analysis, the PFS benefit of ibrutinib + rituximab over FCR was limited to IGHV-unmutated patients. The OS was also significantly improved with ibrutinib + rituximab versus FCR (3-year OS, 98.8% vs 91.5%; P <.001). As expected, there was more myelosuppression and infections in the FCR arm, and there were more atrial fibrillation and hypertension noted with ibrutinib + rituximab. Like the ECOG1912 trial, the investigators for the ALLIANCE group designed a first-line treatment trial for older patients with CLL. The older patients were randomized to BR versus ibrutinib + rituximab versus ibrutinib.[46] The PFS was significantly improved in the two ibrutinib-containing arms compared with that seen in the BR arm (2-year PFS, 74% for the BR arm vs 88% for ibrutinib + rituximab vs 87% for ibrutinib monotherapy; P <.001 for the BR vs ibrutinib arms). Notably, there was no difference in the PFS for the two ibrutinib arms, indicating no additional benefit with the addition of rituximab to ibrutinib. There was no difference in OS among the three treatment arms.

Acalabrutinib is a second generation BTK inhibitor currently approved for both first-line and relapsed CLL.[47] In the ASCEND phase III trial, patients with relapsed or refractory CLL were randomized to receive acalabrutinib monotherapy versus investigator choice therapy (idelalisib + rituximab or BR). Patients had received a median of two prior therapies.[48] After a median follow-up period of 16.1 months, the median PFS was significantly longer with acalabrutinib monotherapy (PFS not reached) compared with investigator's choice (16.5 months; P <.0001). In the ELEVATE-TN phase III trial, patients with previously untreated CLL who were 65 years or older or 18 years or older with either a CIRS score greater than6 or a creatinine clearance of 30 to 69 mL/min were enrolled. Patients were randomized to acalabrutinib monotherapy versus acalabrutinib + obinutuzumab versus chlorambucil + obinutuzumab. The estimated PFSs at 2 years were 93% with acalabrutinib + obinutuzumab, 87% with acalabrutinib monotherapy, and 47% with chlorambucil + obinutuzumab. These trials (ASCEND and ELEVATE-TN) led to the approval of acalabrutinib in both relapsed or refractory and frontline CLL. There is an ongoing head-to-head phase III trial of ibrutinib versus acalabrutinib in patients with relapsed or refractory CLL with either a del(17p) or del(11q).

BCL-2 Inhibitor

CLL cells express high levels of antiapoptotic proteins of the Bcl-2 family, rendering them long-lived and resistant to senescence and death. Navitoclax (ABT-263) is an orally administered small-molecule inhibitor of Bcl-2, Bcl-w, and Bcl-xL. A phase I/II trial of orally administered navitoclax reported antitumor activity in patients with CLL; however, the dose-limiting toxicity was thrombocytopenia.[49] Thrombocytopenia was secondary to the accelerated platelet senescence from inhibition of Bcl-xL in the platelets. Venetoclax (ABT-199) was designed as a molecule with greater affinity for Bcl-2 and reduced affinity for Bcl-xL.[50] Unlike BTK inhibitors, the treatment with venetoclax, especially in combination with CD20 mABs can lead to measurable residual disease (MRD)–negative remissions. Venetoclax was studied in a phase III study in relapsed or refractory CLL. In this study (MURANO trial), 389 patients with relapsed or refractory CLL were randomized to receive venetoclax + rituximab (2 years of venetoclax + 6 months of rituximab) versus six cycles of BR.[51] The 4-year PFS rate was higher with venetoclax + rituximab versus BR (57.3% vs 4.6% (P <.0001).[52] Similarly, 4-year OS was in favor of venetoclax + rituximab arm (85.3% vs 66.8%; P <.0001). In a landmark analysis, MRD at the end of 2 years of venetoclax treatment correlated with PFS. Venetoclax was investigated in a phase III trial in first-line CLL (CLL14 trial).[53] Eligible patients were aged 18 years or older with coexisting conditions (CIRS >6 or creatinine clearance of 30–69 mL/min). Patients received venetoclax + obinutuzumab or chlorambucil + obinutuzumab. Venetoclax and chlorambucil were given for 1 year; obinutuzumab was given for 6 months in both arms. A total of 432 patients were enrolled. At a median follow-up period of 39·6 months, patients in the venetoclax + obinutuzumab arm had a significantly longer PFS than that seen with chlorambucil + obinutuzumab (P<.0001).[54] The median PFS was not reached for the venetoclax + obinutuzumab arm and was 35·6 months for the chlorambucil + obinutuzumab arm. The OS were similar in the two arms.

Phosphoinositide 3-Kinase Inhibitors

PI3K-δ is a critical kinase for activation, proliferation, and survival of B cells and is hyperactive in many B-cell malignancies, including CLL. Idelalisib is a potent, selective, reversible inhibitor of PI3K-δ. A phase I trial of idelalisib was conducted in relapsed and refractory patients with CLL.[55] A total of 54 patients were enrolled with a

median of five prior therapies. The median PFS was 15.8 months. A phase III clinical trial evaluated the activity of idelalisib + rituximab versus rituximab + placebo in patients with relapsed or refractory CLL in whom rituximab monotherapy would be considered appropriate.[56,57] A total of 220 patients were enrolled. This trial demonstrated superior efficacy for combined idelalisib and rituximab over that seen with rituximab and placebo, with a hazard ratio (HR) for PFS of 0.15 (P <.001) and HR for OS of 0.28 (P = .02). Pneumonitis was seen in 4% of the patients treated on the idelalisib + rituximab arm. Because of immune-mediated side effects and risk of infectious complications, the development of idelalisib in first-line CLL has been halted.[58] Duvelisib is a PI3K-δ and -γ inhibitor and is also approved for relapsed CLL based on the results of the DUO trial.[59]

Chimeric Antigen Receptor T-Cell Therapy

Please refer to Chapter 16 for a detailed outline of chimeric antigen receptor T-cell (CAR T) biology, general principles of use, toxicities, and their management. Briefly, CARs are engineered immune receptors introduced ex vivo into T cells, usually autologous, that redirect these cells to react against CLL cells. The CAR is a recombinant protein composed of an antigen-binding domain derived from single-chain Ig variable genes and intracellular signaling domains derived from CD3ζ and costimulatory domains derived from CD28 and/or CD137. The transduced T cells are infused into the patient, where they bind to the target antigen and induce T-cell activation and proliferation, cytokine production, and killing of cells expressing the target antigen. CD19 is the most common target of the current CAR T-cell trials, although other targets are being explored as well (Table 3–5). CAR T products targeting CD19 are approved by the Food and Administration for the treatment of patients younger than 26 years of age with refractory pre-B-acute lymphoblastic leukemia (ALL) or second or greater relapse and for the treatment of diffuse large B-cell lymphoma (DLBCL) in patients who have received two or more prior therapies. In the pivotal study of tisagenlecleucel in pre-B ALL, the CR rate was 83%, and the event-free survival (EFS) was 50% at 1 year.[60] In DLBCL, the ORR with axicabtagene ciloleucel was 82% (54% CR), and 42% of patients remained in remission at 15.4 months.[61] In contrast, response rates in the CLL studies have generally been lower (ORR, 57%–71%; CR, 21%–28%).[62,63] Nevertheless, the treatment appears to have curative potential, as indicated by the fact that two of the original patients treated at the University of Pennsylvania[62] remain in remission 7 years after therapy.[64]

The underlying reasons for poorer responses in patients with CLL compared with those with ALL and DLBCL are not completely clear. In particular, the incidence of relapse because of loss of the CD19 target appears lower than in ALL and DLBCL.[65] One study, from the University of Pennsylvania,[66] demonstrated that the CAR T-cell phenotype in the apheresis product, before infusion, was strongly associated with response. Specifically, higher numbers of memory T cells and lower levels of immune checkpoint molecule expression and markers of T-cell exhaustion were associated with a higher likelihood of CR. This suggests that a patient's T-cell "fitness" may be important in determining the likelihood of responding to treatment with autologous CAR T cells. Attempts are being made to use novel combination

TABLE 3–5 Results of Some Selected Studies of Autologous Chimeric Antigen Receptor T-Cell Therapy Targeting CD19 in Chronic Lymphocytic Leukemia

	Patients (*n*)	Co-stimulation	Treatment Combination	Responses
Porter et al[62] (2015)	14	4-1BB	None	ORR, 57% CR, 28% MRD negative, 28%
Turtle et al[63] (2017)	24 (5 Richter transformation)	4-1BB	None	ORR, 71% CRR, 21% MRD negative, 58%
Gauthier et al[67] (2018)	17	4-1BB	Ibrutinib	ORR, 88% CRR, 83% (evaluable patients) MRD negative, 75%
Gill et al[68] (2018)	19	4-1BB	Ibrutinib	ORR, 71% CRR, 43% MRD negative, 78%
Siddiqi et al[105] (2019)	23	4-1BB	None	ORR, 82% CR, 46% MRD negative, 60%

CR, complete remission; MRD, Measurable residual disease; ORR, overall response rate.

strategies to enhance the response rates to CAR T-cell therapy in patients with CLL. Single-center experiences from the group at the Fred Hutchison Cancer Research Center and The University of Pennsylvania suggest that the combination of ibrutinib with CAR T may enhance response rates while simultaneously reducing the likelihood of severe cytokine release syndrome.[67,68] The combination of lisocabtagene maraleucel with ibrutinib is being explored in the ongoing phase 2, multicenter study TRANSCEND-CLL-04 (NCT03331198).

Stem Cell Transplantation

Because CLL is a disease of older adults, reduced-intensity conditioning (RIC) allogeneic stem cell transplant (allo-SCT) is the most common type of transplant offered to patients with CLL. RIC allo-SCT in CLL leads to 5-year EFS and OS rates of 35% to 45% and 50% to 60%, respectively.[69] Khouri et al[70] reviewed outcomes of 86 patients with CLL who underwent RIC allo-SCT at MDACC. The median age was 58 years. Eighty-three of the 86 patients experienced donor cell engraftment. Overall, the estimated 5-year PFS and OS rates were 36% and 51%, respectively. Notably, immune manipulation by withdrawal of immunosuppression or donor lymphocyte infusions enhanced clinical responses, indicating that CLL is a disease sensitive to immune manipulation. With the introduction of novel targeted therapies, such as BTK inhibitors and venetoclax, the numbers of allo-SCT procedures being performed for CLL are falling dramatically.[71] Nevertheless, allo-SCT will likely continue to remain an important strategy for selected group of patients such as those with high-risk CLL (del(17p) or *TP53* mutation) who are relapsed or refractory to novel agents. The European Research Initiative on CLL and European Society of Bone Marrow Transplant released a paper outlining a proposed risk assessment framework for CLL that includes cytogenetic and molecular features, as well as refractoriness to CIT, targeted agents, or both.[72] This framework assigns patients to high-risk I category if they have failed CIT *and* have a *TP53* abnormality (deletion of chromosome 17p or *TP53* mutation). High-risk category II comprises patients relapsed after CIT *and* a targeted agent, regardless of molecular features. The framework recommends consideration of cellular immunotherapy (CAR T or allo-SCT) for patients in high risk I or high risk II categories. In general, patients in the high risk II category should have a lower threshold for proceeding to allo-SCT. However, this remains a complex area and numerous factors need to be carefully considered when determining whether to proceed with cellular immunotherapy in an individual patient. When assessing patients in high risk I or II categories, the physician must weigh the risk of treatment-related morbidity and mortality from cellular immunotherapy (particularly allo-SCT) against the risk of unsalvageable CLL relapse or Richter transformation (Table 3–6). Complicating this decision is the lack of high-quality prospective data to guide the decision.

Patient Stratification for First-Line Treatment

Based on age, comorbidities, and CLL FISH, *TP53* mutation status, and *IGHV* mutation status, patients can be categorized into several groups:

- **Young patients (typically 65 years or younger) without major comorbidities and *IGHV*-mutated, no del(17p), and no *TP53* mutation:** For these

TABLE 3–6 Factors in Consideration for Cellular Therapy versus Targeted Therapy

Factors in Favor of Cellular Immunotherapy		Factors in Favor of Continuing the Targeted Agent	
Clinical Features (Predictive of Lower TRM)	Disease Features (Predictive of Higher Likelihood of Relapse in the Absence of Cellular Immunotherapy)	Clinical Features (Predictive of Higher TRM)	Disease Features (Predictive of Lower Likelihood of Relapse in the Absence of Cellular Immunotherapy)
Younger age	Refractory to multiple prior therapies	Older age	Received fewer lines of prior therapy
Few comorbid medical conditions	Complex karyotype	Frail, many comorbid medical conditions	Lack of complex karyotype
Well-matched donor (for allo-SCT)		Deep remission (eg, CR with U-MRD)	Deep remission (eg, CR with U-MRD)[a]
Access to CAR T-cell study		No well-matched donor or access to CAR T-cell study	

[a]Although patients who achieve deep remission with targeted therapy (eg, venetoclax + rituximab) are at lower risk of disease progression, these patients may also have better post-transplant outcomes than patients with significant disease burden.
Allo-SCT, allogenic stem cell transplant; CAR T, chimeric antigen receptor T-cell; CR, complete remission; TRM, Transplant-related mortality; U-MRD, undetectable measurable residual disease.

patients, treatment with FCR is appropriate given the very long-term benefit seen in about half of these patients after first-line FCR. Additionally, in the E1912 trial, there was no difference in PFS for FCR versus ibrutinib + rituximab for the *IGHV*-mutated group, at least with the median 4 years of follow-up. If a nonchemotherapy approach is desired, treatment with ibrutinib, acalabrutinib (+/- obinutuzumab) or the combination of venetoclax + obinutuzumab could be considered. Ibrutinib and acalabrutinib are given indefinitely. Venetoclax + obinutuzumab is a lime-limited therapy of 1 year.

- **Older adults or young patients with comorbidities or young patients with *IGHV*-unmutated (no del(17p), no *TP53*-mutation):** For these patients, a nonchemotherapy approach is preferred. Treatment with ibrutinib, acalabrutinib (+/-obinutuzumab), or the combination of venetoclax + obinutuzumab is appropriate.
- **Patients with del(17p) or *TP53*-mutation:** Treatment with a BTK inhibitor such as ibrutinib or acalabrutinib (+/- obinutuzumab) is preferred. Chemotherapy should not be used for these patients.

Supportive Care

Patients with CLL can have a host of complications ranging from immune cytopenias to infectious issues.

Autoimmune Complications of Chronic Lymphocytic Leukemia

Autoimmune hemolytic anemia (AIHA), autoimmune thrombocytopenia (ITP), and pure red cell aplasia (PRCA) develop in some patients with CLL. The incidence of AIHA is 4% to 11% and is 2% to 3% for ITP.[73] PRCA and autoimmune neutropenia (AIN) are both rare (<1%).[74] The pathogenesis is complex. The autoantibodies in autoimmune cytopenia (AIC) associated with CLL are typically polyclonal and usually IgG, indicating that they are not produced by the leukemic clone. Patients with unmutated *IGHV* and high-risk cytogenetics, as well as stereotyped B-cell receptor subsets 3 and 7, are more likely to develop AIHA or ITP.[75,76] Therapeutic agents, particularly purine analog monotherapy, may trigger AIC, possibly because of an imbalance in the ratio of T-regulatory cells to T helper type 17 cells.[77] The risk of treatment-emergent AIC during treatment with targeted agents appears lower. Prednisone is the usual treatment for patients with AIHA and ITP, with a high likelihood of response. However, the majority of patients relapse when treatment is stopped. Intravenous immunoglobulin (IVIG) produces response in 40% of patients, but these responses tend to be transient. CD20 mAbs, particularly rituximab, have also been used to treat patients with autoimmune complications of CLL either as monotherapy or in combination with cyclophosphamide and dexamethasone (RCD regimen).[78] Cyclosporine is another option for treatment of AIC and can produce responses even in patients with steroid-refractory immune cytopenias.[79] The thrombopoietin mimetic eltrombopag showed high response rates with good response durability.[80,81] Splenectomy is reserved for refractory cases.

The role of novel, targeted agents in the treatment of CLL-associated AIC is ill-defined, given patients with steroid-dependent or -refractory AIC were systematically excluded from clinical trials of these agents. However, a recent case series from the Mayo Clinic demonstrated improvement in cytopenias and ability to wean or discontinue immunosuppression in the majority of patients with CLL who had AIC at the time of initiation of ibrutinib.[82] An ongoing clinical trial (NCT03827603) is assessing ibrutinib plus rituximab treatment in the management of patients with steroid-refractory AIHA.

Hypogammaglobulinemia

Hypogammaglobulinemia is a frequent complication of CLL. The most common cause of morbidity in patients with CLL is infection, in part caused by hypogammaglobulinemia. A randomized study evaluated the use of IVIG versus placebo in patients with CLL showed significant reduction in bacterial infections but no difference in the number of life-threatening infections or nonbacterial infections.[83] Replacement therapy with IVIG is indicated for patients with hypogammaglobulinemia and repeated sinobronchial infections.

TRANSFORMATION

Richter Syndrome

The term *Richter syndrome (RS)* refers to the development of aggressive large-cell lymphoma during the course of CLL. Rarely, disease transformation to Hodgkin lymphoma is seen. RS is noted in approximately 5% of patients with CLL. RS is usually associated with worsening systemic symptoms, including B symptoms, elevated LDH, rapid tumor growth, or extranodal involvement. Diagnosis requires tissue biopsy. Positron emission tomography scans help identify sites to direct tissue biopsy, and every attempt should be made to biopsy the site with the maximum SUV.[84] In 80% of patients, the DLBCL is clonally related to the original CLL, which is a marker of poor prognosis (median survival time, ~1 year). In the other 20% of patients, the DLBCL is clonally

unrelated to the original CLL, possibly representing a new neoplasm and the prognosis is similar to that of de novo DLBCL (median survival time, ~5 years). Risk factors associated with development of RS in a patient with CLL include lymph node size greater than 3 cm, number of prior therapies, advanced Rai stage (III or IV), del(17p), del(11q), unmutated *IGHV* gene, short telomere length (<5000 bp), stereotyped B-cell receptors, and expression of CD38, CD49d, or ZAP-70.[85] The presence of a *NOTCH1* mutation is also associated with an increased risk of RS. *TP53* mutation is commonly acquired at the time of CLL transformation and is the most important negative prognostic feature, other than the clonal relationship to the underlying CLL.[85] Other common genetic abnormalities seen in patients with RS include activation of *C-MYC* and inactivation of *CDKN2A,* indicating possible cell cycle deregulation, and *NOTCH1* mutations (commonly in conjunction with trisomy 12).[86,87] The traditional treatment strategy has been intensive CIT such as OFAR (oxaliplatin, fludarabine, cytarabine, and rituximab), hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), and R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, = Oncovin, and prednisone).[88] No direct comparative data exist to guide treatment choice, and this should be individualized according to institutional experience and patient fitness. Allo-SCT remains the only potentially curative option for patients with RS. Two promising approaches to improve outcomes for this group of patients have recently been developed: the first is the use of programmed death 1 inhibitors, with or without ibrutinib. Pembrolizumab monotherapy achieved a 44% ORR (11% CR) among 9 patients with RS,[89] and ibrutinib + nivolumab achieved an ORR of 42% (33% CR) in 24 patients.[90]

Prolymphocytic Transformation

The NCI-IWCLL criteria allow a diagnosis of CLL to be made in the presence of 55% or less prolymphocytes. The presence of greater than 55% prolymphocytes indicates prolymphocytic transformation. PLL is characterized by a high number of circulating prolymphocytes, splenomegaly, minimal lymphadenopathy, and a median survival time of less than 3 years.

HAIRY CELL LEUKEMIA

Classical hairy cell leukemia (cHCL) is an uncommon B-cell lymphoproliferative disorder affecting adults and represents 2% of all leukemia. There is a marked male preponderance. Most patients have cytopenias; splenomegaly is also frequent at presentation. Hairy cells can be seen in the peripheral blood, but their numbers vary. Most typically, cHCL presents with pancytopenia, monocytopenia and a paucity of circulating malignant cells. Patients with large numbers of circulating cells may have hairy cell leukemia variant (HCL-v) or VH4-34 molecular variant (see later). Hairy cells are twice as large as normal lymphocytes, with the nuclei showing a loose chromatin pattern and villus-like cytoplasmic projections (Fig. 3–8) (best viewed under phase-contrast microscopy). Hairy cells typically show positive staining for tartrate-resistant acid phosphatase (TRAP) (Fig. 3–9). Hairy cells infiltrate the bone marrow in an interstitial or focal pattern, with clear zones between cells ("fried-egg"

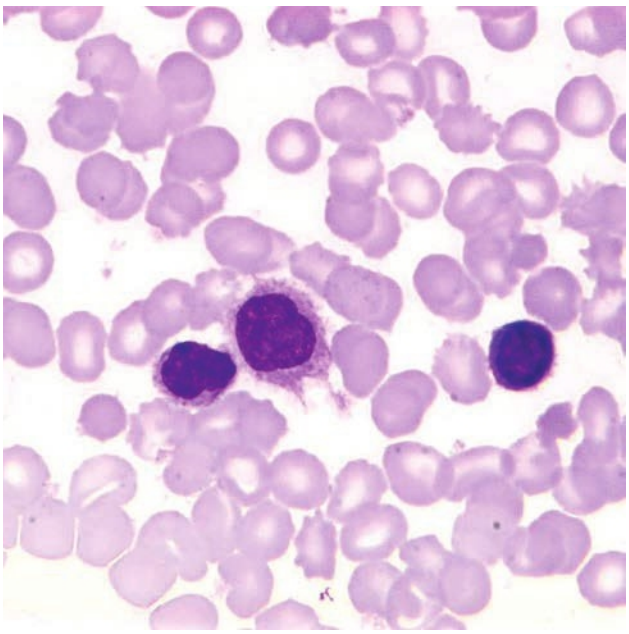


FIGURE 3–8 **Hairy cell in peripheral blood with cytoplasmic projections.**

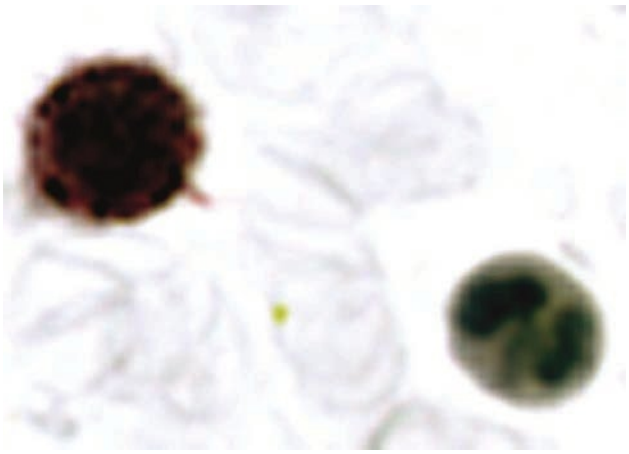


FIGURE 3–9 **Hairy cell staining for tartrate-resistant acid phosphatase (*left*). Note the absence of orange-brown staining in a neutrophil.**

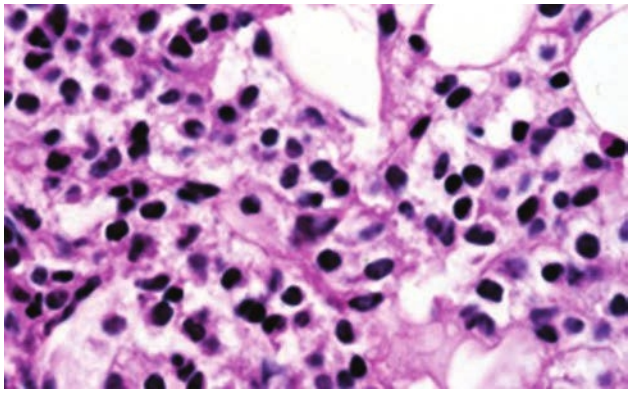


FIGURE 3–10 **Bone marrow involvement by hairy cell leukemia showing a "fried-egg" appearance (hematoxylin and eosin stain).**

appearance) (Fig. 3–10). Marrow reticulin is increased, and aspirates may result in a "dry tap."

Immunophenotypic analysis of hairy cells shows the presence of CD19, CD20, CD22, CD25, and CD103; in contrast to CLL, hairy cells are negative for CD5 and CD23. Hairy cells also stain strongly for surface Ig and FMC-7. HCL-v usually lacks CD25 and CD123 expression. CD200 is a specific marker, being highly expressed in cHCL but not in HCL-v or other morphologically similar lymphoproliferative disorders such as marginal zone lymphoma. Although CD200 is also expressed in CLL, the immunophenotype and morphology in CLL are sufficiently different from cHCL that diagnostic confusion is unlikely to arise.[91] The *BRAF V600E* mutation is present in most patients with cHCL.[92] Notably, patients with HCL-v and the VH4-34 molecular variant of cHCL lack *BRAF* mutations, instead often carrying *MAP2K1* mutations, which result in constitutive MEK1 phosphorylation and downstream ERK activation.[93] This may have implications for both diagnosis and treatment of HCL, and vemurafenib, a BRAF inhibitor, is currently in clinical trials as therapy for relapsed or refractory HCL.

Treatment decisions are usually based on the degree of cytopenia and accompanying complications (eg, bleeding, infections, anemia). Pentostatin and cladribine (2-CDA) are the nucleoside analogs that are the mainstay of treatment of HCL. Pentostatin is administered at 4 mg/m^2 every 2 weeks until maximum response and cladribine is given at 0.1 mg/kg/day as a continuous intravenous (IV) infusion for 7 days, or the same total dose can be administered as a 2-hour infusion over 5 days. Because cladribine offers a more convenient schedule (single course of therapy) and produces remission rates comparable to those achieved with pentostatin, cladribine is more frequently used. Estey et al[94] reported a CR rate of 78% with cladribine in patients who had newly diagnosed or previously treated HCL. One trial evaluated a strategy to improve the initial response to nucleoside analog therapy by adding additional doses of rituximab. Sequential therapy with 8 doses of rituximab 375 mg/m^2 weekly after completion of cladribine achieved a CR rate of 100% and increased MRD negativity from 14% to 74% (including 76% of untreated patients and 64% of patients in first relapse). Five-year failure-free survival (FFS) was 95%. Longer-term follow-up will be required to determine whether this translates into improved FFS for the first-line patients.[95,96] A CR rate of 100% was reported, and after a median follow-up period of 25 months, the median CR duration, PFS, and OS had not been reached. The majority of relapsed patients achieve second remission when retreated with pentostatin or cladribine. The choice of agent may depend on the duration of the first remission: if less than 3 years, use an alternate agent; if more than 5 years, use the same agent. Rituximab may improve results in relapsed cHCL and HCL-v. Of note, after a median follow-up period of 5 years, no patient has relapsed and FFS after second-line cladribine + rituximab was significantly longer (P = .004) than after initial monotherapy (in which median FFS was 6 years).[96] A more recent phase 2 randomized study has demonstrated that concurrent rather than delayed rituximab administration with cladribine is associated with a higher rate of CR. Splenectomy, although performed infrequently, can induce hematologic remission. The use of interferon-α is currently limited to patients unresponsive to nucleoside analogs. These latter two treatments are mainly confined to historical interest. A percentage of patients may relapse with cladribine-resistant disease. In addition, 10% to 20% of patients with the variant form of HCL have a poor response to nucleoside analogs.

Classic and variant hairy cells strongly express CD22. Recombinant immunotoxin, BL22, has been used in the treatment of chemotherapy-resistant HCL. Moxetumomab pasudotox (HA22 or CAT-8015) is derived from BL22, selected for high-affinity for CD22. A second-generation immunotoxin was developed, known as HA22/CAT-8015/moxetumomab pasudotox; this has greater binding affinity for CD22 and was demonstrated to have greater in vitro and in vivo toxicity against lymphoma cell lines and CLL/HCL cells.[97] A pivotal, open-label study demonstrated impressive activity in patients relapsing after at least two lines of prior therapy.[98] Among 80 patients treated, ORR was 75% and CR rate 41%; 85% of the patients in CR were MRD negative by multiparameter flow cytometry in bone marrow. Rapid improvement in hematologic parameters was noted. Median duration of CR and PFS have not been reached. Treatment was generally well-tolerated, with reversible hemolytic uremic syndrome occurring in 7.5% of patients and capillary leak syndrome in 5%.

The importance of constitutive BRAF-MEK-ERK signaling, induced by the *BRAF V600E* mutation in cHCL[92] led to two separate phase II studies being conducted with the BRAF inhibitor vemurafenib. This drug is approved for the treatment of metastatic melanoma,

which also carries the canonical *BRAF V600E* mutation, but is not currently approved for the treatment of HCL. The patient populations were either heavily pretreated or had early relapse after pentostatin therapy. In the Italian study, 6 patients had not responded to or relapsed within 1 year of purine analogue (PA) therapy, and 20 had either relapsed within 1 to 2 years of the first course or within 4 years of the second course of PA therapy. In the US trial, most patients were enrolled based on having received three or more prior courses of PA therapy. Patients received vemurafenib for 12 to 20 weeks in total and could be retreated at progression. ORR and CRR were 96% to 100% and 35% to 42%, respectively. In the Italian study, which had a longer follow-up, median relapse-free survival was 9 months; in the US study, 1-year PFS was 73%. Some patients responded to retreatment at relapse. Toxicity was generally manageable and was similar to that seen in studies of patients with melanoma; it included rash, photosensitivity, palmar or plantar fibrosis, warts, and arthralgias. Dose reduction was required in 50% to 58% of patients. Seven patients developed skin cancer (six nonmelanoma, one superficial spreading melanoma).[99,100]

PROLYMPHOCYTIC LEUKEMIA

PLL is characterized by splenomegaly, a high number of circulating prolymphocytes, minimal lymphadenopathy, and a median survival of less than 3 years. Prolymphocytes are larger and less homogenous than CLL cells; they have abundant clear cytoplasm, clumped chromatin, and a prominent nucleolus (see Figs. 3–7). Prolymphocytes can be of either B- or T-cell type. B-cell PLL cells usually do not express CD5 but stain strongly for surface Ig and FMC-7 (see Table 3–2). T-cell PLL demonstrates postthymic T-cell nature (TdT,$^-$ CD1a,$^-$ CD5+, CD2+, CD7+). A majority of the cases express CD4+ and are CD8.$^-$ Chromosomal abnormalities of chromosome 14 are present in more than 75% of patients. TCL-1 is commonly overexpressed and detectable by immunohistochemistry.

For T-PLL, IV alemtuzumab is the treatment of choice. Dearden et al[101] reported superior results in the first-line setting with IV alemtuzumab compared with results with subcutaneous alemtuzumab. With IV alemtuzumab, an ORR of 91% and CR rate of 81% were reported. Allo-SCT is the preferred consolidation regimen. Pentostatin should be considered for patients with poor response to alemtuzumab or relapsed disease. Retreatment with alemtuzumab is a reasonable option if the duration of the first remission was longer than 12 months.

LARGE GRANULAR LYMPHOCYTIC LEUKEMIA

Large granular lymphocytes (LGLs) are larger than normal lymphocytes and contain azurophilic granules in their cytoplasms (see Fig. 3–6). They normally comprise 10% to 15% of peripheral blood mononuclear cells. Clonal expansion of LGLs can arise from either of the normal cellular counterparts and so may have a natural killer (NK)- or T-cell phenotype; the T-cell phenotype composes 80% of LGL leukemias. T-cell LGL cells have a CD3+/CD57+/CD56$^-$ immunophenotype, and NK-cell LGL cells are CD3$^-$/CD56+/CD57$^-$.[102] T-cell receptor gene rearrangement studies can help establish the clonality. About 40% of patients with NK- and T-cell LGL leukemia were noted to have mutations in the *STAT3* gene.[103] Mutations in *STAT5b* were noted in a smaller subset (2%) of patients.[104] The clinical presentation of LGL leukemia is usually indolent. Cytopenias, including neutropenia with accompanying infections, thrombocytopenia, and anemia, are common. A small percentage of patients with LGL leukemia develop a more aggressive course; these patients tend to have an NK-cell phenotype. Several therapies, including low-dose methotrexate, oral cyclosporine, and oral cyclophosphamide with or without oral prednisone, have all been effective.

MD ANDERSON PRACTICE TIPS

- It is important to assess for *TP53* aberration by performing both FISH for del(17p) and sequencing for *TP53* mutation.
- Repeat prognostic marker testing (CLL FISH panel, *TP53* sequencing) at the time of disease relapse because patients may have acquired additional clonal abnormalities (clonal evolution). IGHV mutation status for an individual patient does not change over time, and therefore, there is no need to repeat, if already known.
- CIT is currently reserved for only young patients with no major comorbidities with mutated IGHV and no *TP53* aberration.
- Approved targeted therapies in first-line CLL include ibrutinib, acalabrutinib, and the combination of venetoclax and obinutuzumab. We generally do not combine BTK inhibitors with CD20 mAB in patients with CLL.
- Patients who have failed targeted therapies, especially those with *TP53* aberrant disease, should be referred for cellular therapies (allo-SCT, CAR T-cell therapies).
- Outcomes of CIT for Richter transformation remain dismal. These patients should be referred for clinical trials.

REFERENCES

1. Jain N, O'Brien S. The shifting paradigm in chronic lymphocytic leukemia: is chemotherapy still relevant? *Cancer J*. 2019;25(6):374-377.
2. Linet MS, Schubauer-Berigan MK, Weisenburger DD, et al. Chronic lymphocytic leukaemia: an overview of aetiology in light of recent developments in classification and pathogenesis. *Br J Haematol*. 2007;139(5):672-686.
3. Mak V, Ip D, Mang O, et al. Preservation of lower incidence of chronic lymphocytic leukemia in Chinese residents in British Columbia: a 26-year survey from 1983 to 2008. *Leuk Lymphoma*. 2014;55(4):824-827.
4. Brown JR. Inherited susceptibility to chronic lymphocytic leukemia: evidence and prospects for the future. *Ther Adv Hematol*. 2013;4(4):298-308.
5. Berndt SI, Skibola CF, Joseph V, et al. Genome-wide association study identifies multiple risk loci for chronic lymphocytic leukemia. *Nat Genet*. 2013;45(8):868-876.
6. Speedy HE, Di Bernardo MC, Sava GP, et al. A genome-wide association study identifies multiple susceptibility loci for chronic lymphocytic leukemia. *Nat Genet*. 2014;46(1):56-60.
7. Damle RN, Wasil T, Fais F, et al. Ig V gene mutation status and CD38 expression as novel prognostic indicators in chronic lymphocytic leukemia. *Blood*. 1999;94(6):1840-1847.
8. Hamblin TJ, Davis Z, Gardiner A, et al. Unmutated Ig V(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia. *Blood*. 1999;94(6):1848-1854.
9. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*. 2010;376(9747):1164-1174.
10. Eichhorst B, Fink AM, Bahlo J, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. *Lancet Oncol*. 2016;17(7):928-942.
11. Thompson PA, Tam CS, O'Brien SM, et al. Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia. *Blood*. 2016;127(3):303-309.
12. Crespo M, Bosch F, Villamor N, et al. ZAP-70 expression as a surrogate for immunoglobulin-variable-region mutations in chronic lymphocytic leukemia. *N Engl J Med*. 2003;348(18):1764-1775.
13. Rassenti LZ, Huynh L, Toy TL, et al. ZAP-70 compared with immunoglobulin heavy-chain gene mutation status as a predictor of disease progression in chronic lymphocytic leukemia. *N Engl J Med*. 2004;351(9):893-901.
14. Dohner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. *N Engl J Med*. 2000;343(26):1910-1916.
15. Puente XS, Pinyol M, Quesada V, et al. Whole-genome sequencing identifies recurrent mutations in chronic lymphocytic leukaemia. *Nature*. 2011;475(7354):101-105.
16. Wang L, Lawrence MS, Wan Y, et al. SF3B1 and other novel cancer genes in chronic lymphocytic leukemia. *N Engl J Med*. 2011;365(26):2497-2506.
17. Strati P, Shanafelt TD. Monoclonal B-cell lymphocytosis and early-stage chronic lymphocytic leukemia: diagnosis, natural history, and risk stratification. *Blood*. 2015;126(4):454-462.
18. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood*. 2018;131(25):2745-2760.
19. Rai KR, Sawitsky A, Cronkite EP, et al. Clinical staging of chronic lymphocytic leukemia. *Blood*. 1975;46(2):219-234.
20. Binet JL, Auquier A, Dighiero G, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. *Cancer*. 1981;48(1):198-206.
21. Wierda WG, O'Brien S, Wang X, et al. Multivariable model for time to first treatment in patients with chronic lymphocytic leukemia. *J Clin Oncol*. 2011;29(31):4088-4095.
22. Rossi D, Rasi S, Spina V, et al. Integrated mutational and cytogenetic analysis identifies new prognostic subgroups in chronic lymphocytic leukemia. *Blood*. 2013;121(8):1403-1412.
23. Hu B, Patel KP, Chen HC, et al. Association of gene mutations with time-to-first treatment in 384 treatment-naive chronic lymphocytic leukaemia patients. *Br J Haematol*. 2019;187(3):307-318.
24. Baliakas P, Jeromin S, Iskas M, et al. Cytogenetic complexity in chronic lymphocytic leukemia: definitions, associations, and clinical impact. *Blood*. 2019;133(11):1205-1216.
25. International CLL-IPI working group. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. *Lancet Oncol*. 2016;17(6):779-790.
26. Condoluci A, Terzi di Bergamo L, et al. International prognostic score for asymptomatic early-stage chronic lymphocytic leukemia. *Blood*. 2020;135(21):1859-1869.
27. Hallek M, Shanafelt TD, Eichhorst B. Chronic lymphocytic leukaemia. *Lancet*. 2018;391(10129):1524-1537.
28. Keating MJ, O'Brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. *J Clin Oncol*. 2005;23(18):4079-4088.
29. Fischer K, Cramer P, Busch R, et al. Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. *J Clin Oncol*. 2012;30(26):3209-3216.
30. Kutsch N, Bahlo J, Robrecht S, et al. Long term follow-up data and health-related quality of life in frontline therapy of fit patients treated with FCR versus BR (CLL10 trial of the GCLLSG). *Hemasphere*. 2020;4(1):e336.
31. Short NJ, Keating MJ, Wierda WG, et al. Fludarabine, cyclophosphamide, and multiple-dose rituximab as frontline therapy for chronic lymphocytic leukemia. *Cancer*. 2015;121(21):3869-3876.
32. Faderl S, Wierda W, O'Brien S, et al. Fludarabine, cyclophosphamide, mitoxantrone plus rituximab (FCM-R) in frontline CLL <70 years. *Leuk Res*. 2010;34(3):284-288.
33. Parikh SA, Keating MJ, O'Brien S, et al. Frontline chemoimmunotherapy with fludarabine, cyclophosphamide, alemtuzumab, and rituximab for high-risk chronic lymphocytic leukemia. *Blood*. 2011;118(8):2062-2068.
34. Strati P, Ferrajoli A, Lerner S, et al. Fludarabine, cyclophosphamide and rituximab plus granulocyte macrophage colony-stimulating factor as frontline treatment for patients with chronic lymphocytic leukemia. *Leuk Lymphoma*. 2014;55(4):828-833.
35. Foon KA, Boyiadzis M, Land SR, et al. Chemoimmunotherapy with low-dose fludarabine and cyclophosphamide and high dose rituximab in previously untreated patients with chronic lymphocytic leukemia. *J Clin Oncol*. 2009;27(4):498-503.
36. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med*. 2014;370(12):1101-1110.
37. Goede V, Fischer K, Engelke A, et al. Obinutuzumab as frontline treatment of chronic lymphocytic leukemia: updated results of the CLL11 study. *Leukemia*. 2015;29(7):1602-1604.
38. Burger JA. Treatment of chronic lymphocytic leukemia. *N Engl J Med*. 2020;383(5):460-473.

39. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2013;369(1):32-42.
40. Byrd JC, Furman RR, Coutre SE, et al. Ibrutinib treatment for first-line and relapsed/refractory chronic lymphocytic leukemia: final analysis of the pivotal phase Ib/II PCYC-1102 study. *Clin Cancer Res*. 2020;26(15):3918-3927.
41. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med*. 2014;371(3):213-223.
42. Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med*. 2015;373(25):2425-2437.
43. Burger JA, Barr PM, Robak T, et al. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. *Leukemia*. 2020;34(3):787-798.
44. Woyach JA, Furman RR, Liu TM, et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. *N Engl J Med*. 2014;370(24):2286-2294.
45. Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. *N Engl J Med*. 2019;381(5):432-443.
46. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. *N Engl J Med*. 2018;379(26):2517-2528.
47. Byrd JC, Harrington B, O'Brien S, et al. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2016;374(4):323-332.
48. Ghia P, Pluta A, Wach M, et al. ASCEND: phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia. *J Clin Oncol*. 2020;38(25):2849-2861.
49. Roberts AW, Seymour JF, Brown JR, et al. Substantial susceptibility of chronic lymphocytic leukemia to BCL2 inhibition: results of a phase I study of navitoclax in patients with relapsed or refractory disease. *J Clin Oncol*. 2012;30(5):488-496.
50. Souers AJ, Leverson JD, Boghaert ER, et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. *Nat Med*. 2013;19(2):202-208.
51. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med*. 2018;378(12):1107-1120.
52. Kater AP, Wu JQ, Kipps T, et al. Venetoclax plus rituximab in relapsed chronic lymphocytic leukemia: 4-year results and evaluation of impact of genomic complexity and gene mutations from the MURANO Phase III study. *J Clin Oncol*. 2020:JCO2000948.
53. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med*. 2019;380(23):2225-2236.
54. Al-Sawaf O, Zhang C, Tandon M, et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2020;21(9):1188-1200.
55. Brown JR, Byrd JC, Coutre SE, et al. Idelalisib, an inhibitor of phosphatidylinositol 3-kinase p110delta, for relapsed/refractory chronic lymphocytic leukemia. *Blood*. 2014;123(22):3390-3397.
56. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2014;370(11):997-1007.
57. Sharman JP, Coutre SE, Furman RR, et al. Final results of a randomized, phase III study of rituximab with or without idelalisib followed by open-label idelalisib in patients with relapsed chronic lymphocytic leukemia. *J Clin Oncol*. 2019;37(16):1391-1402.
58. O'Brien SM, Lamanna N, Kipps TJ, et al. A phase 2 study of idelalisib plus rituximab in treatment-naive older patients with chronic lymphocytic leukemia. *Blood*. 2015;126(25):2686-2694.
59. Flinn IW, Hillmen P, Montillo M, et al. The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. *Blood*. 2018;132(23):2446-2455.
60. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med*. 2018;378(5):439-448.
61. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med*. 2017;377(26):2531-2544.
62. Porter DL, Hwang W-T, Frey NV, et al. Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia. *Sci Transl Med*. 2015;7(303):303ra139-303ra139.
63. Turtle CJ, Hay KA, Hanafi LA, et al. durable molecular remissions in chronic lymphocytic leukemia treated with CD19-specific chimeric antigen receptor-modified T cells after failure of ibrutinib. *J Clin Oncol*. 2017;35(26):3010-3020.
64. Melenhorst JJ, Porter DL, Tian L, et al. Long-term remission of CLL sustained by pauciclonal anti-CD19 chimeric antigen receptor T (CTL019) cell clones. *Blood*. 2018;132(Supplement 1):699-.
65. Hay KA, Turtle CJ. CD19-specific chimeric antigen receptor-modified (CAR)-T cell therapy for the treatment of chronic lymphocytic leukemia in the ibrutinib era. *Immunotherapy*. 2018;10(4):251-254.
66. Fraietta JA, Lacey SF, Orlando EJ, et al. Determinants of response and resistance to CD19 chimeric antigen receptor (CAR) T cell therapy of chronic lymphocytic leukemia. *Nat Med*. 2018;24(5):563-571.
67. Gauthier J, Hirayama AV, Hay KA, et al. Comparison of efficacy and toxicity of CD19-specific chimeric antigen receptor T-cells alone or in combination with ibrutinib for relapsed and/or refractory CLL. *Blood*. 2018;132(suppl 1):299.
68. Gill SI, Vides V, Frey NV, et al. Prospective clinical trial of anti-CD19 CAR T cells in combination with ibrutinib for the treatment of chronic lymphocytic leukemia shows a high response rate. *Blood*. 2018;132(suppl 1):298.
69. Dreger P, Schetelig J, Andersen N, et al. Managing high-risk CLL during transition to a new treatment era: stem cell transplantation or novel agents? *Blood*. 2014;124(26):3841-3849.
70. Khouri IF, Bassett R, Poindexter N, et al. Nonmyeloablative allogeneic stem cell transplantation in relapsed/refractory chronic lymphocytic leukemia: long-term follow-up, prognostic factors, and effect of human leukocyte histocompatibility antigen subtype on outcome. *Cancer*. 2011;117(20):4679-4688.
71. Gribben JG. How and when I do allogeneic transplant in CLL. *Blood*. 2018;132(1):31-39.
72. Dreger P, Ghia P, Schetelig J, et al. High-risk chronic lymphocytic leukemia in the era of pathway inhibitors: integrating molecular and cellular therapies. *Blood*. 2018;132(9):892-902.
73. Dearden C. Disease-specific complications of chronic lymphocytic leukemia. *Hematology Am Soc Hematol Educ Program*. 2008:450-456.
74. Zent CS, Shanafelt T. Management of autoimmune cytopenia complicating chronic lymphocytic leukemia. *Leuk Lymphoma*. 2009;50(6):863-864.
75. Maura F, Visco C, Falisi E, et al. B-cell receptor configuration and adverse cytogenetics are associated with autoimmune hemolytic anemia in chronic lymphocytic leukemia. *Am J Hematol*. 2013;88(1):32-36.
76. Visco C, Maura F, Tuana G, et al. Immune thrombocytopenia in patients with chronic lymphocytic leukemia is associated with stereotyped B-cell receptors. *Clin Cancer Res*. 2012;18(7):1870-1878.

77. De Back TR, Kater AP, Tonino SH. Autoimmune cytopenias in chronic lymphocytic leukemia: a concise review and treatment recommendations. *Expert Rev Hematol*. 2018;11(8):613-624.
78. Kaufman M, Limaye SA, Driscoll N, et al. A combination of rituximab, cyclophosphamide and dexamethasone effectively treats immune cytopenias of chronic lymphocytic leukemia. *Leuk Lymphoma*. 2009;50(6):892-899.
79. Cortes J, O'Brien S, Loscertales J, et al. Cyclosporin A for the treatment of cytopenia associated with chronic lymphocytic leukemia. *Cancer*. 2001;92(8):2016-2022.
80. Paul S, Jain N, Ferrajoli A, et al. A phase II trial of eltrombopag for patients with chronic lymphocytic leukaemia (CLL) and thrombocytopenia. *Br J Haematol*. 2019;185(3):606-608.
81. Visco C, Rodeghiero F, Romano A, et al. Eltrombopag for immune thrombocytopenia secondary to chronic lymphoproliferative disorders: a phase 2 multicenter study. *Blood*. 2019;134(20):1708-1711.
82. Hampel PJ, Larson MC, Kabat B, et al. Autoimmune cytopenias in patients with chronic lymphocytic leukaemia treated with ibrutinib in routine clinical practice at an academic medical centre. *Br J Haematol*. 2018;183(3):421-427.
83. Molica S, Musto P, Chiurazzi F, et al. Prophylaxis against infections with low-dose intravenous immunoglobulins (IVIG) in chronic lymphocytic leukemia. Results of a crossover study. *Haematologica*. 1996;81(2):121-126.
84. Falchi L, Keating MJ, Marom EM, et al. Correlation between FDG/PET, histology, characteristics, and survival in 332 patients with chronic lymphoid leukemia. *Blood*. 2014;123(18):2783-2790.
85. Rossi D, Cerri M, Capello D, et al. Biological and clinical risk factors of chronic lymphocytic leukaemia transformation to Richter syndrome. *Br J Haematol*. 2008;142(2):202-215.
86. Chigrinova E, Rinaldi A, Kwee I, et al. Two main genetic pathways lead to the transformation of chronic lymphocytic leukemia to Richter syndrome. *Blood*. 2013;122(15):2673-2682.
87. Fabbri G, Khiabanian H, Holmes AB, et al. Genetic lesions associated with chronic lymphocytic leukemia transformation to Richter syndrome. *J Exp Med*. 2013;210(11):2273-2288.
88. Tsimberidou AM, Wierda WG, Wen S, et al. Phase I-II clinical trial of oxaliplatin, fludarabine, cytarabine, and rituximab therapy in aggressive relapsed/refractory chronic lymphocytic leukemia or Richter syndrome. *Clin Lymphoma Myeloma Leuk*. 2013;13(5):568-574.
89. Ding W, LaPlant BR, Call TG, et al. Pembrolizumab in patients with CLL and Richter transformation or with relapsed CLL. *Blood*. 2017;129(26):3419-3427.
90. Jain N, Ferrajoli A, Basu S, et al. A phase II trial of nivolumab combined with ibrutinib for patients with Richter transformation. *Blood*. 2018;132(Suppl 1):296-.
91. Foucar K, Falini B, Catovsky D, Stein H. *World Health Organization Classification of Tumors of Haematopoietics and Lymphoid Tissues*. IARC Press; 2008.
92. Tiacci E, Trifonov V, Schiavoni G, et al. BRAF mutations in hairy-cell leukemia. *N Engl J Med*. 2011;364(24):2305-2315.
93. Waterfall JJ, Arons E, Walker RL, et al. High prevalence of MAP2K1 mutations in variant and IGHV4-34-expressing hairy-cell leukemias. *Nat Genet*. 2014;46(1):8-10.
94. Estey EH, Kurzrock R, Kantarjian HM, et al. Treatment of hairy cell leukemia with 2-chlorodeoxyadenosine (2-CdA). *Blood*. 1992;79(4):882-887.
95. Ravandi F, O'Brien S, Jorgensen J, et al. Phase 2 study of cladribine followed by rituximab in patients with hairy cell leukemia. *Blood*. 2011;118(14):3818-3823.
96. Chihara D, Kantarjian H, O'Brien S, et al. Long-term durable remission by cladribine followed by rituximab in patients with hairy cell leukaemia: update of a phase II trial. *Br J Haematol*. 2016;174(5):760-766.
97. Kreitman RJ, Pastan I. Antibody fusion proteins: anti-CD22 recombinant immunotoxin moxetumomab pasudotox. *Clin Cancer Res*. 2011;17(20):6398-6405.
98. Kreitman RJ, Arons E, Tallman MS, et al. High response rate of moxetumomab pasudotox in relapsed/refractory hairy cell leukemia includes eradication of minimal residual disease: potential importance for outcome. *Blood*. 2015;126(23):4161-.
99. Tiacci E, Park JH, De Carolis L, et al. Targeting mutant BRAF in relapsed or refractory hairy-cell leukemia. *N Engl J Med*. 2015;373(18):1733-1747.
100. Falini B, Martelli MP, Tiacci E. BRAF-V600E mutation in hairy cell leukemia: from bench to bedside. *Blood*. 2016.
101. Dearden CE, Khot A, Else M, et al. Alemtuzumab therapy in T-cell prolymphocytic leukemia: comparing efficacy in a series treated intravenously and a study piloting the subcutaneous route. *Blood*. 2011;118(22):5799-5802.
102. Steinway SN, LeBlanc F, Loughran TP Jr. The pathogenesis and treatment of large granular lymphocyte leukemia. *Blood Rev*. 2014;28(3):87-94.
103. Koskela HL, Eldfors S, Ellonen P, et al. Somatic STAT3 mutations in large granular lymphocytic leukemia. *N Engl J Med*. 2012;366(20):1905-1913.
104. Rajala HL, Eldfors S, Kuusanmaki H, et al. Discovery of somatic STAT5b mutations in large granular lymphocytic leukemia. *Blood*. 2013;121(22):4541-4550.

4 Chronic Myeloid Leukemia

Koji Sasaki
Elias Jabbour
Jorge Cortes
Hagop Kantarjian

KEY CONCEPTS

- The survival of patients with chronic myeloid leukemia (CML) has improved significantly since the advent of tyrosine kinase inhibitor (TKI) therapy. With the availability of TKI and proper management, the expected survival of patients with chronic phase CML (CML-CP) is approaching that of the general population.
- Any of the four TKIs approved for frontline therapy of CML-CP may be selected. These include imatinib, dasatinib, nilotinib, and bosutinib. Second-generation TKIs are superior to imatinib in achieving faster and deeper responses compared with imatinib, but survival is similar because of the availability of effective TKI salvage therapies.
- Factors considered in choosing TKI therapy in the frontline setting include patient age, comorbidities, adverse events profile, and disease risk score, as well as the TKI-associated schedule of administration and cost. Kinase domain mutation profile plays no role in selecting an initial TKI but becomes relevant in relapse.
- Most TKIs are reasonably well tolerated with close observation and supportive care. However, each TKI therapy has a distinct toxicity profile that should be considered when deciding on therapy.
- Second- and third-generation TKIs have not been compared head to head. Mutational analysis is required after failure of imatinib or second-generation TKIs, or after progression to accelerated phase CML (CML-AP) or blastic phase (CML-BP). Baseline mutational analysis are not recommended in newly diagnosed CML-CP because it does not help predict treatment outcome.
- Allogeneic stem cell transplant should be considered in patients who progress from CML-CP to CML-AP/CML-BP after TKI therapy failure and who fail second- or third-generation TKI while still in CML-CP.

Chronic myeloid leukemia (CML) is a myeloproliferative disorder of pluripotent hematopoietic stem cells. The Philadelphia (Ph) chromosome results from a reciprocal translocation between chromosomes 9 and 22 and constitutes the cytogenetic hallmark of CML. A critical milestone in CML research was the demonstration that this translocation involved the *ABL1* (v-abl Abelson murine leukemia viral oncogene homolog 1) gene on chromosome 9 and the *BCR* (breakpoint cluster region) gene on chromosome 22 and resulted in the formation of the chimeric *BCR-ABL1* fusion transcript that encodes the constitutively active BCR-ABL1 tyrosine kinase.[1] This in turn is responsible for cell growth and replication through downstream signaling pathways.[2–8] The discovery that *BCR-ABL1* plays a pivotal role in the pathogenesis of CML set the stage for the development of therapeutic strategies aimed specifically at inhibiting this kinase and its downstream signals. Herein, we summarize the current knowledge regarding the molecular biology of CML and the treatment modalities, including novel BCR-ABL1 tyrosine kinase inhibitors (TKIs).

EPIDEMIOLOGY

CML has an incidence of 1 to 2 cases per 100,000 adults. It accounts for approximately 15% of newly diagnosed cases of leukemia in adults.[9] The median age of onset of CML is 60 to 65 years, and the incidence increases with age. There are no known hereditary, geographic, familial, or ethnic associations. There are no known causal etiologies, although an increased risk has been noted with exposure to ionizing radiation.[10]

In 2020, it was estimated that there would be 8450 new cases of CML in the United States, and about 1130 people would die of this disease.[11] In the TKI era, the expected 5-year survival time of patients with CML chronic phase is comparable to that of the general population.[12] Since the introduction of imatinib in 2000, the annual mortality rate in patients with CML has decreased from 10% to 20% to 1% to 2%.[11] Consequently, the prevalence of CML in the United States, estimated at about 30,000 cases in 2000, has increased by approximately 7000 to 8800/year. It was previously estimated that the prevalence of CML cases would reach a plateau of 150,000 to 180,000 or more by the year 2030.[13] However, given the current number of new cases of CML in the United States, the prevalence plateau is now estimated to be 400,000 to 450,000 cases in the United States, which may not be reached until 2040 to 2050.

MOLECULAR BIOLOGY

CML is a clonal myeloproliferative neoplasm derived from an abnormal pluripotent hematopoietic stem cell that has acquired the *BCR-ABL1* fusion gene, usually through t(9;22)(q34;q11.2), also known as Ph, involving the long arms of chromosome 9 and 22. This is translated into a constitutively active oncoprotein, the BCR-ABL1 tyrosine kinase. This oncoprotein activates multiple downstream pathways, including PI3 kinase, nuclear factor-κB, JAK/STAT, RAS, RAF, ERK, MYC, and JNK. Depending on the breakpoint on the *BCR* gene, three main Ph variants can occur. In most patients with CML and in one third of those with Ph-positive acute lymphoblastic leukemia (ALL), the breakpoint maps to the major breakpoint cluster region (M-*bcr*), which spans *BCR* exons 12 to 16 (formerly called b1–b5), giving rise to a fusion transcript with either e13a2 (b2a2) or e14a2 (b3a2) junctions that translates into a 210-kDa protein ($p210^{BCR\text{-}ABL1}$). In two thirds of patients with Ph-positive ALL and rarely in CML, the breakpoints within *BCR* localize to an area of 54.4 kb between exons e2′ and e2, termed the minor breakpoint cluster region (m-*bcr*), giving rise to a fusion transcript e1a2, which translates to a 190-kDa protein ($p190^{BCR\text{-}ABL1}$). A third breakpoint cluster region (μ-*bcr*) has been identified giving rise to a fusion transcript e19a2, which translates to a 230-kDa fusion protein ($p230^{BCR\text{-}ABL1}$) associated with a more indolent CML course and with a phenotype more similar to chronic neutrophilic leukemia.

The Ph chromosome can be detected by conventional cytogenetics in 90% to 95% of the cases. In the remaining 5% to 10% of the Ph-negative cases by cytogenetics, *BCR–ABL1* rearrangement can be recognized with fluorescent in situ hybridization (FISH) technique and high-sensitivity reverse transcriptase polymerase chain reaction (RT-PCR). Additionally, when detected by conventional cytogenetics, 90% of patients have the typical t(9;22), and 5% to 10% of the patients have variant translocations, which can be simple (involving chromosome 9 and a chromosome other than chromosome 22) or complex (involving one or more chromosomes in addition to chromosomes 9 and 22). Patients with Ph-negative *BCR-ABL1* rearranged CML, as well as those with Ph variants have similar response rates to therapy and prognosis compared to patients with Ph-positive CML.

CLINICAL PRESENTATION AND NATURAL HISTORY

There are three separate phases of CML: chronic phase (CP), intermediate or accelerated phase (AP), and terminal or blastic phase (BP). Even though all three represent a stepwise progression of disease from the typically indolent CP to the most aggressive and frequently terminal BP, the natural course of the disease, particularly on adequate treatment with TKIs, may not include progression out of CP, nor will the disease always include all three phases when progressing. Approximately 85% to 90% of patients present in CP. About 50% of patients diagnosed with CML are asymptomatic. The diagnosis often occurs during routine physical examination or blood tests. When present, the symptoms mostly arise from low counts such as anemia and thrombocytopenia causing fatigue and bleeding. Splenomegaly is the most consistent physical finding, detected in 20% to 40% of cases, resulting in early satiety, weight loss, and left upper quadrant pain and fullness. In rare cases, patients may present with features of hyperviscosity from marked leukocytosis, including priapism, stroke, and retinal hemorrhages. Headaches, bone pain, arthralgias, pain from splenic infarction, and fever are more frequent with CML transformation. Most patients who transform to advanced phases evolve into AP before BP, but 20% transition into BP without AP warning signals. CML-AP might be insidious or present with worsening anemia, splenomegaly, and organ infiltration. CML-BP presents as an acute leukemia (myeloid in 60%, lymphoid in 30%, megakaryocytic or undifferentiated in 10%) with worsening constitutional symptoms, bleeding, fever, and infections. Involvement of extramedullary tissues such as the lymph nodes, skin, and soft tissues is generally limited to patients with CML-BP.

Various classifications were used to define the different CML phases. The European LeukemiaNet (ELN) classification defines CML-AP as the presence of any of the following features: 15% or more blasts

TABLE 4–1 Diagnostic Criteria of Accelerated Phase According to MD Anderson Cancer Center (MDACC), International Bone Marrow Transplant Registry (IBMTR), and World Health Organization (WHO)

	MDACC	IBMTR	WHO
Blasts (%)	15–29	10–29	10–19[a]
Blasts + promyelocytes (%)	≥30	≥20	NA
Basophils (%)	≥20	≥20[b]	≥20
Platelets ($\times 10^9$/L)	<100	Unresponsively high or persistently low	<100 or >1000 unresponsive
Cytogenetics	CE	CE	CE not at diagnosis
WBC count	NA	Difficult to control or doubling <5 days	NA
Anemia	NA	Unresponsive	NA
Splenomegaly	NA	Increasing	NA
Other	NA	Chloromas, myelofibrosis	Megakaryocyte proliferation, fibrosis

[a]In the WHO criteria, blastic phase is defined as a blast percentage of 20% or higher. In the MDACC and IBMTR, a definition of blastic phase requires the presence of at least 30% blasts.
[b]Basophils plus eosinophils.
CE, clonal evolution; NA, not applicable; WBC, white blood cell.

in the peripheral blood and/or the bone marrow, 30% or more blasts plus promyelocytes in the peripheral blood and/or the bone marrow, 20% or more basophils in the peripheral blood and/or the bone marrow, platelets 100×10^9/L or less unrelated to therapy, and cytogenetic clonal evolution (Table 4–1). The average survival period of patients in CML-AP was 1 to 2 years before the TKI era. With TKI therapy, the estimated 4-year survival has increased to 60% to 70%. In contrast to CML-AP after CML-CP, de novo CML-AP has a better prognosis with frontline TKI therapy, with an estimated 8-year survival rate of more than 80%, particularly when treated with second-generation TKIs.[14]

A diagnosis of CML-BP requires the demonstration of at least 30% blasts (20% in the World Health Organization classification) in the peripheral blood and/or the bone marrow or the presence of extramedullary blastic foci. The median survival of patients in CML-BP before the introduction of TKI therapy was 2 to 6 months; with TKI- based therapy, it improved to a median of 1 to 3 years, particularly when TKI is combined with chemotherapy.[15]

DIAGNOSIS AND CLINICAL WORK-UP

The typical presentation of CML involves leukocytosis with a left shift including myelocytes and metamyelocytes seen in the peripheral blood. Additionally, basophilia and in some cases eosinophilia can be predominant. The diagnosis of typical CML requires the presence of Ph abnormality, the t(9,22)(q34;q11) by routine karyotype, or the presence of BCR-ABL1 rearrangement noted by FISH or by RT-PCR.[16–18] A FISH analysis relies on the co-localization of large genomic probes specific to the *BCR* and *ABL1* genes. Comparison of simultaneous marrow and blood samples by FISH analysis shows high concordance. FISH studies may have a false-positive range of 1% to 5% depending on the probes used.

RT-PCR amplifies the region around the splice junction between *BCR* and *ABL1*. It is highly sensitive in detecting and monitoring minimal residual disease. Simultaneous peripheral blood and marrow RT-PCR studies show a high level of concordance. False-positive and false-negative results can happen with PCR. A 0.5- to 1-log difference in some samples can occur depending on testing procedures, sample handling, and laboratory experience.[16–18]

Although both FISH and RT-PCR can confirm the presence of the Ph chromosome, a bone marrow aspiration should be performed in all suspected cases of CML at diagnosis. This not only confirms the diagnosis (by cytogenetics) but also helps stage the disease (ie, percentage of blasts and of, basophils; and presence of additional chromosomal abnormalities [clonal evolution]). The Ph chromosome is usually present in 100% of metaphases, often as the sole abnormality. About 10% to 15% of patients have additional chromosomal changes, most frequently involving trisomy 8, isochromosome 17, additional loss of material from 22q or double Ph, or abnormalities involved of chromosome 3. Among these cytogenetic abnormalities, i(17)(q10), -7/del7q, and 3q26.2 translocations, are associated with a particularly poor prognosis.[19] Clonal evolution is considered a criterion of AP, particularly when it occurs during the course of the

disease. Corresponding molecular alterations that follow these changes include deregulation of p53, RB1, C-MYC, and AML-EVI1.

For correlative purpose and monitoring without necessarily performing marrow evaluation studies, a complete cytogenetic response (CCyR; 0% Ph-positive metaphases by cytogenetic) is grossly equivalent to a negative FISH test result (±2%) and *BCR-ABL1* transcripts by International Scale (IS) less than 1%. A partial cytogenetic response (Ph-positive metaphases 1%–35%) is approximately equivalent to *BCR-ABL1* transcripts 10% or less (IS).

The RT-PCR is an important diagnostic tool in CML and should be performed in all suspected CML cases. In patients with Ph-negative CML, which comprises 5% to 10% of the cases of CML, detection of *BCR-ABL1* rearrangement helps establish the diagnosis. RT-PCR also helps determine the type of transcript involved. This is helpful in monitoring disease status and response to therapy. Ninety percent of the cases have of the classical p210 transcripts, e13a2 (b2a2), and e14a2 (b3a2). Less common types include the p190 transcript, (e1a2) and the p230 transcript (e19a2). In 2% of the cases, patients may harbor other variant transcripts, such as e13a3 and e14a3. These variant transcripts along with the p230 transcript e19a2 are not detected by the routine RT-PCR probe. Hence, if RT-PCR is not performed at baseline, patients with these transcripts can be falsely considered to have undetectable transcripts because of treatment.

PROGNOSTIC TOOLS IN CHRONIC MYELOID LEUKEMIA

The different CML phases predict for very different survival probabilities. However, the prognosis is also variable among patients in the same phase of the disease. Several patient and disease characteristics have prognostic impact and were used to generate prognostic models. There are four different scoring systems: Sokal, Euro (Hasford), EUTOS (European Treatment and Outcome Study), and ELTS (EUTOS long-term survival score). Sokal was the first scoring system developed before the interferon (IFN) era. It included age, spleen size, platelet count, and peripheral blast count.[20] It segregated patients into three risk groups with hazard ratios (HRs) of less than 0.8, 0.8 to 1.2, and greater than 1.2, with respective median survival times of 105, 76, and 45 months, respectively. In 1998, the EURO or Hasford score was developed to identify risk groups in CML patients treated with IFN.[21] It included age, spleen size, platelet count, peripheral blood blast count, eosinophils, and basophils. It also stratified patients in low-, intermediate-, and high-risk groups with median survival times of 105, 65, and 45 months, respectively. The EUTOS score was developed in the imatinib era and included spleen size and basophils.[22] This score predicts likelihood of 18-month CCyR rate on imatinib therapy. Last, the ELTS was developed to assess the risk of CML-related death.[23] It includes the same prognostic variables as the Sokal score. Patients are separated into three risk groups with 8-year probabilities of dying from CML of 2%, 6%, and 11%, respectively.

RESPONSE DEFINITION

Response to therapy is initially assessed by measurement of hematologic response criteria. A complete hematologic response (CHR) is defined as normalization of white blood cell (WBC) count to less than 10 $\times$ 10^9/L with a normal differential, platelet count less than 450 $\times$ 10^9/L, and disappearance of splenomegaly and other symptoms of CML. Patients who achieve a CHR are further classified according to the type of cytogenetic response achieved (Table 4–2).

Cytogenetic responses are divided into complete, partial, and minor and are based on a banding karyotype with at least 20 metaphases counted. CCyR corresponds to 0% of all metaphases remaining Ph positive, partial cytogenetic response as 1% to 35% of metaphases being Ph positive, and minor as >35% to 95% Ph-positive metaphases. Although FISH results correlate well with the karyotypic evaluation, cytogenetic response criteria needs further validation with FISH.

Molecular response is assessed by RT-PCR in the peripheral blood or bone marrow.[24] A major molecular response (MMR) is considered when the *BCR–ABL1* transcript is 0.1% or less on the (IS). MR4.0 and MR4.5 are considered when the *BCR-ABL1* transcripts are 0.01% or less and 0.0032% or less on the IS, respectively. A molecular response 5 (MR5) represents achievement of undetectable transcripts of *BCR–ABL1* with at least 100,000 copies of ABL (or equivalent control gene).

FRONTLINE TREATMENT OPTIONS

Since 2000, the treatment of CML has changed dramatically. Conventional chemotherapeutic agents such as hydroxycarbamide (hydroxyurea) are no longer used, except to achieve transient cytoreduction. There are currently four commercially available TKIs for the frontline treatment of CML: imatinib, dasatinib, nilotinib, and bosutinib. Available guidelines support all four as viable

TABLE 4–2 Criteria for Hematologic, Cytogenetic, and Molecular Response and Relapse

Hematologic Response	
Complete	Normalization of peripheral blood counts; WBC count $<10 \times 10^9$/L; platelets $<450 \times 10^9$/L Absence of immature cells such as myelocytes, promyelocytes, or blasts in peripheral blood No signs and symptoms of disease with disappearance of palpable splenomegaly
Cytogenetic Remission[a]	
Complete	No Ph-positive metaphases
Partial	1%–35% Ph-positive metaphases
Minor	>35%–95% Ph-positive metaphases
None	>95% Ph-positive metaphases
Complete and partial cytogenetic responses together constitute major cytogenetic responses, ie, 0%–35% Ph-positive metaphases	
Molecular Remission (MR)[b]	
Early MR	*BCR-ABL1* (IS) ≤10% at 3 and 6 months
Major	*BCR-ABL1* (IS) ≤0.1% or ≥3-log reduction in *BCR-ABL1* mRNA from the standardized baseline
MR4.0	*BCR-ABL1* (IS) ≤0.01% or ≥ 4-log reduction in *BCR-ABL1* mRNA from the standardized baseline
MR4.5	*BCR-ABL1* (IS) ≤0.0032% or ≥ 4.5-log reduction in *BCR-ABL1* mRNA from the standardized baseline
MR5	*BCR-ABL1* (IS) ≤0.001% or undetectable *BCR-ABL1* transcripts with ≥100,000 copies of ABL (or equivalent control gene)
Relapse	
Any sign of loss of hematologic response or cytogenetic relapse	

[a]Cytogenetic response is based on routine karyotype analyzing at least 20 metaphases.
[b]Molecular responses is based on quantitative polymerase chain reaction (real-time polymerase chain reaction).
IS, international score; Ph, Philadelphia chromosome; WBC, white blood cell.

frontline options for the initial management of patients with CML-CP.

Imatinib Mesylate

Imatinib mesylate (STI-571, Gleevec) was the first TKI approved by the Food and Drug Administration (FDA) for the treatment of patients with CML-CP. It is a selective and potent competitive inhibitor of the ATP-binding site of the BCR-ABL1 oncoprotein, as well as c-kit, platelet-derived growth factor receptor α and β, and abl-related gene (ARG).[25] It is given orally with 98% bioavailability and a half-life of 13 to 16 hours. It was first used in patients who developed resistance or intolerance to IFN-α, and resulted in a CCyR of 60% and an estimated 5-year overall survival (OS) rate of 76%.[26]

Based on these results, the phase 3 randomized multinational IRIS (International Randomized study of Interferon-alpha plus cytarabine versus STI571) study compared imatinib 400 mg orally daily with IFN-α in combination with cytarabine (the standard of care at the time) in 1106 newly diagnosed patients with CML-CP.[27] After a median follow-up period of 19 months, outcomes for patients receiving imatinib were significantly better than in those treated with INF-α plus cytarabine. These included the rates of CCyR rate (74% vs 9%; P <.001) and freedom from progression to AP or BP at 12 months (99% vs 93%; P <.001). With a median follow-up period now of 10+ years, the estimated OS rate for patients assigned to imatinib was 83.3% with a cumulative CCyR rate of 83% and a 10-year MMR rate of 93%.[28] Despite the high rate of crossover among patients assigned to receive INF-α plus cytarabine (66%) and the short duration of therapy before crossover (median, 0.8 years), the 10-year survival rates favored the imatinib arm (83.3% vs 78.8%).[28]

Despite the impressive results with imatinib, approximately half of the patients had come off imatinib therapy at the 10-year follow-up time. This highlighted the need for additional treatment options in CML. The development of second generation TKIs helped address this issue, especially in patients who were intolerant to imatinib therapy.

Imatinib Dosage

The phase I imatinib study in patients who had failed prior IFN-α therapy established a clear relationship between dose and response.[29] No significant responses

were observed at doses below 300 mg/day. An arbitrary dosage of 400 mg/day for CP was selected in phase II studies despite the lack of dose-limiting toxicity at doses up to 1000 mg/day (maximum tolerated dose was not defined). Studies of higher dose schedules of imatinib (e.g. 400mg twice daily) were associated with more side effects and no longer term benefits.[30–33]

In a French Spirit study, 636 patients with newly diagnosed CML-CP were randomized to receive either imatinib 400 mg/day alone, imatinib 400 mg/day with cytarabine (20 mg/m^2/day on days 15–28 of each 28-day cycle) or pegylated (peg) IFN-α-2a (90 μg weekly), or imatinib 600 mg/day alone.[34] The 12-month CCyR rates were similar among the four groups, but the MMR and deeper molecular responses rates were significantly higher in patients receiving imatinib and peg IFN-α-2a compared with imatinib 400 mg alone arm (30% vs 14% respectively; $P = .001$). However, this high rate of early and deep responses did not translate into long-term improvement because of the poor tolerance of peg IFN-α-2a.

The CML-study IV was designed to investigate if treatment with imatinib 400mg/day ($n = 400$) could be optimized by doubling the dose ($n = 420$) or by adding IFN ($n = 430$) or cytarabine ($n = 158$) or by using imatinib after IFN failure ($n = 128$).[35] From July 2002 to March 2012, 1551 newly diagnosed patients with CML-CP were randomized into a five-arm study. The study was powered to detect a survival difference of 5% at 5 years. After a median observation time of 9.5 years, the 10-year OS rate was 82%, the 10-year progression-free survival (PFS) rate was 80%, and the 10-year relative survival rate was 92%. Despite a faster response with imatinib 800 mg, the survival difference between standard-dose and higher dose imatinib was only 3% at 5 years (<5%). In a multivariate analysis for survival, standard-dose imatinib was equivalent to other treatment arms. Patients who reached the 6-month *BCR-ABL1* transcripts (IS) less than 1% had a survival advantage of 6% after 10 years regardless of therapy.

Imatinib 400 mg/day is therefore the standard dose for treating patients with newly diagnosed CML-CP.

Imatinib Generics

Imatinib generics are now available. It has been questioned if these are comparable in safety and efficacy to the branded Gleevec. In a multicenter prospective study conducted by the Polish Adult Leukemia Group (PALG) imatinib generic registry, 726 patients with CML-CP were divided into two groups: group A ($n = 99$) consisting of patients who commenced therapy on generic imatinib after CML diagnosis, and group B ($n = 627$) consisting of patients who were switched to generic from branded imatinib.[36] Patients were observed for at least 12 months. In group A, the rates of early molecular response (EMR, *BCR-ABL1* transcript ≤10% at 3 months), CCyR at 6 months, and MMR at 12 months (65%, 53%, and 50% respectively) were comparable to those achieved by branded imatinib. In group B, 64% patients maintained their molecular response, but 15% had worsening of molecular response when switching to generic imatinib. Despite this, only 0.3% and 1.3% of the patients had loss of CCyR and MMR, respectively. Rates of adverse events were also similar between groups A and B and comparable to branded imatinib. Similar data were reported from India. Among 174 patients treated with imatinib generics, response and survival rates were similar to those observed among 1193 patients treated with the branded imatinib. Safety profile was similar as well.[37]

At MD Anderson 38 patients who switched therapy from branded imatinib to generics were evaluated. Before the switch, all patients were in CCyR, 36 (95%) were in MMR, and 28 (74%) in deep molecular response (MR4.5). Patients received generic imatinib for a median of 19.4 months. Molecular responses after switching were stable in 89%, improved in 8%, and worsened in 3% of patients. No patient lost MMR.[38] No significant changes in side-effects were observed after the switch to generic.

Management of Toxicity

Imatinib is overall well tolerated, although adverse events not requiring treatment interruptions or decrease in dosing may occur in 30% to 40% of patients. A list of the most frequently encountered side effects and suggestions for management are included in Table 4–3. Any grade 3 or 4 toxicities related to imatinib require treatment interruption and resumption upon resolution of toxicity or its decrease to grade 1 or less. Subsequent doses should be reduced if recurring or long-lasting side effects are encountered, keeping in mind that dosages below 300 mg/day are not recommended because of lack of adequate activity, unless the patient is already in deep molecular response. Only 2% to 3% of patients exhibit true intolerance to imatinib and require permanent discontinuation. Early recognition and intervention targeting toxicities greatly reduce the need for unnecessary treatment interruptions and dose reductions.

Myelosuppression is common and frequently seen within the first 2 to 3 months of therapy. It is generally self-limited, and dose interruptions are not recommended unless grade 3 neutropenia or thrombocytopenia (ie, neutrophils $<1 \times 10^9$/L, platelets $<50 \times 10^9$/L) develop. Anemia alone usually does not require interruptions or dose adjustments. Treatment is restarted when counts recover above specified thresholds. After treatment interruption, the WBC

TABLE 4–3 Recommended management of the Most Common Adverse Events Associated with Imatinib

Adverse Events	Management
Nausea or vomiting	Take with food or fluids
	Antiemetics
Diarrhea	Loperamide
	Diphenoxylate atropine
Peripheral edema	Diuretics
Periorbital edema	Steroid-containing cream
Skin rash	Avoid sun exposure
	Topical steroids
	Systemic steroids
	(Early intervention is important)
Muscle cramps	Tonic water or quinine
	Electrolyte replacement as needed
	Calcium gluconate
Arthralgia or bone pain	NSAIDs
Elevated transaminases	Hold therapy and monitor closely
	Dose reduction on resolution
Myelosuppression	
Anemia	Treatment interruption or dose reduction usually not indicated
	Erythropoietin or darbopoetin
Neutropenia	Hold therapy if grade ≥3 (ie, ANC $<1 \times 10^9$/L)
	Restart at lower dose if recovery takes >2 weeks
	Consider G-CSF if recurrent or persistent or sepsis
Thrombocytopenia	Hold therapy if grade ≥3 (ie, platelets $<50 \times 10^9$/L)
	Restart at lower dose if recovery takes >2 weeks
	Consider eltrombopag

ANC, absolute neutrophil count; G-CSF, granulocyte colony stimulating factor; IL-10, interleukin-10; NSAID, nonsteroidal antiinflammatory drug.

count should be monitored at least once weekly, and if recovery occurs within 2 weeks, treatment should be resumed with the same dose at which myelosuppression occurred. If recovery takes longer than 2 weeks, the dose could be reduced in increments (eg, from 400 to 300 mg). Hematopoietic growth factors may be beneficial with recurrent or prolonged myelosuppression (eg, erythropoietin or darbepoetin, filgrastim, and eltrombopag).[39,40]

Dasatinib

Dasatinib is a piperazinyl derivative oral second-generation TKI. It has an excellent oral bioavailability and is 350 times more potent in vitro than imatinib.[41,42] It exhibits significant activity against most imatinib-resistant BCR–ABL1 mutations, with the exception of T315I, and a few others, including V299L and F317L.[43] In contrast to imatinib, dasatinib binds to both the active and inactive conformations of BCR–ABL1 and inhibits the Src family of kinases, which may be important in suppressing critical cell signaling pathways.[44]

After evaluation in the salvage setting post imatinib failure, dasatinib was assessed in the frontline setting. The DASISION trial was a phase III, randomized study that compared imatinib 400 mg once daily to dasatinib 100 mg once daily in 519 patients with newly diagnosed CML-CP.[45,46] The primary endpoint was confirmed CCyR (cCCyR) at 12 months, which was higher with dasatinib (77% vs 66%; $P = 0.007$). The rates of molecular responses were significantly higher with dasatinib (MMR 76% vs 64 % $P = .002$; MR 4.5 42% versus 33 %, $P = .025$). Dasatinib induced deeper responses at early time points (3, 6, or 12 months) compared with imatinib. At 3 months, a higher proportion of patients treated with dasatinib achieved

BCR-ABL1 transcripts (IS) 10% or less (84% vs 64%; P <.0001). Meeting this threshold in either arm predicted better PFS and OS. The rate of transformation to AP or BP was lower in patients treated with dasatinib (4.6% and 7.3%, respectively). However, there was no PFS and OS difference at a minimum follow-up of 5 years when the study was terminated.[46] Relevant toxicities included a pleural effusion rate of 28% with dasatinib (mostly grade 1 or 2; 15 patients [6%] discontinued dasatinib because of pleural effusion). Arterio-occlusive events were higher with dasatinib (5% vs 2%). Pulmonary hypertension was reported in 14 (5%) dasatinib-treated patients, with 6 discontinuing the drug.

In another phase II, multicenter trial, patients with newly diagnosed CML-CP were randomized to either dasatinib 100 mg/day or imatinib 400 mg/day.[47] Similar to the DASISION study, higher rates of CCyR (84% vs 69%) and 12-month MMR (59% vs 44%; P = .059) were reported in patients receiving dasatinib. No difference in PFS or OS was reported. Grade 3 and 4 toxicities were most commonly hematologic, including thrombocytopenia, which was more common with dasatinib (18% vs 8%).

A third phase III randomized study, SPIRIT 2, compared dasatinib 100 mg/day with imatinib 400 mg/day.[48] More than 800 patients were treated. The primary endpoint was 5-year event-free survival (EFS). The 24-month CCyR rate was higher with dasatinib compared to imatinib (43% vs 32%). The cumulative incidence of MMR and MR4 were also higher with dasatinib (MMR 83% vs 63%; MR4 78% vs 57%). More imatinib-treated patients proceeded to stem cell transplant (SCT). Although the 5-year failure-free survival (FFS) rate was superior in the dasatinib arm (61% vs 53%), there was no difference in the EFS (91% vs 89%) or the OS (92% vs 91%) between dasatinib and imatinib.[49] Overall, more patients came off therapy because of suboptimal molecular response in the imatinib compared with the dasatinib arm (17% vs 2%), but more patients discontinued therapy because of intolerance in the dasatinib compared with the imatinib arm (30% vs 17%).

Dasatinib is well tolerated. Myelosuppression occurs frequently, with grade 3 or 4 neutropenia or thrombocytopenia in 20%. The most common nonhematologic grade 3 to 4 toxicities at the same dose were pleural effusion (9%), dyspnea (6%), bleeding (4%), diarrhea (3%), and fatigue (3%).

Lower Dose Dasatinib

In early clinical trials evaluating dasatinib, the drug was noted to be active at doses lower than those initially approved for second-line therapy, with a better safety profile.[50] In a randomized trial of four dose schedules of dasatinib (100 mg vs 140 mg/day; single-dose versus twice-daily schedule), dasatinib 100 mg single daily dose was as effective as 140 mg/day with a better safety profile.[51] Investigators from the DASISION trial have reported the ability to maintain the efficacy of dasatinib among patients who had their dose reduced, while improving its safety profile.[52] Based on this rationale, we conducted a phase II study evaluating the efficacy and safety of lower dose dasatinib 50 mg/day in 81 patients with newly diagnosed CML-CP. With a minimal follow-up of 12 months,[53,54] the cumulative rates of MMR, MR4, and MR4.5 by 12 months were 81%, 55%, and 49%, respectively. Twenty-one (25%) patients had treatment interruptions for a median of 13 days (range, 4–64 days). Five (6%) patients developed pleural effusions; four of them required a dose reduction. Two (2%) patients failed to achieve any cytogenetic or molecular response and were taken off study. At a median follow-up time of 24 months, none of the patients had disease transformation to an AP or BP.[54] The 2-year EFS and OS rates were 100%. Such a strategy may have a significant impact on our future practice because of equivalent efficacy, better safety, and a lower cost of care.[54]

Nilotinib

Nilotinib is a structural analog of imatinib with 50 times more potent affinity for the ATP binding site in vitro[55] and more selective activity against unmutated and most mutated forms of BCR–ABL1.[55,56] It is approved at a dose of 400 mg twice daily for patients with CML-CP and CML-AP with resistance or intolerance to imatinib. Nilotinib was also evaluated in newly diagnosed CML-CP. The ENESTnd trial was a large phase 3 international randomized study that compared two doses of nilotinib, 300 mg twice daily and 400 mg twice daily (the dose approved for CML salvage) with imatinib 400 mg once daily as initial therapy for patients with early CML-CP.[57] The primary endpoint was the MMR rate at 12 months, which was higher with both doses of nilotinib compared to imatinib (44% and 43% vs 22%; P <.001). The cumulative incidence of CCyR by 24 months was 87% with nilotinib 300 mg twice daily, 85% with nilotinib 400 mg twice daily, and 77% with imatinib 400 mg/day (P <.001).[57] Cumulative 10-year[58,59] MMR rates were 83% with nilotinib 300 mg twice daily, 80% with nilotinib 400 mg twice daily, and 70% with imatinib.[58] Cumulative 10-year MR4.5 rates were 64% with nilotinib 300 mg twice daily, 62% with nilotinib 400 mg twice daily, and 45% with imatinib, respectively.[58] The incidence of transformation to CML AP or BP was 3.9% with nilotinib 300 mg twice daily, 2.5% with nilotinib 400 mg twice daily, and 8.5% with imatinib. There was no significant difference in outcome among patients

treated with nilotinib and imatinib.[58] The estimated 10-year EFS rates were 92.0%, 96.2%, and 90.3% with nilotinib 300 mg twice daily, nilotinib 400 mg twice daily, and imatinib, respectively.[58] The estimated 10-year survival rates were 87.6%, 90.3%, and 88.3%, respectively.[58] Adverse events resulting in TKI discontinuation were highest with nilotinib 400 mg twice daily dose (35.4%) compared with nilotinib 300 mg twice daily and imatinib (24% and 20%, respectively). Cardiovascular events were noted to be significantly higher with nilotinib, particularly at the higher dose.[58] A second trial from China used the same design and enrolled 267 patients. The MMR rates at 12 months were 52% with nilotinib and 28% with imatinib. The rate of CCyR (84% vs 87%) and PFS (95% each) were similar at 24 months. The rates of progression to CML AP or BP and of survival were similar with nilotinib and imatinib.[59]

Although nilotinib is well tolerated overall, there is a cumulative increased risk of cardiovascular events on therapy. In the 10-year follow-up of the ENESTnd study, the cumulative cardiovascular event rates were 24.8%, 33.4%, and 6.3% with nilotinib 300 mg twice daily, nilotinib 400 mg twice daily, and imatinib 400 mg/day, respectively.[58] Other notable side effects include grade 3 or 4 myelosuppression (neutropenia or thrombocytopenia in 10%–20%). Nonhematologic toxicities include headaches, skin rashes (20%–30%; can be alleviated by dose reduction), elevated indirect bilirubin (10% to 15%), and asymptomatic elevation of lipase and amylase (10% to 15%). Rare cases (<1%) of pancreatitis have been reported. Diabetes may also be exacerbated with nilotinib (10% to 20%).

Bosutinib

Bosutinib is a potent dual SRC/ABL kinase inhibitor.[60] The drug was first approved for treating adults with CML and resistance or intolerance to prior therapy. In 2018, it was approved as first-line treatment of patients with CML-CP.[60] In the multinational phase III randomized BFORE trial, 590 patients with newly diagnosed CML-CP were randomized to bosutinib 400mg/day (n = 268) or imatinib 400mg/day (n = 268). The primary endpoint of the study was MMR at 12 months. Patients treated with bosutinib had a higher rate of MMR at 12 months (47% vs 37%; P = 0.02). Similarly, the 12-month CCyR rate was significantly higher with bosutinib (77% vs 66%; P = .0075). Early molecular responses (*BCR-ABL1* transcripts ≤10% at 3 months) were associated with superior PFS and OS and were achieved more frequently on bosutinib (75% vs 57%). At 2 years, six patients (2.2%) receiving bosutinib and seven patients (2.6%) receiving imatinib experienced disease progression to AP or BP. Among treated patients, 22% of patients receiving bosutinib and 27% of patients receiving imatinib discontinued treatment, most commonly for drug-related toxicity (13% and 9%, respectively). Grade 3 or greater diarrhea (8% vs 0.8%) and increased alanine aminotransferase (19% vs 1.5%) and aspartate aminotransferase (10% vs 2%) levels were more common with bosutinib. Cardiac and vascular toxicities were uncommon. The 2-year cumulative rates of CCyR were 76% and 66% among patients treated with bosutinib and imatinib (P = .0052), respectively. The 2-year cumulative rates of MMR, MR4, and MR4.5 were 57% and 34% (P = .0036), 27% and 10% (P =.0249), and 15% and 3% (P = .0542), respectively.[60] The estimated 2-year survival rates were similar (99% vs 97%).

The MD Anderson Cancer Center Experience

At MD Anderson, several frontline studies ran sequentially and in parallel and evaluated the outcomes of patients with newly diagnosed CML treated (July 2000–September 2013) with imatinib 400 mg/day (n = 68), imatinib 800 mg/day (n = 200), dasatinib 50 mg twice daily or 100 mg/day (n = 106), and nilotinib 400 mg twice daily (n = 108). An analysis of the total experience of 482 patients is summarized in Table 4–4.[55] The experience showed similar benefits with high-dose imatinib and second-generation TKIs in relation to early surrogate endpoints of long-term outcome (CCyR, MMR, MR4.5). Patients treated with imatinib 400 mg/day had a significantly inferior 5-year EFS compared with those treated with high-dose imatinib and second-generation TKIs (P = .009). However, 5-year transformation-free survival (TFS), FFS, and OS were not different by treatment strategy (P = .353, 0.078 and P = .381, respectively). As expected, among patients who achieved CCyR, there was no difference in outcomes regardless of whether MMR or MR4.5 were additionally achieved.[61]

The long-term results of frontline nilotinib and dasatinib therapy were recently published.[62,63] At a median follow-up period of 78 months, among the 122 patients treated with nilotinib 400 mg twice daily, the cumulative CCyR and MMR rates were 91%. Seventy-five percent and 59% of patients achieved MR4.5 and a sustained MR4.5 beyond 2 years, respectively. The estimated 5-year EFS and OS were 89% and 93%, respectively. The corresponding rates at 10 years were 85% and 88%, respectively.[62] At a median follow-up time of 6.5 years, among the 149 patients treated with dasatinib 100 mg/day or 50 mg twice daily, the cumulative CCyR rate at 11 years was 92.6%. The MMR, MR4.5, and sustained MR4.5 rates were 88.2%, 79.5%, and 55%, respectively. The 10-year OS, TFS, EFS, and FFS rates were 89%, 95%, 86%, and 65%, respectively.[63]

TABLE 4–4 The MD Anderson Cancer Center Experience with Frontline Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia

Outcome (%)	Imatinib 400 mg/day (*n* = 68)	Imatinib 800mg/day (*n* = 200)	Dasatinib 100 mg/day (*n* = 106)	Nilotinib 400 mg BID (*n* = 108)
CCyR	87	90	96	93
MMR	76	86	90	91
MR4.5	57	74	73	71
5-year EFS	71	84	93	84
5-year FFS	59	70	76	70
5-year TFS	87	94	96	88
5-year OS	89	93	98	89
Discontinued	43	43	21	25

BID, twice a day; CCyR, complete cytogenetic response; EFS, event-free survival; FFS, failure-free survival; MMR, major molecular response (BCR-ABL1 transcript [IS] ≤0.1%; MR4.5 BCR-ABL-1 [IS] ≤0.0032%); OS, overall survival; TFS, transformation-free survival.

Given the equivalent efficacy and lower toxicity of lower dose dasatinib in our phase II study, dasatinib 50 mg/day has become our standard of care for frontline therapy of patients with CML-CP.

Patient Age and Comorbidities

The patient's age plays a significant role in deciding TKI therapy. Younger individuals have a longer life expectancy. Therefore, in younger patients, the goal is more frequently durable deep molecular responses, preferably undetectable *BCR-ABL1* transcript levels, to allow for consideration of treatment discontinuation. This is more likely to be achieved with second-generation TKIs that induce rapid and significantly deeper molecular responses compared with imatinib. Therapy discontinuation might be less relevant in older patients in whom the goal is survival normalization with minimal adverse events, particularly serious ones (eg, arterio-occlusive events [AOEs], pleural effusions). Imatinib might be a more adequate initial therapy in older patients.

Most TKIs are reasonably well tolerated with close observation and supportive care. Each TKI therapy has a distinct toxicity profile that should be considered when deciding on therapy (Table 4–5). For patients with baseline cardiopulmonary comorbidities such as chronic obstructive pulmonary disease, congestive heart failure, or uncontrolled hypertension or pulmonary arterial hypertension,[64] a TKI other than dasatinib may be favored, given the risk of pleural effusions. Dasatinib also impairs platelet function,[65] and patients on concomitant anticoagulants may be at increased risk for hemorrhagic complications.[66]

Nilotinib has been linked with hyperglycemia and QT interval prolongation and should be used with caution in uncontrolled diabetics and in patients with baseline QT prolongation (routine monitoring of the QT interval is essential). Potassium and magnesium should be repleted to optimal serum levels before starting nilotinib. Nilotinib should be taken on an empty stomach to avoid excess drug exposure. Nilotinib has also been associated with significantly increased incidence of peripheral artery occlusive disease, cerebrovascular accidents, and cardiovascular events.[58] In the 10-year follow-up of the ENESTnd trial,[58] approximately 33.4% of patients experienced vascular events. Cardiovascular events are less common with bosutinib and with imatinib. It is therefore reasonable to choose these for patients with cardiovascular morbidities. Nilotinib may occasionally cause pancreatitis and should be avoided in patients with prior history or risk factors for pancreatic inflammation.

Imatinib is associated with the development of peripheral edema as one of its major side effects. Close monitoring and intermittent use of loop diuretics might mitigate the effects of fluid retention. Other common side effects associated with imatinib include weight gain, fatigue, periorbital edema, bone and muscle aches, and nausea. These are mostly mild to moderate. A decrease in glomerular filtration rate may occur in patients treated with imatinib, but fewer than 5% to 10% experience significant elevations in creatinine with long-term therapy.

Bosutinib is associated with gastrointestinal, hepatic, and renal toxicity. Among patients with such comorbidities, bosutinib should be avoided or used cautiously. Bosutinib should be avoided in patients with inflammatory bowel disease and renal dysfunction.[67]

Cost of Therapy

The prices of TKIs are of concern, given that patients can now remain on TKIs and expect to have a normal

TABLE 4–5 Selecting frontline Tyrosine Kinase Inhibitor Therapy: Comorbidities and Toxicity

Toxicity	Imatinib	Dasatinib	Nilotinib	Bosutinib
Pleural effusion	–	++	–	–
Liver	+	+	+	+
Transaminases	+	+	+	++
Bilirubin	+	–	++	–
Lipase	–	–	++	–
Glucose	–	–	++	–
Diarrhea	+	–	–	++
Rash	+	+	++	+
Bleeding	–	+	–	–
Vascular events	–	–	++	–
QT interval increase	–	+	++	–
Muscle cramps	++	–	–	–
Edema or weight gain	++	–	–	–

lifespan. The cost of cancer drugs has risen drastically over the past decade.[68–73] Most are priced at over $120,000 to $160,000 annually.[68–70] When first approved in the United States, the annual price for imatinib was less than $30,000. Patients treated with imatinib are now living a "normal" life span. [70,71] Paradoxically, with a higher number of patients and a longer duration of therapy, the annual price of imatinib has quadrupled to $132,000. This price is comparable to the cost of second-generation TKIs, all priced above $150,000 per year of therapy.

Generic formulations of imatinib are now available in the United States, although at a higher initial cost than expected. Since 2017, there are several generic imatinib formulations available, and their wholesale price is decreasing rapidly. The price of generic imatinib is $3000 to $8000 per year in Canada and $400 per year in India. With the availability of generic imatinib at a relatively lower cost compared with second-generation TKIs, one may offer generic imatinib to patients in the frontline setting with low- and intermediate-risk disease and second-generation TKIs to those with high-risk disease.[73]

At MD Anderson, we assessed the treatment value of second-generation TKIs compared with imatinib to achieve treatment-free remission (TFR) in patients with CML using a decision analytical model.[73] Different modeled scenarios were considered. Incremental cost-effectiveness ratios (ICERs) were calculated, and cost effectiveness was assessed using two societal willingness-to-pay thresholds: $50,000 per quality-adjusted life-year (QALY) in all markets and $200,000 per QALY in the United States. None of the explored scenarios showed a good treatment value for using second-generation TKIs at the current prices in the United States or at the price of $30,000 to $40,000 per year elsewhere. The Austrian groups reported the frontline therapy with nilotinib yielded ICERs of 121,400 € per QALY compared with frontline imatinib without second-line TKI after imatinib failure; nilotinib followed by dasatinib yielded 152,400 € per QALY compared with imatinib followed by nilotinib after imatinib failure.[72] To be cost effective, the cost of second-generation TKIs should be less than $25,000 per year.[73–75] Under the same conditions in developing nations, the annual price of second-generation TKIs should not exceed $10,000 per year of therapy.

Finally, lower dose dasatinib and generic second-generation TKIs may constitute a cost-effective strategy by allowing the achievement of an optimal response as well as TFR at a lower cost.

Disease Characteristics and Risk Score

The CML risk score plays an important role in deciding the type of TKI therapy. Patients who score low by the Sokal[20] or Hasford[21] prognostic models responding optimally to all TKIs with higher rates of deep molecular response with second-generation TKIs. The outcomes differ with intermediate- and high-risk disease in which the use of second-generation TKIs demonstrate significantly higher deep molecular response (MR4.5) and with a lower risk of transformation. In the ENESTnd study, in which patients were categorized based on the Sokal scoring system, in the intermediate group, the rate of transformation was 10% in the

imatinib arm versus 1% to 2% in the nilotinib arm; in the high-risk group, the rate of transformation was 14% in the imatinib arm versus 5% to 9% in the nilotinib arm.[57, 58]

MONITORING RESPONSE

Monitoring includes routine complete blood counts with differential, cytogenetics, and molecular analysis for *BCR-ABL1* transcript levels and for BCR-ABL1 kinase domain mutations (Table 4–6). The monitoring of complete blood counts should be implemented every 1 to 2 weeks until complete hematologic response and later every 3 months, more frequently if clinically indicated.[36] Conventional cytogenetic testing should be performed to assess the presence of additional chromosomal abnormalities, particularly i(17)(q10), -7/del7q, and 3q26.2 rearrangements, associated with a relatively adverse prognosis.[19]

At diagnosis, all patients with leukocytosis suspected to be CML should undergo bone marrow aspiration and biopsy to establish the diagnosis, assess percentages of blasts and basophils, and evaluate the presence of clonal evolution. Currently, bone marrow evaluation is recommended at diagnosis, for failure to reach suggested response milestones, and for any sign of loss of hematologic and cytogenetic response.[76] An alternative technique to determine cytogenetic response is with the use of FISH or RT-PCR (or both) on peripheral blood. If a patient is responding optimally and the FISH study result is negative at 6 or 12 months or *BCR-ABL1* transcripts (IS) are less than 1%, it may be reasonable to omit further marrow examination because the patient is likely to be in stable CCyR.[77,78]

For patients in durable CCyR during TKI therapy, intermittent molecular monitoring every 3 to 6 months using quantitative RT-PCR is acceptable and useful but may lead to erroneous changes in treatment because of discordant results between laboratories or even within the same laboratory. The trend of quantitative RT-PCR is more reliable to avoid the overinterpretation of the variability of RT-PCR results. The additional benefit of the achievement of MMR among patients in CCyR remains unclear. Irrespective of MMR, a similar survival rate was reported in patients who received imatinib or second-generation TKI and achieved CCyR.[12,79–82]

The clinical impact of early molecular response has been shown in a number of studies. A *BCR-ABL1* transcript level <10% (IS) at 3 months of TKI therapy has been shown to divide patients into high- and low-risk categories for long-term outcomes (ie,, progression to BP, death).[79,83,84] The DASCERN, a randomized, open-label, international phase 2b trial, evaluated the impact of *BCR-ABL1* transcripts >10% (IS) at 3 months after initial treatment with imatinib 400 mg/day in patients with CML-CP who achieved complete hematologic response. Patients were randomized to receive dasatinib 100 mg/day or higher dose of imatinib.[85] Patients who switched to dasatinib 100 mg/day achieved a 12-month MMR rate of 29% compared with 13% among patients who continued imatinib ($P = .005$). However, the clinical outcome of PFS and OS were similar between groups with the median follow-up period of 30 months.[85]. A follow-up measurement at 6 months will help define patients clearly in need of a change in therapy.[87–96] Experts have suggested that a follow-up measurement at 6 months will help define patients clearly in need of a change in therapy.[93] This has been retrospectively analyzed by several large groups.[94–96] Two independent studies reported similar survival in patients who did or did not achieve *BCR-ABL1* transcript levels >10% (IS) at 3 months.[95,96] Patients who continued the same TKI therapy and achieved *BCR-ABL1* transcripts (IS) less than 10% at 6 months of TKI therapy maintained similar long-term outcome compared with patients with *BCR-ABL1* transcripts (IS) <10% at 3 months of therapy. The *BCR-ABL1* transcripts (IS) <10% at 6-month is the first milestone for survival. The 4-year OS rates were 100% and 74% in patients with the *BCR-ABL1* transcripts (IS) <10% and

TABLE 4–6 Main Features of the Monitoring Techniques Available for Chronic Myeloid Leukemia

Parameter	Cytogenetics	FISH	PCR
No cells evaluated	20	200	<10,000
Rapidity (days)	14–21	1–3	7–10
Source	BM	BM or PB	BM or PB
Clonal evolution	Yes	No	No
False negativity	NA	Yes	Yes
False positivity	No	≤10%	NA

BM, bone marrow; FISH, fluorescent in situ hybridization; NA, not applicable; PB, peripheral blood; PCR, polymerase chain reaction.

>10% at 6-month of TKI therapy. Given the observed worse survival in patients on frontline imatinib, it may be reasonable to switch imatinib to a second-generation TKI for patients with *BCR-ABL1* transcripts (IS) >10% after 6 months of therapy. Although suboptimal response is associated with a statistically significant probability of worse survival, the consideration of allogeneic SCT should be deferred because patients with suboptimal response on second-generation TKI still had an estimated survival rate of 81%.[46]

WHEN TO SWITCH TYROSINE KINASE INHIBITOR THERAPY

Achievement of CCyR by 12 months and maintenance of CCyR thereafter is associated with improved survival, similar to that of a general population. With standard-dose imatinib, CCyR should be expected by 12 months of therapy, but it may be reasonable to expect CCyR with second-generation TKIs within 3 to 6 months of treatment.[98]

Patients who do not achieve a complete hematologic response by 3 months should be considered for a change in TKI treatment unless it is related to poor adherence. Considering a change in treatment at 3 or 6 months for *BCR-ABL1* transcript level >10% for patients on imatinib or second-generation TKIs, very early switching has not yet been shown to influence the long-term outcomes.[99] As such, it can be advocated that if the transcript level at 3 months is greater than 10%, providers should perform serial molecular monitoring between 3 and 6 months for definitive treatment response evaluation.[93] If patients retain >10% transcript levels (IS) at 6 months, a change in therapy is indicated because the chance of CCyR would be low. A 3-month value of 10% (IS) may not be accurate: in a report in one sample collected at 3 months and tested 96 times, the mean value was 11% (range, 5%–16%), with only 31% of tests being 10% or less.[100] This approach also applies to patients on second-generation TKIs.[99] Another study randomized patients in CCyR on imatinib for at least 2 years to continue imatinib or switch to nilotinib.[101] Switching to nilotinib induced deeper molecular responses but did not translate into an improvement in PFS or in other meaningful outcomes.

Patients who meet all the relevant benchmarks in the first 12 months are monitored periodically using molecular testing with or without FISH (molecular testing only if *BCR-ABL1* transcripts (IS) consistently <0.1%). If there are clear signs of possible failure, patients should undergo a bone marrow examination with cytogenetic analysis and molecular testing, including analysis for mutations. Any degree of cytogenetic relapse calls for a change of therapy. Fluctuating molecular levels during continuous CCyR would prompt closer monitoring and a compliance assessment. Some CML experts advocate a change of therapy for a documented consistent loss of MMR after 3 to 4 years of therapy (*BCR-ABL*1 transcripts (IS) >0.1%), particularly if transcript levels (IS) are consistently above 0.3% to 0.5%.

The new ELN 2020 recommendations and the National Comprehensive Cancer Network guidelines propose the achievement of TFR as an important goal of therapy in CML. This is discussed later.

Multiple studies consistently reported the association of CCyR within 1 year of therapy (or later) with improved survival compared with lesser degrees of response. Thus, the primary endpoint of TKI therapy is the achievement of CCyR. MMR (*BCR-ABL1* transcripts [IS] ≤0.1%) was not associated with improvement of survival, but was associated with improved EFS and stable CCyR. Treatment discontinuation can be considered for patients who achieved deep molecular response such as CMR (nonmeasurable *BCR-ABL1* transcripts). The use of allo-SCT and the switch to other TKI should not be considered for patients who achieved CCyR without MMR or CMR. The lack of major cytogenetic response (Ph-positive metaphases ≤35%; *BCR-ABL1* transcripts [IS] ≤10%) by 6 months may justify the TKI switch to a second-generation TKI. The achievement of CCyR within 3 to 6 months of frontline second-generation TKI therapy improved outcomes. Recommendations are summarized in Table 4–7, which are mostly consistent with the 2020 ELN recommendations.[93]

MANAGEMENT OF TYROSINE KINASE INHIBITOR RESISTANCE

Given that the survival of patients with CML is approaching that of the general population with long-term TKI therapy, and given that some patients may fail on a particular TKI therapy because of intolerance or resistance, the number of patients who have a history of at least one TKI resistance has been increasing. One of the mechanisms of TKI resistance is the acquisition of point mutations in the BCR-ABL1 kinase domain. The acquired mutation of kinase decreases the affinity of TKI, which impairs the activity of TKIs. Although second-generation TKI can overcome imatinib-resistant BCR-ABL1 kinase domain mutations, novel mutations resistant to second-generation TKI emerged through clonal selection. The gatekeeper mutation, T315I mutation, causes resistance to currently available TKIs except ponatinib.[102]

Although suboptimal response suggests TKI resistance or intolerance, TKI compliance and drug–drug interactions should be evaluated before the decision to switch TKI. The range of estimated rates of imatinib

TABLE 4–7 Response Definitions to Imatinib in Chronic Phase Chronic Myeloid Leukemia (2020 European LeukemiaNet Recommendations)

	Optimal	Warning	Failure
Baseline	NA	High-risk ACA, high-risk ELTS score	NA
3 months	≤10%	>10%	>10% if confirmed within 1–3 months
6 months	≤1%	>1%–10%	>10%
12 months	≤0.1%	>0.1%–1%	>1%
Any time	≤0.1%	>0.1%–1%, loss of ≤0.1%[a]	>1%, resistance mutations, high-risk ACA

For patients aiming at treatment-free remission (TFR), the optimal response (at any time) is BCR-ABL1 ≤0.01% (MR4).
A change of treatment may be considered if major molecular response (MMR) is not reached by 36–48 months.
[a]Loss of MMR (BCR-ABL1 > 0.1%) indicates failure after TFR.
ACA, additional chromosome abnormalities in Philadelphia chromosome–positive cells; ELTS, EUTOS long-term survival score; NA not applicable.

adherence was from 75% to 90% with worse outcome in patients with lower adherence.[103, 104] The monitoring of adherence is encouraged in younger patients, those with chronic toxicities, and those on higher dose of TKI therapy.[102]

SECOND- AND THIRD-GENERATION TYROSINE KINASE INHIBITORs

Second-generation TKIs were originally approved as second-line therapy for patients with CML-CP who failed frontline imatinib. Second-line TKI therapy with nilotinib, dasatinib, or bosutinib achieved high CCyR and MMR rates in patients who had suboptimal response or resistant to frontline imatinib therapy after initial optimal response. Although the dose escalation of imatinib to 800 mg/day may overcome resistance to standard-dose imatinib, the switch to second-generation TKI is a more effective strategy to achieve response.[105,106] In patients who failed frontline imatinib therapy, second-line second-generation TKIs, including nilotinib,[107,108] dasatinib,[106,108] or bosutinib,[89] achieved higher rates of major cytogenetic response, CCyR, and MMR compared with high-dose imatinib therapy.[109] The achievement of higher rates of CCyR and MMR translated into higher rates of PFS. These consistent results of second-generation TKI studies after imatinib failure suggest that an earlier switch from imatinib to a second-generation TKI may be more effective than a switch at the time of progression or at the time of losing hematologic or cytogenetic response. Patients in suboptimal response with frontline standard-dose imatinib had a higher rates of 12-month CMR when standard-dose imatinib was switched to nilotinib compared with high-dose imatinib.[110] Earlier change from standard-dose imatinib to dasatinib before the loss of MCyR resulted in higher rates of responses (CCyR and MMR) and improved clinical outcomes, including 2-year EFS, TFS, and OS.[106] Despite the limitations of various designs of clinical trials, the earlier intervention before the loss of major cytogenetic response (or equivalent) was associated with better outcomes.

Bosutinib was originally approved for the treatment of patients with imatinib-resistant or -intolerant CML.[89] The bosutinib dose of 500 mg/day was chosen with the potential for dose escalation to 600 mg/day for patients with suboptimal response on the phase 2 clinical trial. Among 288 patients enrolled, more than two thirds of patients had a history of imatinib resistance. Thirty-one percent of patients achieved MCyR within 6 months of bosutinib therapy (primary endpoint); 41% achieved CCyR. Although bosutinib does not have activity on T315I mutations, bosutinib has maintained activity in most imatinib-resistant mutations. Durable responses were observed in both imatinib-resistant and imatinib-intolerant groups. Common toxicities included gastrointestinal (GI) symptoms (diarrhea, nausea, and vomiting) and skin rash. Eighty-four percent of patients had all grades of diarrhea, and 9% had grade 3 diarrhea. Myelosuppression and liver function test abnormalities were common. A strategy of sequential dose escalation of bosutinib (200 mg/day for 2 weeks; 300 mg/day from 2 weeks to 3 months; 400 mg/day at 3 months if *BCR-ABL1* transcript level >1% [IS] at 3 months) and otherwise continue 300 mg/day may be considered in older patients with CML and frontline failure to one prior TKI (both resistance and intolerance).[111] Lower *BCR-ABL1* transcript levels were observed in 67% of patients. The dose-escalation strategy resulted in lower incidences of diarrhea (all grades, 16%; grade 3, 8%) and liver function test abnormalities (all grades, 22%; grade 3, 10%; and grade 4, 2%).[111]

Ponatinib is an FDA-approved third-generation TKI that exhibits activity against T315I mutation.[91] Preclinical studies showed ponatinib was 500 times more active in inhibiting *BCR-ABL1* than imatinib.[112] The FDA approved ponatinib at an initial dose of

45 mg orally daily for the treatment of patients with T315I-mutated CML and Ph-positive ALL and in patients for whom no other TKI therapy was indicated based on the results of the phase II PACE (Ponatinib Ph-positive acute lymphoblastic leukemia [ALL] and CML Evaluation) trial. The PACE trial included 449 patients with heavily pretreated all-stage CML (CP, AP, and BP) and Ph-positive ALL. Patients who had a prior history of intolerance or resistance to dasatinib or nilotinib and who had T315I mutation were eligible.[113] Patients enrolled were stratified by disease phase and T315I mutation status (absent or present). Among 267 patients with CML-CP, a 12-month MCyR was observed in 56% and 70% of patients overall and patients with a T315I mutation, respectively. There was a trend for higher rates of response in patients who received fewer prior TKI therapies. At the final 5-year result of the PACE trial, 60%, 40%, and 24% of patients achieved MCyR, MMR, and MR4.5, respectively; 82% and 59% of patients who achieved MCyR and MMR maintained response at 5 years.[102] The 5-year PFS and OS were 53% and 73%, respectively. AOEs, including cardiovascular, cerebrovascular, and peripheral vascular events, were observed in 84 (31%) patients and severe AOEs in 69 (26%). Common treatment-emergent adverse events (≥40%) in patients with CML-CP included skin rash (47%), abdominal pain (46%), thrombocytopenia (46%), headache (43%), dry skin (42%), and constipation (41%).[102, 113] Less common but notable adverse events were grade 3 or 4 skin rashes (4%), pancreatitis (7%), atrial fibrillation (6%), and grade 3 or 4 hypertension (14%).

As of June 2020, ponatinib labeling includes a warning for arterial thrombosis, including cardiovascular, cerebrovascular, and peripheral arterial thrombosis, and hepatotoxicity.[114] The PACE trial reported that AOEs were more frequent in older patients with previous history of cardiovascular events and with cardiovascular risk factors, including hypertension, diabetes, or hyperlipidemia. Patients with a longer history of CML since the diagnosis and patients taking higher doses of ponatinib were at higher risk for AOEs.[102]

A randomized, open-label, phase 2 trial of ponatinib in patients with resistant chronic-phase CML (OPTIC) evaluated the efficacy and safety of a range of ponatinib doses.[115] Patients were randomized to one of three starting doses of ponatinib at 45, 30, and 15 mg/day. Doses were reduced to 15 mg/day upon achievement of *BCR-ABL1* transcript levels <1% (IS). The AOEs and serious AOEs were 5% and 2%, 4% and 3%, and 1% and 0%, respectively. The achievement of *BCR-ABL1* 1% or less (IS) was observed in 38.7%, 27.4%, and 26.5% at the dose of 45 mg/day, 30 mg/day, and 15 mg/day, respectively; the achievement of MMR was observed in 14.7%, 17.8%, and 19.1%, respectively. To minimize the risk of AOEs, it may be reasonable to start ponatinib 30 mg/day (except in T315I-mutated CML where 45mg/D is better) and lower the dose to 15 mg/day when *BCR-ABL1* transcript <1% (IS) are achieved.

Novel Tyrosine Kinase Inhibitors

Although currently FDA-approved TKIs have shown significant survival improvement in CML-CP, the development of novel TKIs continues in order to overcome the resistance of T315I mutation and to pursue less toxic options. Asciminib is a novel allosteric BCR-ABL1 TKI that blocks BCR-ABL1 in an active conformation through binding a myristoyl site of the BCR-ABL1 oncoprotein.[116] The mechanism is different from all other TKIs and targets both the unmutated and mutated BCR-ABL1, levels including T315I mutation. In a phase 1 trial, adults with CML-CP or CML-AP who failed at least two TKIs (resistance or intolerance) were treated with asciminib. Among 150 patients enrolled, 141 patients had CML-CP and 9 patients had CML-AP.[117] Patients received asciminib once or twice daily at doses of 10 to 200 mg/day. Among 34 patients who lost hematologic response, 32 (92%) achieved a complete hematologic response; among 57 patients who lost cytogenetic response, 31 (54%) achieved CCyR. Among 91 evaluable patients, 44 (48%) achieved MMR by 12 months, including 8 (57%) ponatinib resistant or intolerant patients. In patients with a T315I mutation before asciminib, 5 (28%) patients achieved an MMR. Dose-limiting toxicities included asymptomatic elevations of lipase levels and clinical pancreatitis. A phase III randomized trial is ongoing in patients who failed two TKIs without T315I mutation and who are randomized to either asciminib or bosutinib.

Olverembatinib (HQP1315), a novel orally active potent third-generation TKI, enrolled 101 patients, including 87 patients with CML-CP and 14 patients with CML-AP who were resistant or intolerant to two or more prior TKIs or with T315I mutation after one or more prior TKIs. Sixty-two (61%) patients had T315I mutation.[118] Olverembatinib was administered every other day on a 28-day cycle; the dose escalation was 30, 40, and 50 mg. With a median follow-up period of 13 months, the rates of CHR, MCyR, CCyR, and MMR in patients with CML-CP were 94.5%, 69.1%, 60.5%, and 37.2%, respectively. Common adverse events included grade 3 or 4 thrombocytopenia and grade 1 skin pigmentation and hypertriglyceridemia. Two pivotal studies in patients with CML-CP and CML-AP are ongoing.

Vodobatinib (K0706), a novel third-generation TKI, was tested in a phase I trial in patients who failed 3 or more TKIs or who had comorbidities that limited the use of second-and third-generation TKI.[119] Among 35 patients, vodobatinib was given at dosage range of

12mg to 240mg daily. The recommended phase II dose was 174 mg/day. At 240 mg/day, two dose-limiting toxicities were grade 3 dyspnea, grade 2 noncardiac chest pain, and grade 2 shortness of breath caused by fluid retention. Among 27 patients treated 7 patients achieved CCyR. A phase 2 study of vodobatinib in patients who have received multiple prior TKIs is ongoing.

PF-114 is a fourth-generation oral TKI that has activity against wild-type and BCR-ABL1 mutations, including T315I.[120] A phase I trial in patients with CML-CP/CML-AP failing two or more TKIs or T315I mutations reported on 17 patients treated with PF-114 200 mg to 600 mg. The maximum tolerated dose was 600 mg (grade 3 psoriasis-like skin lesions). The recommended dose was 300 mg/day with 6 of 11 patients achieving MCyR; 4 of 11 patients achieved MMR.

Selection of a Second- or Third-Line Generation Tyrosine Kinase Inhibitor Option

Bone marrow examination should be performed at the time of treatment failure to evaluate the phase of CML and to document any evidence of clonal evolution. BCR-ABL1 kinase domain mutations should be examined to guide the selection of the salvage TKI option.[103,104,121,122] Among second-generation TKIs, the decreased sensitivity of TKI to BCR-ABL1 mutations were reported in vitro and in vivo.[103,104,121,122] In the presence of Y253H, E255K/V, and F359C/V, mutations either dasatinib or bosutinib are favorite options. In the presence of V299L and F317L mutations, nilotinib can be considered. In the absence of BCR-ABL1 mutations, patient comorbidities, toxicity profile, and cost should be considered.

Bosutinib has activity in most imatinib-resistant CML clones.[89] Bosutinib may be a reasonable salvage option in patients after frontline imatinib failure and who have comorbidities that may increase the risk of adverse events observed with dasatinib or nilotinib (eg, AOEs, pleural effusion, pulmonary hypertension). Common distinct adverse events include diarrhea and other GI complaints,[123] and liver function and renal abnormalities. Patients with underlying kidney dysfunction should be monitored closely.[67]

In T315I-mutated CML, ponatinib should be considered. Ponatinib can be considered in patient with at least one second-generation TKI resistance. Notable toxicities include AOEs, pancreatitis, hypertension, and severe skin rash. Although the risk of AEOs is not negligible, the treatment benefit from ponatinib outweighs the risks in most patients with a T315I mutation. The risks of AOEs can be minimized at reduced doses and optimal management of cardiovascular risk factors.

Second- and third-generation TKIs have not been compared head to head. Selection of one or the other is based on the side effect profiles, mutation profile, drug interactions, compliance issues, and the patient's preexisting medical conditions. Mutational analysis is required after failure of imatinib or second-generation TKIs or after progression to CML-AP or CML-BP.

Allogeneic Stem Cell Transplantation

TKI therapy has drastically changed the outcome of patients with CML-CP. Since 2000, the number of patients who underwent allo-SCT has decreased. Although the majority of patients who achieved deep molecular remission have a stable clinical course, approximately 1% to 2% of patients develop TKI-resistant CML every year. Given the increased prevalence of CML, the number of patients requiring allo-SCT may start to increase. Allo-SCT is an important curative option in patients who fail at least two TKIs or who harbor a T315I mutation if ponatinib is not effective.[124,125] Prior TKI exposure did not affect the outcome after allo-SCT lower burden of CML may have a better outcome.[125]

The financial burden and availability of allo-SCT and TKI therapy needs to be considered. The estimated cost of allo-SCT, a curative one-time procedure, is $500,000 in the United States but only $12,000 to $20,000 in developing countries.[126,127] Given the low annual cost of genetic imatinib of $400 to $1000 per year, allo-SCT should not be considered before TKI therapy since the survival of patients with CML-CP is approaching that of a general population[12]. Given the estimated survival of CML-CP for 30+ years from diagnosis, the total estimated cost would be $12,000 ($400 × 30 years), which is comparable to the lowest cost of allo-SCT in developing countries. Generic imatinib therapy has also significantly lower medical costs than allo-SCT. In patients with imatinib-resistant or -intolerant CML, the financial comparison of medical costs with second- or third-generation TKIs versus allo-SCT should be discussed.[127] In nations with financial constraints, allo-SCT could be offered as a salvage treatment option. Recommendations for the role and timing of allo-SCT in patients with CML are outlined in Table 4–8.[128]

TREATMENT-FREE REMISSION (TFR)

Multiple clinical trials of TFR evaluated the discontinuation of TKI therapy in patients who achieved deep molecular remission to aim at a functional cure of CML. The Stop Imatinib (STIM) trial evaluated treatment discontinuation in 100 patients on imatinib with undetectable transcripts for at least 2 years.[129]

TABLE 4–8 Recommendations Regarding the Role and Timing of Allogeneic Stem Cell Transplant (Allo-SCT) in Chronic Myeloid Leukemia

Status	TKIs	Allogeneic HSCT
AP, BP	Interim treatment to MRD	If in remission
Imatinib of first-line second-generation TKI treatment failure in CP, with T315I mutation	Ponatinib	If not responding well to ponatinib
Imatinib or first-line second-generation TKI treatment failure in CP, no clonal evolution, no mutations, good initial response to imatinib	Long-term treatment with TKI in second-line setting	Third line after second TKI treatment failure
Imatinib or first-line second-generation TKI treatment failure in CP, with clonal evolution, with mutations resistant to second-generation TKIs, no CyR to imatinib	Interim treatment with ponatinib eventually to MRD	As soon as possible if no response to ponatinib
Older patients (age older than 70 years), after imatinib treatment failure	Long-term treatment with TKI in second-line setting	Forego allo SCT for many years or for the patient lifetime (maximize quality of life)

AP, accelerated phase; BP, blast phase; CML, chronic myeloid leukemia; CP, chronic phase; CyR, cytogenetic response; MRD, minimal residual disease; TKI, tyrosine kinase inhibitor.

Molecular relapse was observed in 42 (61%) patients; 40 patients relapsed within 6 months of TKI discontinuation. At the time of molecular relapse, the reintroduction of imatinib achieved undetectable transcripts in 26 (62%) patients and decreased transcript levels in 16 (38%) patients. TFR was evaluated in multiple studies for patients with a frontline second-generation TKI with different criteria regarding the depth and duration of molecular remission.[130–133]

The European Stop Kinase Inhibitor (EURO-SKI) trial is the largest study of TKI discontinuation.[133] It included 821 patients with CML on frontline imatinib, nilotinib, or dasatinib in deep molecular remission, at least MR4 (*BCR-ABL1* transcript [IS] <0.01%). The molecular recurrence-free survival, defined as the time period from the date of TKI discontinuation to the date of the first event (loss of MMR or death) or censoring was 52% at 2 years. When the same TKI was resumed at the time of molecular relapse (ie,, the loss of MMR) among 321 patients, 81% reachieved a molecular response (MMR or MR4). A multivariate logistic regression showed the duration of MR4 for more than 3 years and the duration of TKI therapy for more than 6 years were prognostic factors. We have reported similar findings in our experience. With a median follow-up period of 30 months, a longer duration of TKI therapy was associated with higher TFR rates. In patients who achieved a sustained MR4.5 for more than 5 years, the TFR rate was 92%.[134] This suggests that longer duration of sustained MR4.5 may translate into improved TFR outcome.

A long-term periodic molecular monitoring is mandatory during TFR. With a follow-up over 15 years of a single institution experience of treatment discontinuation, 128 patients were treated with frontline imatinib (61%), frontline second-generation TKI (11%), and second line second-generation TKI (28%) and entering first TFR (TFR1).[135] With a median follow-up period of 6.5 years, 65 patients had a molecular relapse, including 9 (14%) relapses after 2 years; 1 patient relapsed at 6.4 years of TKI discontinuation. Patients with late molecular relapse had a long-term period of *BCR-ABL1* fluctuations between MR4 and MMR. We have reported an anecdotal case of sudden progression to myeloid BP under TFR.[136] The incidence of late molecular relapse and potential sudden progression to BP suggest the necessity of long-term follow-up of patients in TFR.

Initially, second-generation TKI therapy was reported to have a relatively higher TFR rate compared with that of first-generation imatinib. Successful TFR without TKI therapy over years will benefit younger patients given that their expected survival is longer.[137] However, the expected percentages of TFR was low; approximately 20% to 25% and 30% to 45% with imatinib and second-generation TKIs, respectively. Multiple randomized clinical trials have consistently reported that treatment with frontline second-generation TKIs achieved higher rates of deep molecular response, and more patients taking second-generation TKIs will be potential candidates for TFR compared with imatinib at the expense of financial costs and toxicities.[58,73] The use of second-generation TKI will cost $917,056 additionally over 10 years to achieve moderate improvement of QALY. The analysis of the incremental cost-effective ratio showed the use of second-generation TKIs will cost more than $22,000,000 to achieve a gain of 1 QALY from the replacement

of frontline generic imatinib with second-generation TKIs. The financial burden of the selection of TKI and the decision of frontline TKI should consider the potential cure fraction carefully.[73–75]

Novel combinations of TKI have been under evaluation in order to increase the fraction of functional cure. These combination strategies aim to target dormant CML stem cells in patients with deep molecular remission over years. CML stem cells may stay in a quiescent state, which may contribute to the relative resistance to TKI therapy.[138] The strategies include the combination of TKI with pegylated IFN-α2b,[139–142] Bcl-2 inhibitors such as venetoclax,[143] JAK2 inhibitors,[144] hypomethylating agents,[145] and immune-mediated treatments such as PD-1 inhibitors and dendritic cell vaccination.[146]

ADVANCED STAGE CHRONIC MYELOID LEUKEMIA

Second- or third-generation TKIs should be considered as initial therapy for patients with advanced stage CML followed by allo-SCT.[147–149] Although the addition of TKIs to chemotherapy improves survival in patients with CML-BP, survival remains suboptimal.[150] Combinations of TKIs and chemotherapy achieved response rates of 40% and 70% to 80% in nonlymphoid and lymphoid CML-BP. The median survivals are 6-12 months and 12-24 months, respectively. The median survival time of 477 patients with CML-BP treated with a TKI was 12 months.[15] Stem cell transplant confers the best outcome for patients in remission after the combination of TKI with intensive chemotherapy. The combination of fludarabine-high dose cytarabine-idarubicin with ponatinib 30 mg/day achieved responses in 11/16 (69%) patients with CML-BP.[151] Five patients achieved MMR after induction therapy; 9 patients proceeded to allo-SCT. The survival rate was 50% at 12 months.

Allo-SCT remains the only curative therapy for CML-AP and CML-BP (cure rates of 40% and 10% to 20%, respectively). The presence of clonal evolution as the only AP criterion is associated with EFS rates of 60%. In patients with CML-AP treated with TKI therapy, 80% achieved hematologic response; the estimated 4-year survival rate was 40% to 55%. In patients with CML-BP, the response rate was 40% and the median survival 9 to 12 months. TKI-naïve patients with de novo CML-AP have a higher survival rate with frontline TKI therapy than patients who progress from CML-CP to CML-AP. The survival rate of de novo CML-AP with TKI therapy were 60%.[14,149]

Allo-SCT should be considered in patients who progress from CML-CP to CML-AP after TKI therapy failure and who fail second- or third-generation TKI in case of de novo CML-AP. The combination of TKI with chemotherapy is an alternative treatment option for patients who are not optimal candidates for allo-SCT or as a bridge therapy to allo-SCT in remission. TKI therapy before allo-SCT does not increase the risk of transplant-related mortality.[152–154] When allo-SCT is performed in patients in CML-AP or CML-BP, posttransplant maintenance TKI therapy should be considered.

FUTURE PERSPECTIVES

Since the advent of TKI therapy, the survival of patients with CML is approaching that of the general population. In 2021, therapeutic options have expanded, including five commercially available TKIs (imatinib, dasatinib, nilotinib, bosutinib, and ponatinib), omacetaxine, and traditional agents, including hydroxyurea, IFN-α, cytarabine and hypomethylating agents. Optimal survival requires optimal monitoring for signs of resistance, optimal decisions regarding switching TKI therapy in case of resistance or intolerance, compliance and adherence to TKIs, and considering allo-SCT in case of multiple TKI failures. Once in deep molecular remission over years of TKI therapy, patients become potential candidates for TFR to aim at functional cure without TKI therapy. The increase in the fraction of functional cure without TKI therapy has a significant impact on the financial burden of patients and their families, as well as on the health care systems, given the prevalence of CML is expected to increase in the United States and worldwide. Therefore, it is important to continue the research aimed at long-term TFR in patients with CML. TKIs-based combinations with available (Bcl-2 inhibitors, JAK2 inhibitors, peg IFN-α2, omacetaxine, decitabine, immunotherapy) or other investigational therapies are in progress. These strategies may eradicate CML stem cells and obviate the need for indefinite TKI therapy to maintain optimal survival. Further understanding of the downstream pathways of *BCR-ABL1* signaling may help develop new strategies to target CML stem cells.

MD ANDERSON PRACTICE TIPS

- At diagnosis, all patients with leukocytosis and suspected for CML should undergo bone marrow aspiration and biopsy to establish the diagnosis, assess percentages of blasts and basophils, and evaluate the presence of clonal evolution.
- With multiple TKIs available for patients with newly diagnosed CML-CP, there are several considerations when choosing a starting agent such as patient status (age and comorbidities, TKI toxicity profile), cost of treatment, and disease characteristics and risk score.
- Given the equivalent efficacy and lower toxicity of lower dose dasatinib, dasatinib 50 mg/day has become our standard of care for frontline therapy of patients with CML-CP.
- To minimize the risk of arterio-occlusive AOEs, it may be reasonable to start ponatinib 45mg/day in T315I-mutated CML and 30 mg/day in other resistant CML-CP, and lower the dose to 15 mg/day when *BCR-ABL1* transcripts below 1% (IS) are achieved.
- The use of allogeneic-SCT and the switch to other TKI should not be considered for patients who achieve CCyR without MMR or deep molecular response.
- A long-term periodic molecular monitoring is mandatory during TFR. Patients with late molecular relapse had a long-term period of *BCR-ABL1* transcripts fluctuations between MR4 and MMR. The incidence of late molecular relapse suggest the necessity of long-term follow-up of patients in TFR.

REFERENCES

1. Rowley JD. Letter: a new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. *Nature*. 1973;243:290-293.
2. Mandanas RA, Leibowitz DS, Gharehbaghi K, et al. Role of p21 RAS in p210 bcr-abl transformation of murine myeloid cells. *Blood*. 1993;82:1838-1847.
3. Okuda K, Matulonis U, Salgia R, et al. Factor independence of human myeloid leukemia cell lines is associated with increased phosphorylation of the proto-oncogene Raf-1. *Exp Hematol*. 1994;22:1111-1117.
4. Raitano AB, Halpern JR, Hambuch TM, Sawyers CL. The Bcr-Abl leukemia oncogene activates Jun kinase and requires Jun for transformation. *Proc Natl Acad Sci U S A*. 1995;92:11746-11750.
5. Sawyers CL, Callahan W, Witte ON. Dominant negative MYC blocks transformation by ABL oncogenes. *Cell*. 1992;70:901-910.
6. Shuai K, Halpern J, ten Hoeve J, et al. Constitutive activation of STAT5 by the BCR-ABL oncogene in chronic myelogenous leukemia. *Oncogene*. 1996;13:247-254.
7. Carlesso N, Frank DA, Griffin JD. Tyrosyl phosphorylation and DNA binding activity of signal transducers and activators of transcription (STAT) proteins in hematopoietic cell lines transformed by Bcr/Abl. *J Exp Med*. 1996;183:811-820.
8. Ilaria RL Jr, Van Etten RA. P210 and P190(BCR/ABL) induce the tyrosine phosphorylation and DNA binding activity of multiple specific STAT family members. *J Biol Chem*. 1996;271:31704-31710.
9. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin*. 2010;60:277-300.
10. Corso A, Lazzarino M, Morra E, et al. Chronic myelogenous leukemia and exposure to ionizing radiation—a retrospective study of 443 patients. *Ann Hematol*. 1995;70:79-82.
11. American Cancer Society. *Cancer Facts & Figures 2020*. American Cancer Society; 2020.
12. Sasaki K, Strom SS, O'Brien S, et al. Relative survival in patients with chronic-phase chronic myeloid leukaemia in the tyrosine-kinase inhibitor era: analysis of patient data from six prospective clinical trials. *Lancet Haematol*. 2015;2:e186-e193.
13. Huang X, Cortes J, Kantarjian H. Estimations of the increasing prevalence and plateau prevalence of chronic myeloid leukemia in the era of tyrosine kinase inhibitor therapy. *Cancer*. 2012;118:3123-3127.
14. Ohanian M, Kantarjian HM, Shoukier M, et al. The clinical impact of time to response in de novo accelerated-phase chronic myeloid leukemia. *Am J Hematol*. 2020 Jun 17. doi: 10.1002/ajh.25907. Epub ahead of print.
15. Jain P, Kantarjian HM, Ghorab A, et al. Prognostic factors and survival outcomes in patients with chronic myeloid leukemia in blast phase in the tyrosine kinase inhibitor era: cohort study of 477 patients. *Cancer*. 2017;123:4391-4402.
16. Jabbour E, Cortes JE, Kantarjian HM. Molecular monitoring in chronic myeloid leukemia: response to tyrosine kinase inhibitors and prognostic implications. *Cancer*. 2008;112:2112-2118.
17. Kantarjian H, Schiffer C, Jones D, Cortes J. Monitoring the response and course of chronic myeloid leukemia in the modern era of BCR-ABL tyrosine kinase inhibitors: practical advice on the use and interpretation of monitoring methods. *Blood*. 2008;111:1774-1780.
18. Schoch C, Schnittger S, Bursch S, et al. Comparison of chromosome banding analysis, interphase- and hypermetaphase-FISH, qualitative and quantitative PCR for diagnosis and for follow-up in chronic myeloid leukemia: a study on 350 cases. *Leukemia*. 2002;16:53-59.
19. Wang W, Cortes JE, Tang G, et al. Risk stratification of chromosomal abnormalities in chronic myelogenous leukemia in the era of tyrosine kinase inhibitor therapy. *Blood*. 2016;127:2742-2750.
20. Sokal JE, Cox EB, Baccarani M, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. *Blood*. 1984;63:789-799.
21. Hasford J, Pfirrmann M, Hehlmann R, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. Writing Committee for the Collaborative CML Prognostic Factors Project Group. *J Natl Cancer Inst*. 1998;90:850-858.
22. Hasford J, Baccarani M, Hoffmann V, et al. Predicting complete cytogenetic response and subsequent progression-free survival in 2060 patients with CML on imatinib treatment: the EUTOS score. *Blood*. 2011;118:686-692.
23. Pfirrmann M, Baccarani M, Saussele S, et al. Prognosis of long-term survival considering disease-specific death in patients with chronic myeloid leukemia. *Leukemia*. 2016;30:48-56.
24. Guo JQ, Lin H, Kantarjian H, et al. Comparison of competitive-nested PCR and real-time PCR in detecting BCR-ABL fusion transcripts in chronic myeloid leukemia patients. *Leukemia*. 2002;16:2447-2453.
25. Druker BJ, Tamura S, Buchdunger E, et al. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. *Nat Med*. 1996;2:561-566.
26. Kantarjian H, Sawyers C, Hochhaus A, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. *N Engl J Med*. 2002;346:645-652.
27. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2003;348:994-1004.
28. Hochhaus A, Larson RA, Guilhot F, et al. Long-term outcomes of imatinib treatment for chronic myeloid leukemia. *N Engl J Med*. 2017;376:917-927.
29. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med*. 2001;344:1031-1037.
30. Cortes JE, Kantarjian HM, Goldberg SL, et al. High-dose imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: high rates of rapid cytogenetic and molecular responses. *J Clin Oncol*. 2009;27:4754-4759.
31. Cortes JE, Baccarani M, Guilhot F, et al. Phase III, randomized, open-label study of daily imatinib mesylate 400 mg versus 800 mg in patients with newly diagnosed, previously untreated chronic myeloid leukemia in chronic phase using molecular end points: tyrosine kinase inhibitor optimization and selectivity study. *J Clin Oncol*. 2010;28:424-430.
32. Baccarani M, Druker BJ, Branford S, et al. Long-term response to imatinib is not affected by the initial dose in patients with Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: final update from the Tyrosine Kinase Inhibitor Optimization and Selectivity (TOPS) study. *Int J Hematol*. 2014;99:616-624.
33. Baccarani M, Rosti G, Castagnetti F, et al. Comparison of imatinib 400 mg and 800 mg daily in the front-line treatment of high-risk, Philadelphia-positive chronic myeloid leukemia: a European LeukemiaNet Study. *Blood*. 2009;113:4497-4504.
34. Preudhomme C, Guilhot J, Nicolini FE, et al. Imatinib plus peginterferon alfa-2a in chronic myeloid leukemia. *N Engl J Med*. 2010;363:2511-2521.
35. Hehlmann R, Lauseker M, Saussele S, et al. Final evaluation of randomized CML-study IV: 10-year survival and evolution of terminal phase. *Blood*. 2017;130(suppl 1):897.
36. Sacha T, Góra-Tybor J, Szarejko M, et al. A multicenter prospective study on efficacy and safety of imatinib generics: a

report from Polish Adult Leukemia Group imatinib generics registry. *Am J Hematol*. 2017;92:E125-e128.
37. Madhav D. India generic imatinib in chronic myeloid leukemia: survival of the cheapest. *Blood*. 2016;128(22):630.
38. Abou Dalle I, Kantarjian H, Burger J, et al. Efficacy and safety of generic imatinib after switching from original imatinib in patients treated for chronic myeloid leukemia in the United States. *Cancer Med*. 2019;8:6559-6565.
39. Deininger MW, O'Brien SG, Ford JM, Druker BJ. Practical management of patients with chronic myeloid leukemia receiving imatinib. *J Clin Oncol*. 2003;21:1637-1647.
40. Shoukier M, Borthakur G, Jabbour E, et al. The effect of eltrombopag in managing thrombocytopenia associated with tyrosine kinase therapy in patients with chronic myeloid leukemia and myelofibrosis. *Haematologica*. 2020;Online ahead of print.
41. O'Hare T, Walters DK, Stoffregen EP, et al. In vitro activity of Bcr-Abl inhibitors AMN107 and BMS-354825 against clinically relevant imatinib-resistant Abl kinase domain mutants. *Cancer Res*. 2005;65:4500-4505.
42. Tokarski JS, Newitt JA, Chang CY, et al. The structure of dasatinib (BMS-354825) bound to activated ABL kinase domain elucidates its inhibitory activity against imatinib-resistant ABL mutants. *Cancer Res*. 2006;66:5790-5797.
43. Lombardo LJ, Lee FY, Chen P, et al. Discovery of N-(2-chloro-6-methyl- phenyl)-2-(6-(4-(2-hydroxyethyl)- piperazin-1-yl)-2-methylpyrimidin-4- ylamino)thiazole-5-carboxamide (BMS-354825), a dual Src/Abl kinase inhibitor with potent antitumor activity in preclinical assays. *J Med Chem*. 2004;47:6658-6661.
44. Shah NP, Tran C, Lee FY, et al. Overriding imatinib resistance with a novel ABL kinase inhibitor. *Science*. 2004;305:399-401.
45. Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2010;362:2260-2270.
46. Cortes JE, Saglio G, Kantarjian HM, et al. Final 5-year study results of DASISION: the dasatinib versus imatinib study in treatment-naïve chronic myeloid leukemia patients trial. *J Clin Oncol*. 2016;34:2333-2340.
47. Radich JP, Kopecky KJ, Appelbaum FR, et al. A randomized trial of dasatinib 100 mg versus imatinib 400 mg in newly diagnosed chronic-phase chronic myeloid leukemia. *Blood*. 2012;120:3898-3905.
48. O'Brien SG, Hedgley C, Adams S, et al. Spirit 2: an NCRI randomised study comparing dasatinib with imatinib in patients with newly diagnosed CML. *Blood*. 2014;632:517.
49. O'Brien S, Cork L, Bandeira V, et al. Spirit 2: final 5 year analysis of the UK National Cancer Research Institute randomized study comparing imatinib with dasatinib in patients with newly diagnosed chronic phase CML. *Blood*. 2018;132:457-.
50. Talpaz M, Shah NP, Kantarjian H, et al. Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. *N Engl J Med*. 2006;354:2531-2541.
51. Shah NP, Rousselot P, Schiffer C, et al. Dasatinib in imatinib-resistant or -intolerant chronic-phase, chronic myeloid leukemia patients: 7-year follow-up of study CA180-034. *Am J Hematol*. 2016;91:869-874.
52. Cortes J, Hochhaus A, Kantarjian H, et al. Impact of dose reductions on 5-year efficacy in newly diagnosed patients with chronic myeloid leukemia in chronic phase (CML-CP) from DASISION. *J Clin Oncol*.2017;35(15 suppl):7051.
53. Naqvi K, Jabbour E, Skinner J, et al. Early results of lower dose dasatinib (50mg daily) as frontline therapy for newly diagnosed chronic-phase chronic myeloid leukemia. *Cancer*. 2018;124:2740-2747.
54. Naqvi K, Jabbour E, Skinner J, et al. Long-term follow-up of lower dose dasatinib (50 mg daily) as frontline therapy in newly diagnosed chronic-phase chronic myeloid leukemia. *Cancer*. 2020;126:67-75.
55. Weisberg E, Manley PW, Breitenstein W, et al. Characterization of AMN107, a selective inhibitor of native and mutant Bcr-Abl. *Cancer Cell*. 2005;7:129-141.
56. Golemovic M, Verstovsek S, Giles F, et al. AMN107, a novel aminopyrimidine inhibitor of Bcr-Abl, has in vitro activity against imatinib-resistant chronic myeloid leukemia. *Clin Cancer Res*. 2005;11:4941-4947.
57. Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2010;362:2251-2259.
58. Kantarjian HM, Hughes TP, Larson RA, et al. Long-term outcomes with frontline nilotinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: ENESTnd 10-year analysis. Leukemia. 2021 Feb;35(2):440-453.
59. Wang J, Shen ZX, Saglio G, et al. Phase 3 study of nilotinib vs imatinib in Chinese patients with newly diagnosed chronic myeloid leukemia in chronic phase: ENESTchina. Blood 2015;125(18):2771-2778.
60. Cortes JE, Gambacorti-Passerini C, Deininger MW, et al. Bosutinib versus imatinib for newly diagnosed chronic myeloid leukemia: results from the randomized BFORE trial. *J Clin Oncol*. 2018;36:231-237.
61. Jain P, Kantarjian H, Alattar ML, et al. Long-term molecular and cytogenetic response and survival outcomes with imatinib 400 mg, imatinib 800 mg, dasatinib, and nilotinib in patients with chronic-phase chronic myeloid leukaemia: retrospective analysis of patient data from five clinical trials. *Lancet Haematol*. 2015;2:e118-e128.
62. Masarova L, Cortes JE, Patel KP, et al. Long-term results of a phase 2 trial of nilotinib 400 mg twice daily in newly diagnosed patients with chronic-phase chronic myeloid leukemia. *Cancer*. 2020;126:1448-1459.
63. Maiti A, Cortes JE, Patel KP, et al. Long-term results of frontline dasatinib in chronic myeloid leukemia. *Cancer*. 2020;126:1502-1511.
64. Montani D, Bergot E, Günther S, et al. Pulmonary arterial hypertension in patients treated by dasatinib. *Circulation*. 2012;125:2128-2137.
65. Quintás-Cardama A, Han X, Kantarjian H, Cortes J. Tyrosine kinase inhibitor-induced platelet dysfunction in patients with chronic myeloid leukemia. *Blood*. 2009;114:261-263.
66. Quintás-Cardama A, Kantarjian H, Ravandi F, et al. Bleeding diathesis in patients with chronic myelogenous leukemia receiving dasatinib therapy. *Cancer*. 2009;115:2482-2490.
67. Cortes JE, Gambacorti-Passerini C, Kim DW, et al. Effects of bosutinib treatment on renal function in patients with Philadelphia chromosome-positive leukemias. *Clin Lymphoma Myeloma Leuk*. 2017;17:684-695.e6.
68. Kantarjian H, Mathisen MS, Lipton JH. Having "skin in the game" and allowing cross-border importation of drugs to lower high prices of cancer drugs. *JAMA Oncol*. 2015;1:729-730.
69. Kantarjian H, Patel Y. High cancer drug prices 4 years later—progress and prospects. *Cancer*. 2017;123:1292-1297.
70. Kantarjian H, Rajkumar SV. Why are cancer drugs so expensive in the United States, and what are the solutions? Mayo Clinic proceedings Mayo Clinic 2015;90:500-504.
71. The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts. *Blood*. 2013;121:4439-4442.
72. Rochau U, Sroczynski G, Wolf D, et al. Cost-effectiveness of the sequential application of tyrosine kinase inhibitors for the treatment of chronic myeloid leukemia. *Leuk Lymphoma*. 2015;56:2315-2325.

73. Shih YT, Cortes JE, Kantarjian HM. Treatment value of second-generation BCR-ABL1 tyrosine kinase inhibitors compared with imatinib to achieve treatment-free remission in patients with chronic myeloid leukaemia: a modelling study. *Lancet Haematol*. 2019;6:e398-e408.
74. Yamamoto C, Nakashima H, Ikeda T, et al. Analysis of the cost-effectiveness of treatment strategies for CML with incorporation of treatment discontinuation. *Blood Adv*. 2019;3:3266-3277.
75. Larson RA, Conti R, Padula WV, et al. What Is the most cost-effective strategy for treating newly diagnosed chronic myeloid leukemia (CML) after imatinib loses patent exclusivity? *Blood*. 2014; 124:738.
76. National Comprehensive Cancer Network. *Chronic Myeloid Leukemia.* Version 3.2020. National Comprehensive Cancer Network, March 2020.
77. Testoni N, Marzocchi G, Luatti S, et al. Chronic myeloid leukemia: a prospective comparison of interphase fluorescence in situ hybridization and chromosome banding analysis for the definition of complete cytogenetic response: a study of the GIMEMA CML WP. *Blood*. 2009;114:4939-4943.
78. Kantarjian H, Cortes J. Considerations in the management of patients with Philadelphia chromosome-positive chronic myeloid leukemia receiving tyrosine kinase inhibitor therapy. *J Clin Oncol*. 2011;29:1512-1516.
79. Jabbour E, Kantarjian HM, Saglio G, et al. Early response with dasatinib or imatinib in chronic myeloid leukemia: 3-year follow-up from a randomized phase 3 trial (DASISION). *Blood*. 2014;123:494-500.
80. Hehlmann R, Lauseker M, Jung-Munkwitz S, et al. Tolerability-adapted imatinib 800 mg/d versus 400 mg/d versus 400 mg/d plus interferon-α in newly diagnosed chronic myeloid leukemia. *J Clin Oncol*. 2011;29:1634-1642.
81. Kantarjian HM, Shan J, Jones D, et al. Significance of increasing levels of minimal residual disease in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in complete cytogenetic response. *J Clin Oncol*. 2009;27:3659-3663.
82. Sasaki K, Kantarjian HM, Jain P, et al. Conditional survival in patients with chronic myeloid leukemia in chronic phase in the era of tyrosine kinase inhibitors. *Cancer*. 2016;122:238-248.
83. Marin D, Ibrahim AR, Lucas C, et al. Assessment of BCR-ABL1 transcript levels at 3 months is the only requirement for predicting outcome for patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. *J Clin Oncol*. 2012;30:232-238.
84. Jain P, Kantarjian H, Nazha A, et al. Early responses predict better outcomes in patients with newly diagnosed chronic myeloid leukemia: results with four tyrosine kinase inhibitor modalities. *Blood*. 2013;121:4867-4874.
85. Cortes JE, Jiang Q, Wang J, et al. Dasatinib vs. imatinib in patients with chronic myeloid leukemia in chronic phase (CML-CP) who have not achieved an optimal response to 3 months of imatinib therapy: the DASCERN randomized study. *Leukemia*. 2020;34(8):2064-2073.
86. Kantarjian HM, Giles FJ, Bhalla KN, et al. Nilotinib is effective in patients with chronic myeloid leukemia in chronic phase after imatinib resistance or intolerance: 24-month follow-up results. *Blood*. 2011;117:1141-1145.
87. Giles FJ, le Coutre PD, Pinilla-Ibarz J, et al. Nilotinib in imatinib-resistant or imatinib-intolerant patients with chronic myeloid leukemia in chronic phase: 48-month follow-up results of a phase II study. *Leukemia*. 2013;27:107-112.
88. Nicolini FE, Turkina A, Shen ZX, et al. Expanding Nilotinib Access in Clinical Trials (ENACT): an open-label, multicenter study of oral nilotinib in adult patients with imatinib-resistant or imatinib-intolerant Philadelphia chromosome-positive chronic myeloid leukemia in the chronic phase. *Cancer*. 2012;118:118-126.
89. Cortes JE, Kantarjian HM, Brümmendorf TH, et al. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. *Blood*. 2011;118:4567-4576.
90. Khoury HJ, Cortes JE, Kantarjian HM, et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. *Blood*. 2012;119:3403-3412.
91. O'Hare T, Shakespeare WC, Zhu X, et al. AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. *Cancer Cell*. 2009;16:401-412.
92. Sasaki K, Kantarjian H, O'Brien S, et al. Prediction for sustained deep molecular response of BCR-ABL1 levels in patients with chronic myeloid leukemia in chronic phase. *Cancer*. 2018;124:1160-1168.
93. Hochhaus A, Baccarani M, Silver RT, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. *Leukemia*. 2020;34:966-984.
94. Neelakantan P, Gerrard G, Lucas C, et al. Combining BCR-ABL1 transcript levels at 3 and 6 months in chronic myeloid leukemia: implications for early intervention strategies. *Blood*. 2013;121:2739-2742.
95. Nazha A, Kantarjian H, Jain P, et al. Assessment at 6 months may be warranted for patients with chronic myeloid leukemia with no major cytogenetic response at 3 months. *Haematologica*. 2013;98:1686-1688.
96. Branford S, Yeung DT, Parker WT, et al. Prognosis for patients with CML and >10% BCR-ABL1 after 3 months of imatinib depends on the rate of BCR-ABL1 decline. *Blood*. 2014;124:511-518.
97. Hehlmann R, Lauseker M, Saußele S, et al. Assessment of imatinib as first-line treatment of chronic myeloid leukemia: 10-year survival results of the randomized CML study IV and impact of non-CML determinants. *Leukemia*. 2017;31:2398-2406.
98. Jabbour E, Kantarjian HM, O'Brien S, et al. Front-line therapy with second-generation tyrosine kinase inhibitors in patients with early chronic phase chronic myeloid leukemia: what is the optimal response? *J Clin Oncol*. 2011;29:4260-4265.
99. Cortes JE, De Souza CA, Ayala M, et al. Switching to nilotinib versus imatinib dose escalation in patients with chronic myeloid leukaemia in chronic phase with suboptimal response to imatinib (LASOR): a randomised, open-label trial. *Lancet Haematol*. 2016;3:e581-e591.
100. Branford S. Monitoring and defining early response: Where to draw the line? Best Pract Res Heamtol. 2016; 29: 284– 294.
101. Hughes TP, Leber B, Cervantes F, et al. Sustained deep molecular responses in patients switched to nilotinib due to persistent BCR-ABL1 on imatinib: final ENESTcmr randomized trial results. *Leukemia*. 2017;31:2529-2531.
102. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. *Blood*. 2018;132:393-404.
103. Jabbour E, Branford S, Saglio G, et al. Practical advice for determining the role of BCR-ABL mutations in guiding tyrosine kinase inhibitor therapy in patients with chronic myeloid leukemia. *Cancer*. 2011;117:1800-1811.
104. Müller MC, Cortes JE, Kim DW, et al. Dasatinib treatment of chronic-phase chronic myeloid leukemia: analysis of responses according to preexisting BCR-ABL mutations. *Blood*. 2009;114:4944-4953.
105. Jabbour E, Kantarjian HM, Jones D, et al. Imatinib mesylate dose escalation is associated with durable responses in patients with chronic myeloid leukemia after cytogenetic failure on standard-dose imatinib therapy. *Blood*. 2009;113:2154-2160.

106. Kantarjian H, Pasquini R, Lévy V, et al. Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia resistant to imatinib at a dose of 400 to 600 milligrams daily: two-year follow-up of a randomized phase 2 study (START-R). *Cancer*. 2009;115:4136-4147.
107. Garcia-Gutierrez JV, Herrera P, Abalo LL, et al. Impact of second-generation tyrosine kinase inhibitors as second line treatment for patients with chronic myeloid leukemia. *Blood*. 2011;118:632.
108. Goh HG, Jootar S, Kim HJ, et al. Efficacy of nilotinib versus high-dose imatinib in early chronic phase CML patients who have suboptimal molecular responses to standard-dose imatinib (RE-NICE multicenter study). *Blood*. 2011;118:632.
109. Sasaki K, Kantarjian H, Jabbour E, et al. Frontline therapy with high-dose imatinib versus second generation tyrosine kinase inhibitor in patients with chronic-phase chronic myeloid leukemia - a propensity score analysis. *Haematologica*. 2016;101:e324-e327.
110. Yeung DT, Osborn M, White DL, et al. Upfront imatinib therapy in CML patients with rapid switching to nilotinib for failure to achieve molecular targets or intolerance achieves high overall rates of molecular response and a low risk of progression—an update of the TIDEL-II trial. *Blood*. 2011;118:632.
111. Castagnetti F, Gugliotta G, Bocchia M, et al. Dose optimization in elderly CML patients treated with bosutinib after intolerance or failure of first-line tyrosine kinase inhibitors. *Blood*. 2019:134(suppl):496.
112. Zhou T, Commodore L, Huang WS, et al. Structural mechanism of the Pan-BCR-ABL inhibitor ponatinib (AP24534): lessons for overcoming kinase inhibitor resistance. *Chem Biol Drug Des*. 2011;77:1-11.
113. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. *N Engl J Med*. 2013;369:1783-1796.
114. Inclusig (ponatinib) Prescribing Information. ARIAD Pharmaceuticals. 2020. Accessed online July 06, 2021 at: https://www.iclusig.com/pdf/ICLUSIG-Prescribing-Information.pdf
115. Cortes JE, Lomaia E, Turkina A, et al. Interim analysis (IA) of OPTIC: a dose-ranging study of three ponatinib (PON) starting doses. *J Clin Oncol*. 2020;38:7502-.
116. Wylie AA, Schoepfer J, Jahnke W, et al. The allosteric inhibitor ABL001 enables dual targeting of BCR-ABL1. *Nature*. 2017;543:733-737.
117. Hughes TP, Mauro MJ, Cortes JE, et al. Asciminib in chronic myeloid leukemia after ABL kinase inhibitor failure. *N Engl J Med*. 2019;381:2315-2326.
118. Jiang Q, Hunag X, Chen Z, et al. An updated safety and efficacy results of phase 1 study of HQP1351, a novel 3rd generation of BCR-ABL tyrosine kinase inhibitor (TKI), in patients with TKI resistant chronic myeloid leukemia. *Blood*. 2019;134(suppl 1):493.
119. Cortes J, Kim DW, Nicolini F, et al. Phase 1 trial of K0706, a novel oral BCR-ABL1 tyrosine kinase inhibitor (TKI): in patients with chronic myelogenous leukemia (CML) and Philadelphia positive acute lymphoblastic leukemia (Ph+ ALL) failing ≥ 3 prior TKI therapies: initial safety and efficacy. *Blood*. 2019;134(suppl 1):4158.
120. Turkina AG, Vinogradova O, Lomaia E, et al. PF-114: a 4th generation tyrosine kinase-inhibitor for chronic phase chronic myeloid leukaemia including BCRABL1T315I. *Blood*. 2019;134:1638.
121. Cortes J, Jabbour E, Kantarjian H, et al. Dynamics of BCR-ABL kinase domain mutations in chronic myeloid leukemia after sequential treatment with multiple tyrosine kinase inhibitors. *Blood*. 2007;110:4005-4011.
122. Hughes T, Saglio G, Branford S, et al. Impact of baseline BCR-ABL mutations on response to nilotinib in patients with chronic myeloid leukemia in chronic phase. *J Clin Oncol*. 2009;27:4204-4210.
123. Jabbour E, Kantarjian H, Ghanem H, et al. The achievement of a 3-month complete cytogenetic response to second-generation tyrosine kinase inhibitors predicts survival in patients with chronic phase chronic myeloid leukemia after imatinib failure. *Clin Lymphoma Myeloma Leuk*. 2013;13:302-306.
124. Lee SJ, Kukreja M, Wang T, et al. Impact of prior imatinib mesylate on the outcome of hematopoietic cell transplantation for chronic myeloid leukemia. *Blood*. 2008;112:3500-3507.
125. Nicolini FE, Basak GW, Kim DW, et al. Overall survival with ponatinib versus allogeneic stem cell transplantation in Philadelphia chromosome-positive leukemias with the T315I mutation. *Cancer*. 2017;123:2875-2880.
126. Ruiz-Argüelles GJ, Tarin-Arzaga LC, Gonzalez-Carrillo ML, et al. Therapeutic choices in patients with Ph-positive CML living in Mexico in the tyrosine kinase inhibitor era: SCT or TKIs? *Bone Marrow Transplant*. 2008;42:23-28.
127. Jaime-Pérez JC, Heredia-Salazar AC, Cantú-Rodríguez OG, et al. Cost structure and clinical outcome of a stem cell transplantation program in a developing country: the experience in northeast Mexico. *Oncologist*. 2015;20:386-392.
128. Jabbour E, Kantarjian H, Cortes J. Use of second- and third-generation tyrosine kinase inhibitors in the treatment of chronic myeloid leukemia: an evolving treatment paradigm. *Clin Lymphoma Myeloma Leuk*. 2015;15:323-334.
129. Mahon FX, Réa D, Guilhot J, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. *Lancet Oncol*. 2010;11:1029-1035.
130. Ross DM, Branford S, Seymour JF, et al. Safety and efficacy of imatinib cessation for CML patients with stable undetectable minimal residual disease: results from the TWISTER study. *Blood*. 2013;122:515-522.
131. Ross DM, Masszi T, Gómez Casares MT, et al. Durable treatment-free remission in patients with chronic myeloid leukemia in chronic phase following frontline nilotinib: 96-week update of the ENESTfreedom study. *J Cancer Res Clin Oncol*. 2018;144:945-954.
132. Rea D, Nicolini FE, Tulliez M, et al. Prognostication of molecular relapses after dasatinib or nilotinib discontinuation in chronic myeloid leukemia (CML): a FI-LMC STOP 2G-TKI study update. *Blood*. 2019;134(suppl 1):30.
133. Saussele S, Richter J, Guilhot J, et al. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial. *Lancet Oncol*. 2018;19:747-757.
134. Chamoun K, Kantarjian H, Atallah R, et al. Tyrosine kinase inhibitor discontinuation in patients with chronic myeloid leukemia: a single-institution experience. *J Hematol Oncol*. 2019;12:1.
135. Rousselot P, Loiseau C, Delordd, et al. A report on 114 patients who experienced treatment free remission in a single institution during a 15 years period: long term follow-up, late molecular relapses and second attempts. *Blood*. 2019;134(suppl 1):27.
136. Alfayez M, Richard-Carpentier G, Jabbour E, et al. Sudden blastic transformation in treatment-free remission chronic myeloid leukaemia. *Br J Haematol*. 2019;187:543-545.
137. Jabbour E. Chronic myeloid leukemia: first-line drug of choice. *Am J Hematol*. 2016;91:59-66.
138. Holyoake TL, Vetrie D. The chronic myeloid leukemia stem cell: stemming the tide of persistence. *Blood*. 2017;129:1595-1606.
139. Simonsson B, Gedde-Dahl T, Markevärn B, et al. Combination of pegylated IFN-α2b with imatinib increases molecular response rates in patients with low- or intermediate-risk chronic myeloid leukemia. *Blood*. 2011;118:3228-3235.

140. Hjorth-Hansen H, Stentoft J, Richter J, et al. Safety and efficacy of the combination of pegylated interferon-α2b and dasatinib in newly diagnosed chronic-phase chronic myeloid leukemia patients. *Leukemia*. 2016;30:1853-1860.
141. Hochhaus A, Burchert A, Saussele S, et al. Nilotinib vs nilotinib plus pegylated interferon α (Peg-IFN) induction and nilotinib or Peg-IFN maintenance therapy for newly diagnosed BCR-ABL1 positive chronic myeloid leukemia patients in chronic phase (TIGER study): the addition of Peg-IFN is associated with higher rates of deep molecular response. *Blood*. 2019;134(suppl 1):495.
142. Ko TK, Chuah CT, Huang JW, et al. The BCL2 inhibitor ABT-199 significantly enhances imatinib-induced cell death in chronic myeloid leukemia progenitors. *Oncotarget*. 2014;5:9033-9038.
143. Carter BZ, Mak PY, Mu H, et al. Combined targeting of BCL-2 and BCR-ABL tyrosine kinase eradicates chronic myeloid leukemia stem cells. *Sci Transl Med*. 2016;8:355ra117.
144. Gallipoli P, Cook A, Rhodes S, et al. JAK2/STAT5 inhibition by nilotinib with ruxolitinib contributes to the elimination of CML CD34+ cells in vitro and in vivo. *Blood*. 2014;124:1492-1501.
145. Schnekenburger M, Grandjenette C, Ghelfi J, et al. Sustained exposure to the DNA demethylating agent, 2'-deoxy-5-azacytidine, leads to apoptotic cell death in chronic myeloid leukemia by promoting differentiation, senescence, and autophagy. *Biochem Pharmacol*. 2011;81:364-378.
146. Held SA, Heine A, Mayer KT, et al. Advances in immunotherapy of chronic myeloid leukemia CML. *Curr Cancer Drug Targets*. 2013;13:768-774.
147. Apperley JF, Cortes JE, Kim DW, et al. Dasatinib in the treatment of chronic myeloid leukemia in accelerated phase after imatinib failure: the START a trial. *J Clin Oncol*. 2009;27:3472-3479.
148. le Coutre PD, Giles FJ, Hochhaus A, et al. Nilotinib in patients with Ph+ chronic myeloid leukemia in accelerated phase following imatinib resistance or intolerance: 24-month follow-up results. *Leukemia*. 2012;26:1189-1194.
149. Ohanian M, Kantarjian HM, Quintas-Cardama A, et al. Tyrosine kinase inhibitors as initial therapy for patients with chronic myeloid leukemia in accelerated phase. *Clin Lymphoma Myeloma Leuk*. 2014;14:155-162.e1.
150. Strati P, Kantarjian H, Thomas D, et al. HCVAD plus imatinib or dasatinib in lymphoid blastic phase chronic myeloid leukemia. *Cancer*. 2014;120:373-380.
151. Copeland M, Slade D, Byrne J, et al. FLAG-IDA and ponatinib in patients with blast phase chronic myeloid leukaemia: results from the phase I/II UK trials acceleration programme matchpoint trial. *Blood*. 2019;134(suppl 1):497.
152. Jabbour E, Cortes J, Kantarjian H, et al. Novel tyrosine kinase inhibitor therapy before allogeneic stem cell transplantation in patients with chronic myeloid leukemia: no evidence for increased transplant-related toxicity. *Cancer*. 2007;110:340-344.
153. Oehler VG, Gooley T, Snyder DS, et al. The effects of imatinib mesylate treatment before allogeneic transplantation for chronic myeloid leukemia. *Blood*. 2007;109:1782-1789.
154. Carpenter PA, Snyder DS, Flowers ME, et al. Prophylactic administration of imatinib after hematopoietic cell transplantation for high-risk Philadelphia chromosome-positive leukemia. *Blood*. 2007;109:2791-2793.

5

Myelodysplastic Syndromes: The MD Anderson Cancer Center Approach

Kelly Chien
Carlos Bueso-Ramos
Guillermo Garcia-Manero

KEY CONCEPTS

- The term *myelodysplastic syndrome (MDS)* refers to a very heterogeneous group of myeloid disorders. In a majority of patients, MDS results from defects in a primitive hematopoietic stem cell compartment.
- Individuals with evidence of clonal hematopoiesis are at increased risk of developing MDS.
- Prognosis is calculated using a number of variables, including degree of cytopenia, percentage of blasts, cytogenetic alterations, and more recently genomic annotation.
- Using either the International Prognostic Scoring System or the Revised International Prognostic Scoring System, patients are divided into those with lower and higher risk disease.
- For patients with lower-risk disease, treatment approaches include growth factors, iron chelation, luspatercept, lenalidomide (for del5q- MDS), hypomethylating agents (HMAs; azacitidine or decitabine) or antithymocyte globulin–-based therapy (for patients with hypoplastic MDS). Allogeneic stem cell transplantation (allo-SCT) is reserved for younger patients with poor risk features.
- For patients with higher risk disease, the main treatment options include the HMAs and less frequently acute myeloid leukemia–like therapy. Allo-SCT should be considered in candidate patients early in the course of the disease in responding patients. Clinical trials should be considered for a majority of patients with MDS.

Myelodysplastic syndromes (MDSs) refer to a group of hematopoietic disorders characterized by ineffective hematopoiesis and increased risk of transformation to acute myeloid leukemia (AML). The median age of patients with MDS is 70 to 75 years. It is likely that environmental factors play an important role in the pathogenesis of this disease. MDSs are classified according to the World Health Organization (WHO) criteria, and a number of prognostic scores can be used to calculate survival and risk of transformation. Cytogenetic, genomic, and epigenetic alterations are common in MDS and help in the prediction of prognosis and potentially in the selection of therapy. Over the past decade, we have witnessed significant improvements in supportive care and therapeutic modalities for patients with MDS. These include growth factors, luspatercept, immune modulatory agents (lenalidomide), and hypomethylating agents (HMAs; 5-azacitidine and decitabine), with new oral formulations. We also better understand patient subgroups, such as those with hypomethylating failure disease. In this chapter, we summarize our knowledge of MDS and the treatment approach we use at MD Anderson Cancer Center (MDACC).

THE MD ANDERSON APPROACH TO PATIENTS WITH MYELODYSPLASTIC SYNDROMES

Approximately 350 to 400 patients are referred to MDACC annually with a diagnosis of MDS, and nearly 20% of these patients receive a different diagnosis. In most instances, the final diagnosis is AML or a form of higher risk MDS. Other benign and malignant conditions are also diagnosed. In a study of 915 patients referred to MDACC between 2005 and 2009,12% of patients were reclassified after evaluation at MDACC using very strict criteria.[1] This justifies our practice to repeat a confirmatory bone marrow aspiration and biopsy at the time of initial MDS evaluation at MDACC.

After the diagnosis is confirmed, the next important step is to calculate the "risk" of the patient. Many clinicians and investigators still use the International Prognostic Scoring System (IPSS)[2] score to perform such analysis, but more precise models, such as the Revised International Prognostic Scoring System (IPSS-R), have been developed.[3–5] Patients with low or intermediate-1 risk by the IPSS or those with less than 10% blasts in the bone marrow are considered as having lower-risk disease, and those with excess blasts or intermediate-2 or high-risk disease are considered as having higher risk disease. When using the IPSS-R, patients with very low, low, and some subsets of intermediate risk are considered as having lower-risk disease, whereas those with high, very high and some subsets of intermediate risk are considered as having higher risk disease.[6]

Patients with lower-risk disease can be candidates for a wide range of interventions, depending on their specific characteristics and transfusion needs. Patients with minimal cytopenias, who are transfusion independent, have a low percentage of blasts in the bone marrow, and have normal cytogenetics are more frequently observed because their 4-year survival rate is close to 80%.[4] At the other end of the spectrum, older patients with significant cytopenias and transfusion needs can have very poor prognoses, particularly if their cytogenetics are abnormal.[4] The median survival time of these patients is less than 12 months; around 60% to 70% of patients with MDS are in this category, but there are few interventions known to alter the natural history of these patients. Transfusion and growth factor support are usually initiated. Interventions, such as lenalidomide, have significant activity in improving red blood cell (RBC) counts in patients with deletion of chromosome 5[7] but are significantly less active in patients without this alteration.[8] The role of the HMAs 5-azacitidine and decitabine is less clear in this situation, although they are frequently used. allo-SCT is not frequently used up front in patients with lower-risk disease,[9] and delaying transplantation until the time of progression is associated with longer survival times even if transplant outcomes are poorer when performed at that time. A new subset of patients has emerged with lower-risk disease but also with hypomethylating failure.[10] The prognosis of these patients is poor, and new investigational strategies are needed.

Treatment decisions are relatively simpler for patients with higher risk MDS. The data with HMA indicate that treatment with these agents improves survival significantly compared with supportive care or low-dose chemotherapy approaches. The optimal approach for patients younger than age 60 to 65 years with MDS is unclear. These patients can be treated with HMA or an AML-like induction therapy or can be considered for up-front allo-SCT. No study has compared these treatments in younger patients. An approach followed by our group is to stratify patients based on cytogenetics. Younger patients with normal karyotypes are offered induction therapy with an AML-like approach followed when possible by allo-SCT. In contrast, younger patients with abnormal karyotypes receive HMA-based therapy followed by allo-SCT. It is not our routine to proceed with up-front transplant in patients with excess blasts. Older patients benefit significantly from the use of HMAs, and there is no upper age limit that may contraindicate their use.[11] Finally, the group of patients with higher risk disease and hypomethylating failure constitute a major unmet medical need.[12]

A comprehensive review of current knowledge in MDS is provided next. Current areas of intense research are the development of newer forms of therapy for patients with newly diagnosed disease and strategies for patients who have relapsed or not responded to HMA-based therapy.

EPIDEMIOLOGY AND ETIOLOGY

The incidence of MDS increases with age. Most patients diagnosed with this condition are older than 60 years old; the median age at diagnosis is 75 years.[13] The incidence is higher in men than women, with a 2:1 ratio.[13] The incidence in the United States is 30 to 35 individuals per million per year with a relative yearly increase in the reported incidence, probably related to increase awareness of the disease and reporting efforts.[14]

The risk of developing MDS is related to the individual's racial background. In the United States, the incidence is highest in the white population.[13] Patients with MDS from Asia present at a younger age.[15] The underlying cause of this phenomenon is not known but may reflect genetic differences between different racial groups. Asian patients have a similar frequency of karyotype abnormalities as European and American cohorts, although they may have less frequent alterations of chromosomes 5 and 7.[15–17] The combination of younger age at diagnosis and lack of chromosome 7 alterations can explain the longer survival times observed in patients from Asia.

There is no known cause of MDS, but genetic or environmental risk factors may contribute. Genetic syndromes, such as Down syndrome, Bloom syndrome, and Fanconi anemia, are associated with an increased risk of MDS, which often presents earlier in life.[18,19] Genetic polymorphisms that influence the activity of enzymes responsible for metabolizing toxic chemicals or chemotherapy drugs may influence an individual's predisposition to MDS. Polymorphisms have been described in the cytochrome p450 3A, glutathione-*S*-transferase, and NAD(P)H quinine oxidoreductase enzyme systems that increase the risk of developing myeloid malignancies.[20–22]

Environmental agents may contribute to the development of MDS by causing toxic damage to hematopoietic stem cells. A causal relationship between occupational exposures to benzene and radiation and the development of myeloid malignancy has been demonstrated.[23] Exposure to organic solvents and pesticides has also been implicated in the development of MDS.[24–26] There is no correlation between MDS and socioeconomic status.[25]

The most significant risk factor for the development of MDS is previous exposure to chemotherapy or radiotherapy used to treat other cancers. Treatment-related MDS (t-MDS) constitutes a minority of MDS diagnoses but may be increasing in prevalence with improved survival rates after successful cancer therapies for tumors. Usually, t-MDS presents 5 to 6 years after initial cancer treatment and generally has a poor prognosis.[27] Patients treated for lymphoma are at risk of this long-term complication.[28] Patients who undergo autologous hematopoietic stem cell transplantation have a higher risk, approximately 10% to 15% of developing treatment-related MDS or AML, with incidence rates in some centers of up to 10%.[29] In our experience with t-MDS at MDACC in 281 patients, most of the risk was associated with complex cytogenetics or presence and alteration of chromosome 7.[30]

CLINICAL AND LABORATORY FEATURES

Most patients with MDS are diagnosed incidentally during routine complete blood cell count (CBC) analysis or because of nonspecific symptoms. Anemia is the most common cytopenia in MDS and is associated with fatigue. A lower percentage of patients presents with bleeding or bruising secondary to thrombocytopenia or with infections related to neutropenia. Physical examination is often normal. Hepatosplenomegaly may be present in patients with chronic myelomonocytic leukemia (CMML) or overlap myeloproliferative neoplasms. A change in the severity of cytopenia or rapid worsening of symptoms may indicate disease transformation. Patients suspected to have MDS transformation require prompt investigation because 20% to 30% of patients develop acute leukemia throughout their disease course.[2]

Initial assessment should include a CBC, reticulocyte count, and serum chemistry, including vitamin B_{12} and folate, iron studies with ferritin, and erythropoietin (EPO) level examination. Other causes of cytopenias or MDS-mimicking syndromes (eg, HIV [human immunodeficiency virus], other infections, autoimmune disorders, or copper deficiency) should be ruled out through appropriate tests. A bone marrow aspirate and biopsy with samples taken for an iron stain and cytogenetic and molecular studies are essential. Morphologic assessment of the disease is still required for MDS. Cytogenetic studies may confirm the presence of clonal hematopoiesis and provide additional important prognostic information. Analysis of specific gene mutations, such as *TET2*, *DNMT3A*, *ASXL1*, *TP53*, splicing factors, *NRAS*, *FLT3*, *IDH1*, *IDH2*, and *JAK2*, may improve our prognostic and predictive evaluation and allow for the use of targeted interventions using selective inhibitors (eg, *FLT3*, *JAK2*, or *IDH1/2* inhibitors) or earlier consideration of allo-SCT. However, it should also be noted that these molecular abnormalities[31] may be present in older individuals with or without cytopenias and may not necessarily point to an MDS diagnosis.

Clonal hematopoiesis of indeterminate potential is a phenomenon in which clonal somatic mutations are present in hematopoietic cells from older individuals with no evidence of a hematologic disorder.[32,33] These patients have been found to have an increased risk of hematologic neoplasms, therapy-related myeloid neoplasms, and cardiovascular disease.[34–37] Whereas the presence of a somatic mutation in the presence of cytopenias with no diagnostic criteria for MDS is considered clonal cytopenia of undetermined significance (CCUS),[38,39] individuals with cytopenias but no dysplasia are considered to have idiopathic cytopenia of undetermined significance (ICUS). The distinction between ICUS and CCUS is important because the risk of developing MDS and AML increases from 9% to 82% at 5 years in the presence of highly predictive mutation patterns.[39,40]

BONE MARROW FEATURES

Morphologic Analysis

Table 5–1 shows the different subsets of MDS under the 2016 WHO MDS classification.[41] Morphologic classification of MDS is based on a 500-cell differential count on the bone marrow aspirate and leukocyte

TABLE 5–1 Classification of Myelodysplastic Syndromes (MDS) According to 2016 World Health Organization Criteria

MDS with single-lineage dysplasia (MDS-SLD)
MDS with multilineage dysplasia (MDS-MLD)
MDS with ring sideroblasts (MDS-RS)
MDS-RS with single-lineage dysplasia (MDS-RS-SLD)
MDS-RS with multilineage dysplasia ()MDS-RS-MLD)
MDS with isolated del(5q)
MDS with excess blasts (MDS-EB-1, -2)
MDS, unclassifiable (MDS-U)
Refractory cytopenia of childhood

differential performed on the blood smear. This analysis determines the percentage of blasts present in the blood and bone marrow and provides an assessment of the number of myeloid lineages involved in the dysplastic process, and the iron stain determines the presence and number of ring sideroblasts.[42]

As shown in Figure 5–1, blood cell abnormalities on the peripheral blood smear are variable.[42] RBCs may be macrocytic and frequently display anisopoikilocytosis. Polychromasia or basophilic stippling may be present. Dysplastic granulocytes may show abnormal folding of the nucleus, and cytoplasmic granules are often reduced or absent. Platelets are of variable size and may also be hypogranular. The presence of circulating blast cells or an excess of monocytes is important for the classification of high-risk MDS and CMML, respectively.

Definitive diagnosis requires a bone marrow aspirate and biopsy. The bone marrow is usually normocellular or hypercellular, reflecting that hematopoiesis is ineffective. Abnormal maturation of hematopoietic cells results in a variable proportion of myeloblasts that are significantly increased in the more aggressive MDS. Morphologic abnormalities found in the nucleus of erythroblasts include nuclear budding, internuclear bridging, karyorrhexis, multinuclearity, and megaloblastoid changes (see Fig. 5–1). Cytoplasmic features include the presence of ring sideroblasts and abnormal vacuolization. Abnormal or absent granulation is a common feature of dysplastic granulocyte series. Aberrant nuclear folding of the neutrophil precursor can produce a dysplastic bilobed nucleus, the pseudo–Pelger-Huet anomaly. Megakaryocytes may have a very variable morphology, and a small dysplastic form called the micromegakaryocyte is a typical finding. A normal megakaryocyte has a polyploid nucleus that can be altered with dysplasia to produce hypolobulation or nuclei that are dispersed throughout the cell. The bone marrow biopsy provides the best assessment of the overall cellularity and allows examination of the architecture of the marrow and surrounding bone (Fig. 5–2). The presence of fibrosis can be assessed on biopsy with specific stains for reticulin and collagen. In normal bone marrow, the immature blast cells are frequently located near the endosteal surface. In MDS, these cells may be distant to this site and form aberrant clusters referred to as abnormal localization of immature precursors. Immunohistochemical staining of biopsies can aid diagnosis, with CD34 staining to identify blast and progenitor cells and CD42 or CD62 for quantitation and assessment of megakaryocytes (see Fig. 5–2).[43]

Nonclonal diseases may cause dysplastic morphologic changes in blood cells. Secondary causes of dysplasia should be excluded in the initial assessment and can potentially complicate the diagnosis. Blood cell dysplasia is seen with exposure to heavy metals or antituberculous therapies, vitamin B_{12} and folate deficiency, HIV infection, excessive alcohol consumption,[42] and occasionally normal aging.[44] Dysplastic features are commonly observed after chemotherapy or with the therapeutic use of granulocyte colony-stimulating factor (G-CSF). These diagnoses should be assessed in the history and may require exclusion with further laboratory testing. Diagnostic difficulties may occur in patients with marked hypocellularity of the bone marrow and in patients with prominent fibrosis because there are often very few cells in the aspirate sample to allow morphologic assessment of dysplasia. For patients with prominent hypocellularity of the marrow, it may be difficult to distinguish from aplastic anemia, for which morphologic dysplasia of the erythroid lineage may also be observed. In cases of marked fibrosis, bone marrow aspiration is often unsuccessful. Some patients with mild dysplastic changes in the bone marrow and a normal karyotype are difficult to definitively diagnose at initial presentation and may require a period of observation to confirm the underlying diagnosis. These patients require review with repeat investigations performed in 3 to 6 months.

Cytogenetic and Molecular Analyses

A cytogenetic abnormality is found in 40% to 50% of patients with primary MDS and lower-risk disease; it is higher in patients with more advanced MDS. Cytogenetic analysis of hematopoietic cells derived from the bone marrow aspirate provides important prognostic and predictive information and may direct therapy (eg, lenalidomide therapy with deletion 5q or earlier allo-SCT with complex or adverse karyotypes). A karyotypic abnormality provides evidence for the presence of a clonal blood disorder, which may be particularly important if the morphologic changes are not clear. Typically, cytogenetic analysis assesses 20 bone marrow metaphases.[43] Multiple different cytogenetic abnormalities have been described and are summarized in Table 5–2.[45] No specific cytogenetic abnormalities characterize MDS. Unlike AML and chronic myeloid leukemia, genetic translocations are rare in MDS, but deletions are common.

The presence or absence of a cytogenetic abnormality has a marked influence on prognosis.[45] The median survival time of patients with normal karyotypes is approximately 53 months compared with less than 12 months for patients with three or more cytogenetic abnormalities, known as a complex karyotype. Del(5q) and del(20q) are associated with a favorable prognosis. However, when these abnormalities are present in association with other cytogenetic abnormalities, especially as a component of a complex karyotype, the prognosis is poor. Abnormalities of chromosome 7, usually deletions, are associated with a poor prognosis regardless of the presence or absence of other abnormalities. Complex

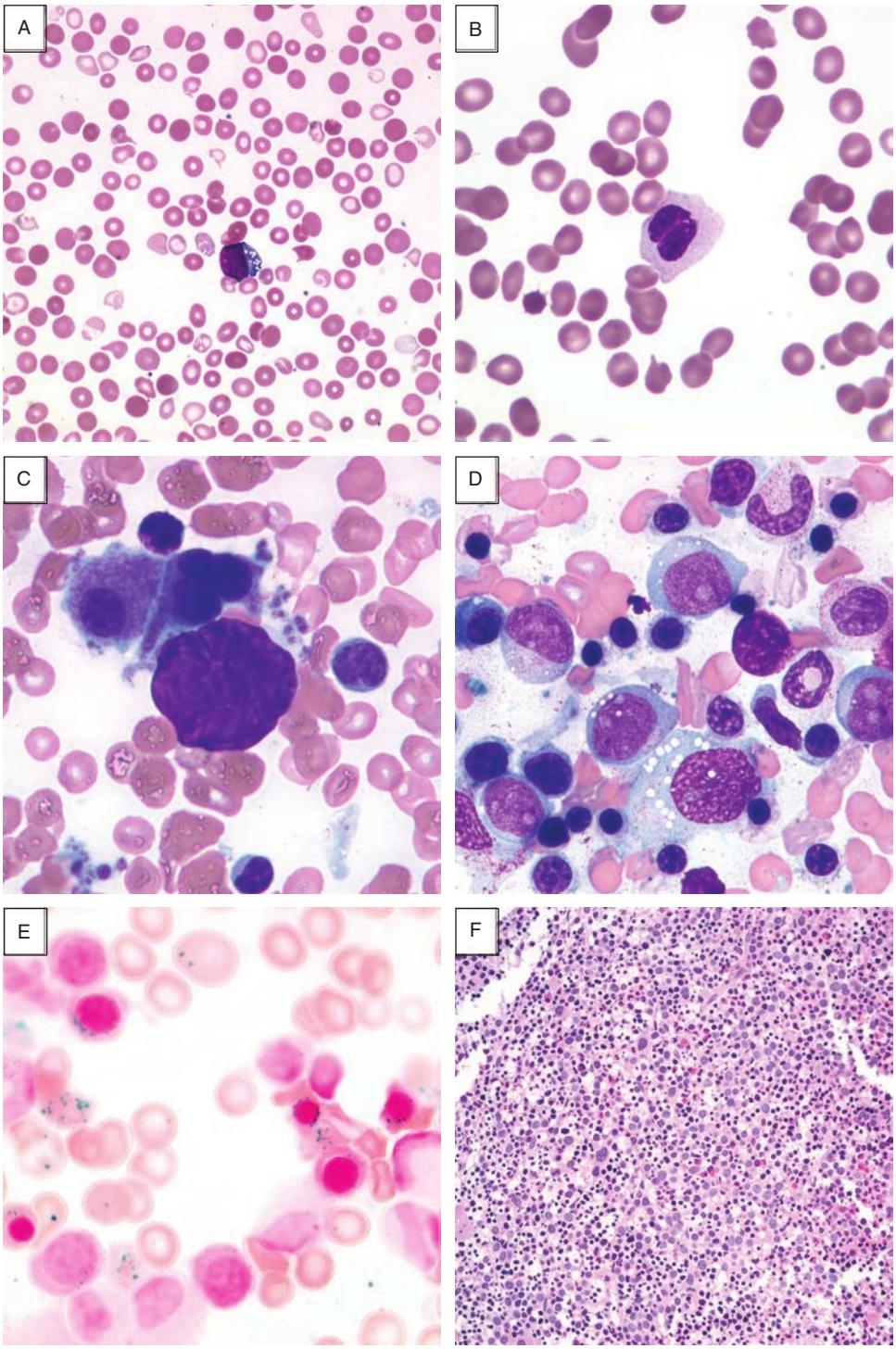


FIGURE 5–1 Morphologic features of peripheral blood and bone marrow in the myelodysplastic syndromes. **A.** Peripheral blood film from a patient with refractory anemia with excess blasts-1. The erythrocytes show hypochromasia, anisocytosis, and macroovalocytes. There is also an occasional blast (*center*). **B.** Peripheral blood film from a patient with refractory cytopenia with multilineage dysplasia demonstrating pseudo–Pelger-Huet cell (*center*) with hypercondensed chromatin and bilobed nuclei and hypogranular cytoplasm. **C.** Dysplastic small megakaryocytes, some with monolobated or with separated nuclei and mature granular cytoplasm in the bone marrow aspirate, from a patient with refractory anemia with excess blasts. **D.** Increased blasts, dysgranulopoiesis, and dyserythropoiesis in the bone marrow aspirate from a patient with refractory anemia with excess blasts. **E.** Ring sideroblasts and Pappenheimer bodies from a patient with refractory anemia with ring sideroblasts. **F.** Hypercellular (100%) bone marrow biopsy with increased immature cells and dysplastic megakaryocytes in a 70-year-old man with refractory anemia with excess blasts.

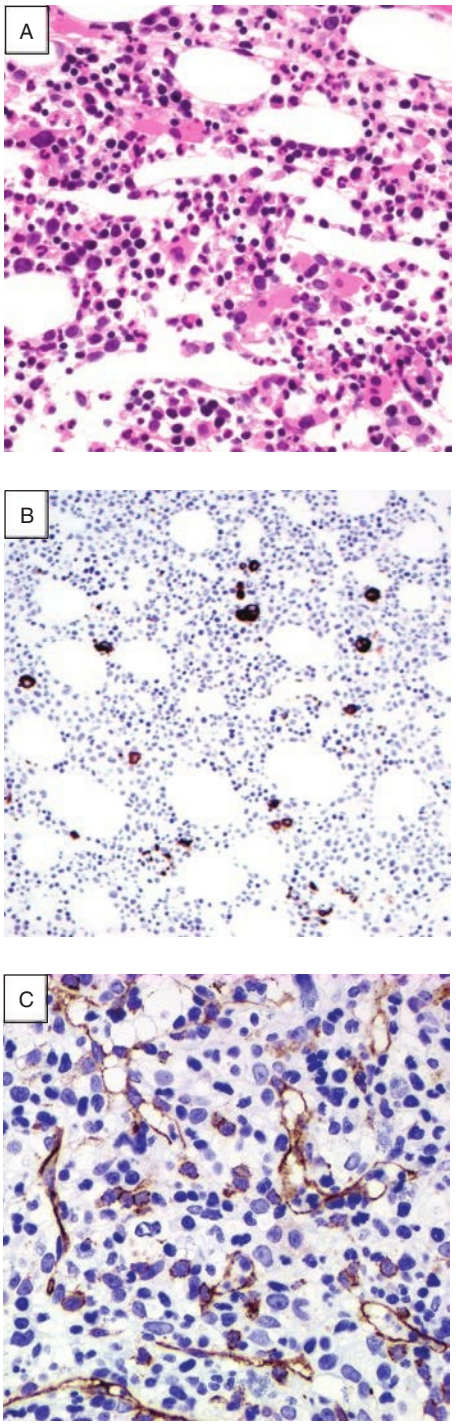


FIGURE 5–2 **Morphologic and immunohistochemical feature of bone marrow biopsy in the myelodysplastic syndromes. A. Trephine bone marrow biopsy with numerous dysplastic monolobated megakaryocytes in a 60-year-old female patient with refractory anemia with excess blasts type 1. B. CD61 immunohistochemical stain highlighting many dysplastic micromegakaryocytes. CD61 may be helpful in detecting dysplastic micromegakaryocytes to aid in confirming dysmegakaropoiesis and abnormal translocation of megakaryocytes to endosteal surfaces. C. CD34 immunohistochemical staining highlighting the presence of an increased number of blasts and increased blood vessels.**

cytogenetic abnormalities are more frequently observed in patients with increased marrow blasts. Progressively worse prognoses are observed with increasing karyotypic complexity. Patients with six or more abnormalities have a very poor median survival time of 5 months.[45] In 2012, a comprehensive scoring cytogenetic system was developed using data from 2902 patients.[46] This analysis resulted in 19 new cytogenetic categories and 5 prognostic subgroups, as shown in Figure 5–3, which serves as the basis for the IPSS-R scoring system.[5]

Treatment-related MDS has a particularly high incidence of cytogenetic abnormalities, with karyotypic changes observed in 70% to 90% of cases.[27,30,45] A high incidence of abnormalities is associated with an unfavorable prognosis for this group of patients. Abnormalities of chromosomes 5 and 7 are frequently observed after exposure to alkylating agents.[47,48] Translocations involving 11q23 are seen after treatment with topoisomerase II inhibitors.[47]

The high frequency of chromosomal deletions has prompted interest in the identification of epigenetic repressive alterations, such as aberrant DNA methylation in MDS. Aberrant DNA methylation of multiple promoter CpG islands has been associated with poor prognosis in MDS.[49] At this point, we do not have evidence of specific molecular pathways that are epigenetically inactivated in MDS.

An association between a genetic abnormality and disease phenotype was reported in a few specific subsets of MDS. An example is the 5q- syndrome.[50] A minority of patients with an interstitial deletion of chromosome 5q display an indolent anemia with relative preservation of the platelet count associated with hypolobated megakaryocytes in the bone marrow (Fig. 5–4). This array of findings is called the 5q- syndrome and is recognized as a separate diagnostic entity in the current WHO classification. The genetic defect within the deleted region that is responsible for the disease is not known. Research has focused on one candidate gene, *SPARC*, that may potentially contribute to the malignant phenotype.[51] *CTNNA1* is another gene on chromosome 5q identified to be important in MDS and AML but without specific features of the 5q- syndrome.[52] *RPS14* was identified as haploinsufficient in 5q- MDS and is involved in ribosomal biogenesis; its deficiency has a role in anemia in this syndrome.[53] It is likely that a complex network of genes cooperate in the pathogenesis of this syndrome. Indeed, microRNA 145 and 146a have been found to be involved in the biology of 5q- syndrome.[54]

A small number of patients have been described with a deletion of 17p associated with abnormalities in the *p53* gene. This specific disorder has a poor prognosis and may be suspected when morphologic characteristics of prominent dysgranulopoiesis, including neutrophils exhibiting the Pelger-Huet anomaly and abnormal vacuolization, are present.[55] Acquired

TABLE 5–2 Frequency of Common Karyotypic Abnormalities Among 2008 World Health Organization (WHO) Classifications and French-American-British (FAB) Subgroups

		Karyotype, *n* (%)					
Classification	**Patients (*n*)**	**Normal**	**del(5q)**	**–7/del(7q)**	**+8**	**–20/del(20q)**	**Complex**
All FAB	1949	942 (48.3)	295 (15.1)	209 (10.7)	162 (8.3)	86 (4.4)	282 (14.5)
RA	573	267 (46.6)	139 (24.3)	30 (5.2)	37 (6.5)	31 (5.4)	47 (8.2)
RARS	252	147 (58.3)	23 (9.1)	24 (9.5)	14 (5.6)	9 (3.6)	20 (7.9)
RAEB	415	179 (43.1)	71 (17.1)	60 (23.8)	39 (9.4)	21 (5.1)	98 (23.6)
RAEB-t	305	132 (43.3)	38 (12.5)	50 (16.4)	30 (9.8)	16 (5.2)	68 (22.3)
CMML	272	170 (62.5)	4 (1.5)	23 (8.5)	18 (6.6)	2 (<1)	12 (4.4)
All WHO	595	285 (47.8)	110 (18.5)	53 (8.9)	40 (6.7)	22 (3.7)	71 (11.9)
5q- syndrome	61	0 (0.0)	61 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
RA	56	38 (67.9)	3 (6.5)	5 (10.9)	1 (2.2)	1 (2.2)	6 (13.0)
RARS	26	23 (88.5)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)
RCMD	164	88 (53.7)	11 (6.7)	20 (12.2)	12 (7.3)	8 (4.8)	18 (11.0)
RCMD-RS	77	34 (44.2)	8 (10.4)	8 (10.4)	8 (10.4)	3 (3.9)	12 (15.6)
RAEB-I	90	42 (45.7)	16 (17.8)	10 (11.1)	5 (5.6)	4 (4.4)	15 (16.7)
RAEB-II	121	60 (49.6)	11 (9.1)	8 (6.6)	13 (10.7)	5 (4.1)	19 (15.7)

RA, refractory anemia; RAEB-I, refractory anemia with excess blasts-I; RAEB-II, refractory anemia with excess blasts-II; RAEB-T, refractory anemia with excess blasts in transformation; RARS, refractory anemia with ring sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RCMD-RS, refractory cytopenia with multilineage dysplasia with ring sideroblasts

hemoglobin H disease produces RBC changes on the blood smear reminiscent of a-thalassemia. This RBC phenotype is secondary to decreased expression of a-globin within the bone marrow MDS clone and is associated with a mutation in the *ATRX* gene in most cases.[56] These rare syndromes represent a small minority of patients with MDS, and specific gene defects are not identified in most patients.

Several groups have used large-scale single-nucleotide polymorphism (SNP) arrays in MDS.[57] This has allowed the identification of areas of microdeletions and uniparenteral disomy in MDS.[58] It is likely

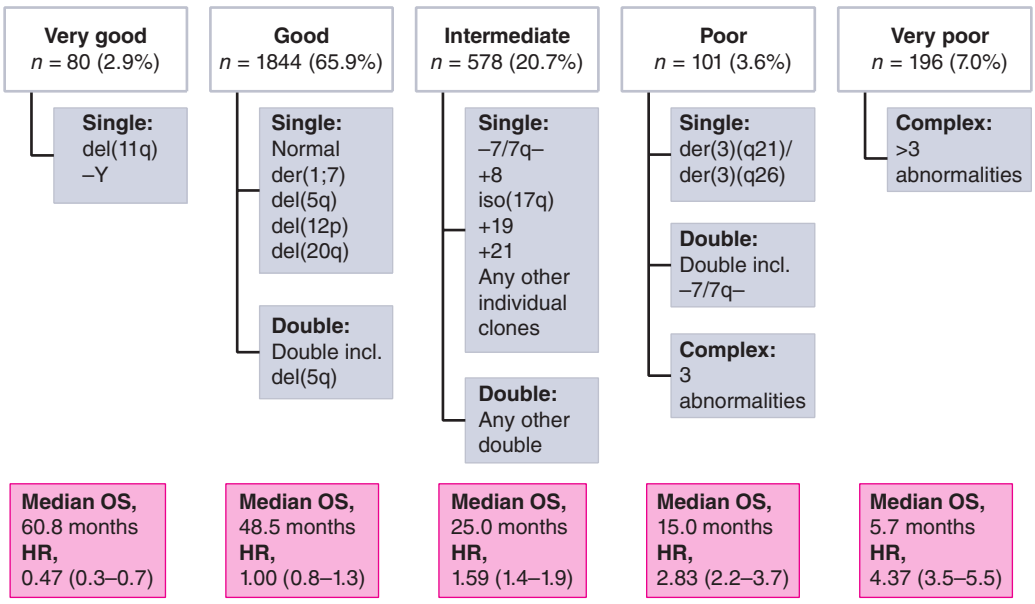


FIGURE 5–3 Cytogenetic score and corresponding prognoses. HR, hazard ratio; OS, overall survival.

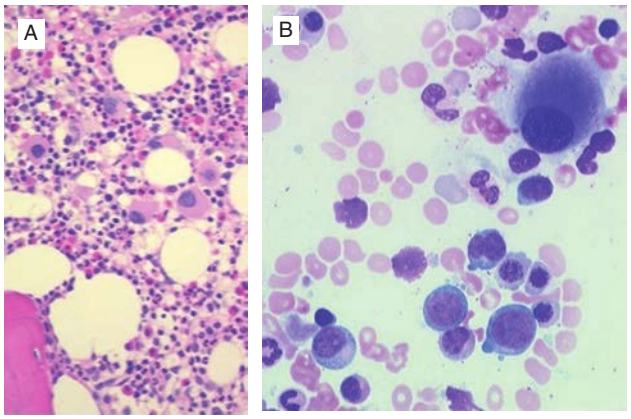


FIGURE 5–4 **A and B. Bone marrow morphology of myelodysplastic syndrome with deletion of chromosome 5.**

that these genomic regions harbor genes important in MDS, such as *c-CBL*.[59]

Over the past several years, we have accumulated significant information regarding genomic alterations in MDS, and the data are summarized in Figure 5–5.[31,60] Common mutations affect genes involved in gene splicing (eg, *SF3B1, SRSF2, U2AF1*), epigenetic regulators (eg, *TET2, DNMT3A, ASXL1,* and *EZH2*), and DNA repair and cell cycle control genes (eg, *PPM1D, TP53)*. The presence of mutations in *TP53* and *EZH2* is associated with poor prognoses.[31] Correlation of specific genomic alterations with gene expression patterns may explain some of the phenotypic features of the disease.[61]

Other Bone Marrow Studies

Flow cytometry is not required for the routine diagnosis of MDS, but it may sometimes provide valuable supplementary information. Flow cytometry can confirm the presence of specific myeloid lineages within the marrow and may also identify aberrant expression of cell surface markers indicative of a clonal cell population. This may have diagnostic significance in confirming abnormal hematopoiesis, particularly in the setting of inconclusive morphologic changes and a normal karyotype. Quantitation of the number of CD34-positive cells in the bone marrow may assist in the differentiation of hypoplastic MDS from aplastic anemia. In MDS, the number of CD34 cells is usually normal or increased, compared with aplastic anemia, for which it is frequently reduced.[62]

Fluorescent in situ hybridization techniques using probes specific for specific chromosomes (ie, covering chromosomes 5,7, 8, and 20) have not been fully standardized in MDS. Their use should not be consider standard of care in MDS and cannot yet replace conventional cytogenetics.

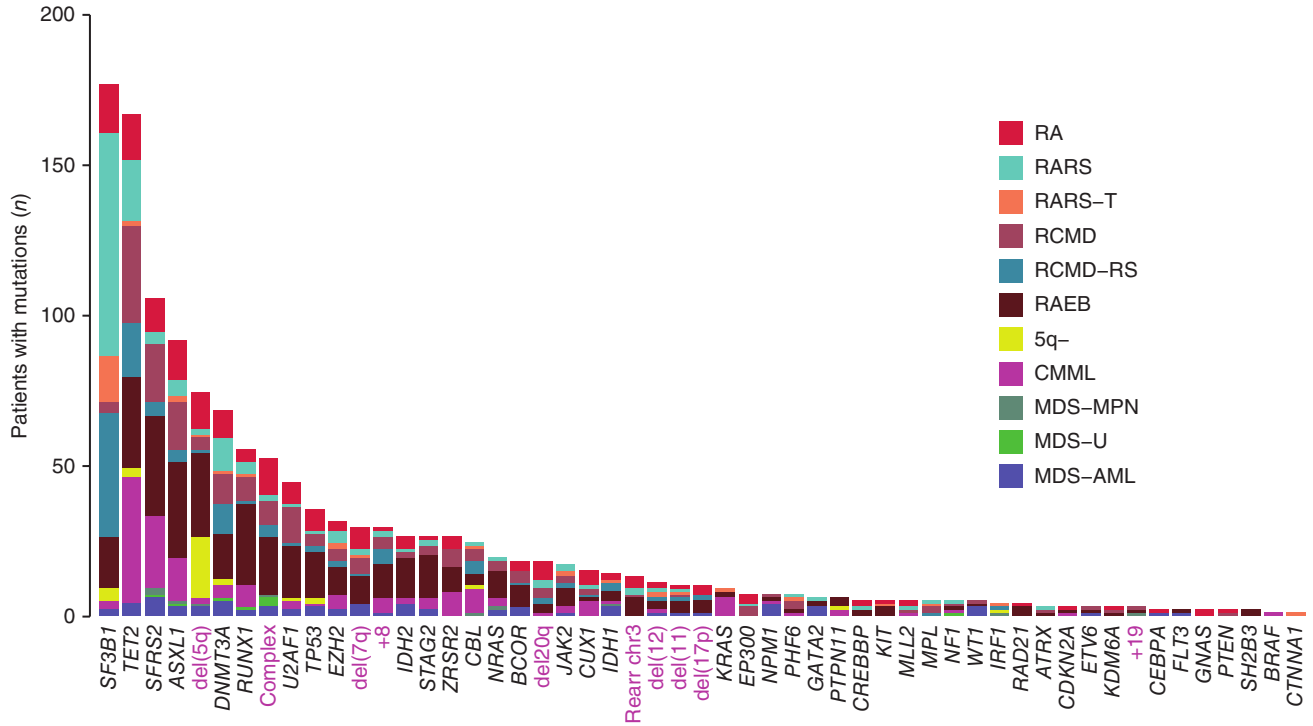


FIGURE 5–5 **Molecular data in myelodysplastic syndrome.**

DIAGNOSIS

The classification systems used to group different MDS have evolved over time with increased understanding of the biology and genetics of the disease. The first widely accepted classification was that proposed by the French-American-British (FAB) study group.[63] The FAB categorized MDS primarily on the percentage of blasts in the peripheral blood and bone marrow, with disease entities defined by increased numbers of blasts associated with a more aggressive clinical course. Patients with a bone marrow blast percentage greater than 30% were considered to have AML. This classification used only morphologic criteria to define disease groups and provided a framework that allowed the study of the natural history of MDS and its response to therapy.

The WHO classification of MDS was developed with the objective of using all features of disease biology, including morphology, cytogenetics, immunophenotype, and clinical behavior.[64] This classification was last updated in 2016 (see Table 5–1).[41] In the original WHO classification, the importance of morphologic assessment of blast percentage within the bone marrow and peripheral blood was retained, although the threshold level for the diagnosis of acute leukemia was altered. Patients with more than 20% bone marrow blasts were considered to have AML. Patients with 20% to 29% blasts had a similar prognosis as patients with greater than 30% blasts. Within the WHO MDS categories with an increased blast percentage, the magnitude of the blast elevation was quantified between MDS with excess blasts (MDS-EB) types 1 and 2, reflecting the worse prognosis of patients with an elevated blast count.[2,5] In patients with a normal proportion of blast cells within the bone marrow, the relatively indolent MDS with ring sideroblasts (MDS-RS) introduced in the FAB system were further delineated by assessment for the presence of multilineage dysplasia. Patients with dysplastic maturation limited to the erythroid lineage have a more favorable prognosis than patients with cytopenia and dysplasia present in multiple myeloid lineages. Also, the WHO introduced the 5q- syndrome as a separate diagnostic entity primarily on the basis of a genetic abnormality rather than morphologic features alone. Deletions involving chromosome 5q are relatively common in MDS, and the WHO classification tightly defined the syndrome as MDS with isolated del(5q) associated with anemia, a preserved or increased platelet count, and hypolobated megakaryocytes on the bone marrow biopsy (see Fig. 5–4). The WHO classification has been validated by a number of independent groups.[65,66] The 2016 WHO classification included the following changes: (1) replacing the terms "refractory anemia" and "refractory cytopenia" with "myelodysplastic syndrome" because of the minor impact of specific cytopenias and classification; (2) demonstrating 1% blasts on at least two separate occasions to diagnose MDS, unclassified (MDS-U); (3) changing the denominator for calculating blast percentage to all nucleated bone marrow cells rather than "nonerythroid cells"; (4) not including +8, -Y, or del(20q) as MDS-defining in the absence of morphologic features; and (5) excluding genomic data from classification but including specific mutations, such as *TP53* and *SF3B1*, on prognosis.[41]

PROGNOSIS

The prognosis of patients with MDS is heterogeneous. The development of clinical systems that allow accurate prognostication of individual patients into low- and high-risk categories has proven essential to guide rational management decisions and allow the introduction of investigational drug protocols. The IPSS, shown in Table 5–3, is the most widely used system for assessment of prognosis and treatment planning.[2] It provides an assessment of the prognosis of patients with primary MDS at the time of initial diagnosis. It was designed by the retrospective analysis of a large pool of 816 patients with MDS and followed the natural history of the disease to determine important factors related to patient outcome. Overall survival and the risk of transformation to acute leukemia were related to the number of blood cytopenias, the percentage of myeloblasts in the bone marrow, and the presence of specific cytogenetic abnormalities. The risk associated with cytogenetic abnormalities was determined to be good if a normal diploid karyotype, isolated del(5q), isolated del(20q), or isolated -Y were present. Poor-risk abnormalities were defined as abnormalities involving chromosome 7 or complex karyotypes with the presence of three or more karyotypic abnormalities. All other cytogenetic abnormalities were considered intermediate risk. The IPSS weighed these variables to produce a score that stratifies patients into four separate risk groups: low, intermediate-1, intermediate-2, and high risk (see Table 5–3). Survival and risk of transformation to acute leukemia are then predicted from cohorts of different ages, as illustrated in Table 5–3B. Patients classified as IPSS low and intermediate-1 risks are generally considered to have lower-risk MDS, and patients classified as having IPSS intermediate-2 and high are grouped into those with higher-risk MDS.

Lower-risk MDS is typically treated more conservatively than higher risk MDS. Prognostication in this lower-risk group may be particularly important because it is unclear at this time whether some lower-risk patients may benefit from early therapeutic intervention. To determine which lower-risk patients should be considered for treatment protocols investigating early

TABLE 5–3 International Prognostic Scoring System (IPSS)

A. IPSS Score: Sum of the Three Listed Prognostic Factors					
Score	**0**	**0.5**	**1**	**1.5**	**2**
BM blasts (%)	<5	5–10	—	11–20	21–30
Karyotype[a]	Good	Intermediate	Poor		
Cytopenias[b]	0/1	2/3			

B. Prognosis Determined by IPSS Score					
		Median Survival (years)			
Risk Group	**IPSS Score**	**≤60 years**	**>60 years**	**≤70 years**	**>70 years**
Low	0	11.8	4.8	9	3.9
Intermediate-1	0.5–1.0	5.2	2.7	4.4	2.4
Intermediate-2	1.5–2.0	1.8	1.1	1.3	1.2
High	≤2.5	0.3	0.5	0.4	0.4

[a]Good: normal, -Y, del(5q), del(20q); poor: complex (≤3 abnormalities) or chromosome 7 anomalies; intermediate: other abnormalities.
[b]Cytopenias are defined as hemoglobin concentration <10 g/dL, neutrophils $<1.5 \times 10^9$/L, and platelets $<100 \times 10^9$/L.
BM, bone marrow.

intervention, patients with lower-risk MDS at MDACC were analyzed to further stratify prognosis in low and intermediate-1 risk IPSS groupings (Table 5–4).[4] Factors associated with worse prognosis in this lower-risk group included thrombocytopenia (platelets $<50 \times 10^9$/L), anemia (hemoglobin concentration <10 g/dL), older age (older than 60 years), blast count greater than 4%, and a karyotype that was not diploid or del(5q) (Table 5–4A). This model stratified lower-risk patients into three subgroups by score—0 to 2, 3 to 4, and 5 to 7—with median

TABLE 5–4 A Lower-Risk Myelodysplastic Syndrome Prognostication Model.

A			
Adverse Factor	**Coefficient**	***P* Value**	**Assigned Score**
Unfavorable cytogenetics	0.203	<.0001	1
Age 60 years or younger	0.348	<.0001	2
Hemoglobin <10 (g/dL)	0.216	<.0001	1
Platelets $<50 \times 10^9$/L	0.498	<.0001	2
$50–200 \times 10^9$/L	0.277	.0001	1
BM blasts ≤4%	0.195	.0001	1

B			
Score	**Patients (*n*)**	**Median Survival Time (months)**	**4-Year Survival (%)**
0	11	NR	78
1	58	83	82
2	113	51	51
3	185	36	40
4	223	22	27
5	166	14	9
6	86	16	7
7	13	9	NA

The score is calculated in patients with myelodysplastic syndrome and an International Prognostic Scoring System score of low or intermediate-1. **A.** Significant characteristics by multivariate analysis. Each one has an assigned score. The calculated total score can then be used in **B** to predict the median and 4-year survival times.
BM, bone marrow.

survival periods of 80, 27, and 14 months, respectively (Table 5–4B). Increased ferritin and β_2-microglobulin were also associated with worse survival, but these factors were not included in the prognostic model. Because patient survival was significantly different between these lower-risk categories, investigation of early intervention protocols in lower-risk patients with relatively poor survival may be warranted.

We described the cause of death of patients with lower-risk MDS.[67] Approximately 80% of patients died from a complication intrinsic to MDS and not because of disease progression, which only occurred in 10% to 20% of patients. The most frequent cause of death was infection followed by bleeding. Patients with increased percentage of blasts and monosomy 7 had an increased risk of transformation to AML.[67]

The IPSS determines risk at the time of initial diagnosis, but it does not provide information regarding changes in risk as patients progress through their disease course. A dynamic prognostication system has been developed to address this deficiency and provides a score that is predictive of survival and leukemic transformation over time. The WHO classification-based Prognostic Scoring System weighs three variables: WHO diagnostic classification, karyotype abnormalities categorized according to the IPSS criteria, and transfusion requirement.[3] This stratifies patients into five disease groups that demonstrate different survival and risk of evolution to acute leukemia over time. Very low-risk patients in this classification have an overall mortality rate that was not different from the general population. This model incorporates changes in the disease risk profile over time, allowing further refinement in prediction of survival and leukemic progression as the disease progresses. A model has been developed by MDACC that includes CMML and accounts for both de novo and secondary disease, allowing for prognostication at any time during the course of MDS.[68] The characteristics of this model are shown in Table 5–5.

The presence of fibrosis on the bone marrow biopsy occurs in a minority of patients with MDS, but this pathological feature is not incorporated into routine diagnostic classifications or prognostic systems. Fibrosis is more frequently observed in patients with multilineage dysplasia or with karyotype abnormalities and, when present, is associated with a more rapid progression to severe bone marrow failure and shortened survival.[69] In younger patients, it may warrant early consideration of allo-SCT.

An international consortium developed a new MDS classification known as the IPSS-R.[5] The basis for this effort was to improve on known limitations of the initial IPSS. IPSS-R includes a refined cytogenetic annotation and newer thresholds of cytopenias and blast percentages.[46] Table 5–6 shows the characteristics of this new classification. The IPSS-R divides patients into five categories (very low, low, intermediate, high, and very high risk). Algorithms have been developed to calculate expected survival and time to progression based on age and IPSS-R score. The IPSS-R should be considered the standard tool to calculate prognosis in patients with MDS and is now incorporated

TABLE 5–5 MD Anderson Cancer Center Model of Risk Stratification for Myelodysplastic Syndromes

A. Simplified Myelodysplastic Syndrome Risk Score		
Prognostic Factor	**Coefficient**	**Points[a]**
Performance status ≤2	0.267	2
Age (years)		
60–64	0.179	1
≤65	0.336	2
Platelets ($\times 10^9$/L)		
<30	0.418	3
30–49	0.270	2
50–199	0.184	1
Hemoglobin <12 g/dL	0.274	2
BM blasts		
5–10 (%)	0.222	1
11–29 (%)	0.260	2
WBC count >20 × 10^9/L	0.258	2
Karyotype: chromosome 7 abnormality or complex ≤3 abnormalities	0.479	3
Prior transfusion, yes	0.107	1

(*Continued*)

TABLE 5–5 MD Anderson Cancer Center Model of Risk Stratification for Myelodysplastic Syndromes (*Cont.*)

B. Estimated Overall Survival by Prognostic Score				
		Survival		
Score	Patients, *n* (%)	Median (Months)	% At 3 Years	% At 6 Years
Low				
0–4	157 (16)	54	63	38
Intermediate-1				
5	111 (12)	30	40	14
6	116 (12)	23	29	14
Intermediate-2				
7	127 (13)	14	19	8
8	106 (11)	13	13	4
High				
9	97 (10)	10	10	2
≤10	244 (25)	5	2	0

C. Estimated Overall Survival by Four Levels of Prognostic Score Points				
		Survival		
Score	Patients, n (%)	Median (months)	Score	Patients, n (%)
0–4	157 (16)	54	63	38
5–6	227 (24)	25	34	13
7–8	233 (24)	14	16	6
≤9	341 (36)	6	4	0.4

[a]Score points were obtained by dividing the coefficients by 0.15 and rounding to the nearest integer.
BM, bone marrow; WBC, white blood cell

in a majority of modern clinical trials. Furthermore, patients with intermediate-risk MDS by IPSS-R were further stratified based on age (66 years or older), peripheral blood blast count 2% or greater, and need for RBC transfusions (Table 5–7)[6]; patients with scores of 0 or 1 were considered intermediate-favorable risk, and those with scores of 2 to 4 were considered intermediate-adverse risk. Finally, it is likely that all these classifications will be modified with the incorporation of molecular genomic data.

Patients with MDS are older and may have other comorbidities. We have calculated the impact of comorbidities using the Adult Comorbidity Evaluation-27 (ACE-27) comorbidity score on the outcome of patients with MDS.[70,71] This analysis indicated synergism between the presence of comorbidity and disease score. The same was observed when ACE-27 was calculated with IPSS-R and in conjunction with genomic data.[71,72]

TABLE 5–6 Revised International Prognostic Scoring System (IPSS-R)

A. Prognostic Score Values							
Prognostic Variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	NA	Good	NA	Intermediate	Poor	Very poor
BM blast (%)	≤2	NA	>2% to <5%	NA	5%-10%	>10%	NA
Hemoglobin	≥10	NA	8 to <10	<8	NA	NA	NA
Platelets	≥100	50 to <100	<50	NA	NA	NA	NA
ANC	≥0.8	<0.8	NA	NA	NA	NA	NA

(*Continued*)

B. Prognostic Risk Categories and Outcomes by Score *(Cont.)*						
Risk Category	**Risk Score**					
Very low	≤1.5					
Low	>1.5–3					
Intermediate	>3–4.5					
High	>4.5–6					
Very high	>6					
	Patients (*n*)	**Very Low**	**Low**	**Intermediate**	**High**	**Very High**
Patients (%)	7012	19	38	20	13	10
Survival, all[a]		8.8	5.3	3.0	1.6	0.8
		(7.8–9.9)	(5.1–5.7)	(2.7–3.3)	(1.5–1.7)	(0.7–0.8)
Hazard ratio		0.5	1.0	2.0	3.2	8.0
(95% CI)		(0.46–0.59)	(0.93–1.1)	(1.8–2.1)	(2.9–3.5)	(7.2–8.8)
Patients (%)	6,485	19	37	20	13	11
AML/25%[a,b]		NR	10.8	3.2	1.4	0.73
		(14.5–NR)	(9.2–NR)	(2.8–4.4)	(1.1–1.7)	(0.7–0.9)
Hazard ratio		0.5	1.0	3.0	6.2	12.7
(95% CI)		(0.4–0.6)	(0.9–1.2)	(2.7–3.5)	(5.4–7.2)	(10.6–15.2)

[a]Median, years (95% confidence interval [CI]); $P < .001$.
[b]Median time to 25% AML evolution (95% CIs); $P < .001$.
AML, acute myeloid leukemia; ANC, absolute neutrophil count; NA, not applicable; NR, not reached.

TABLE 5–7 Prognostic Score for patients with Intermediate-Risk Myelodysplastic Syndromes by IPSS-R

Adverse Factor	Coefficient	*P* Value	Assigned Score
Age 66 years or older	0.87	<.0001	2
Peripheral blood blasts ≥2%	0.52	0.009	1
RBC transfusion	0.51	0.003	1

RBC, red blood cell.

THERAPY

The number of effective drug treatments available to treat MDS has expanded in recent years, providing different management alternatives. Some treatments improve hematopoietic function and alleviate symptoms related to blood cytopenias; other therapies alter the natural history of the disease and improve survival. Both approaches may be appropriate in different clinical contexts, and many patients receive various combinations of treatments throughout their disease course.

The goals of therapy in MDS vary in different patient populations. A management plan should consider the patient's age, comorbidities, and disease risk. Patients with lower-risk MDS most commonly experience problems related to chronic anemia, and the disease may remain stable for prolonged periods. If these patients are older, they may best be managed with relatively nontoxic therapies that aim to maintain quality of life. Treatment options include transfusions of blood products, growth factor therapies (ie, EPO with or without colony-stimulating factors), iron chelation, luspatercept, and non–growth factor therapies with immune modulators (lenalidomide) and epigenetic drug treatment (azacitidine or decitabine). Higher risk MDS has a poor prognosis and forms a continuum with AML. Aggressive therapies may be warranted in these higher risk patients to eradicate the malignant clone and improve survival. Intensive therapies may include high-dose chemotherapy and consideration of allo-SCT in younger patients. Intensive treatment protocols are not suitable for all patients because they expose the patient to significant risks of treatment-related morbidity and mortality. An algorithm for treatment approaches at MDACC is shown in Figure 5–6, with specific therapies based on lower-risk and higher-risk MDS shown in Figure 5–7.[73]

Assessing response to treatment in MDS can be complex as treatment goals in low- and high-risk disease may be different. Clinical response criteria in

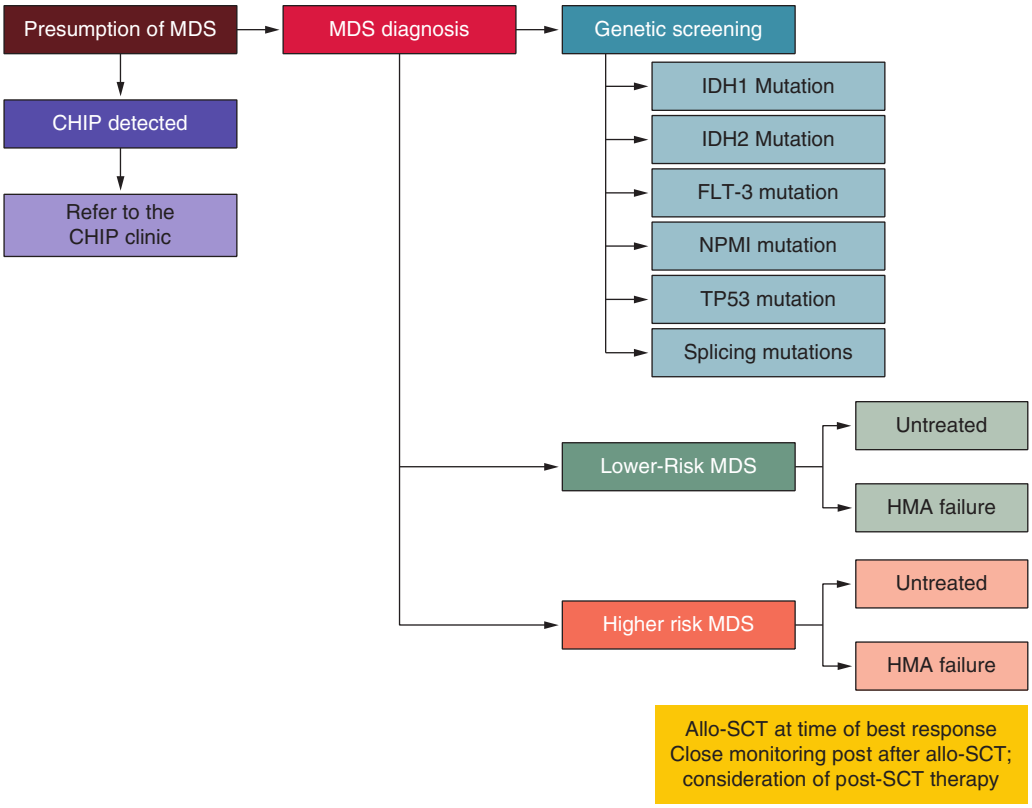


FIGURE 5–6 **A MD Anderson Cancer Center approach to the management of patients with myelodysplastic syndromes (MDSs). allo-SCT, allogeneic stem cell transplant; CHIP, clonal hematopoiesis of indeterminate potential; HMA, hypomethylating agent; SCT stem cell transplant.**

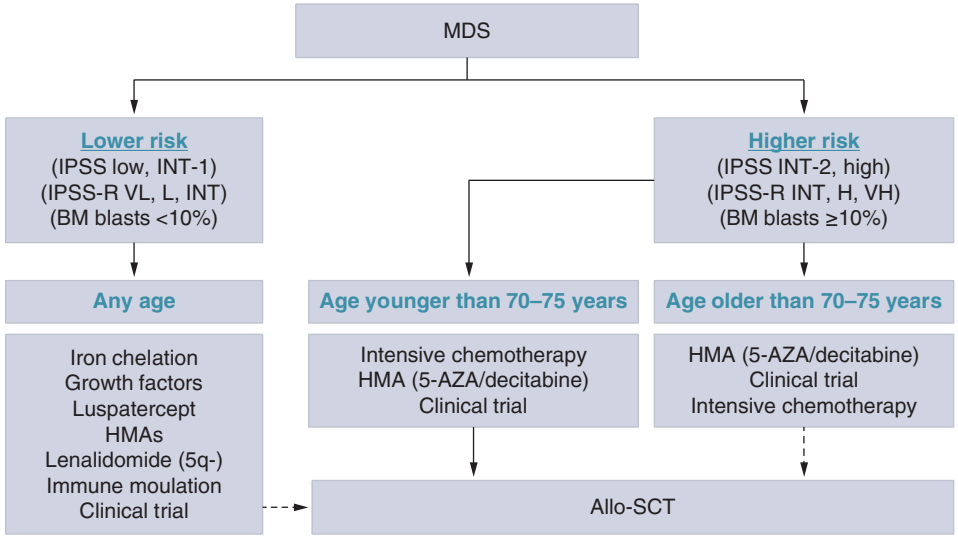


FIGURE 5–7 **Risk-based treatment algorithm for patients with myelodysplastic syndromes (MDs). allo-SCT, allogeneic stem cell transplant; BM, bone marrow; 5-AZA, 5-azacitidine; HMA, hypomethylating agent; INT, intermediate; IPSS, International Prognostic Scoring System; IPSS-R, Revised International Prognostic Scoring System; L, low; VH, very high; VL, very low; H, high VH, very high.**

lower-risk disease usually measure improvements in peripheral blood cell counts and quality-of-life factors. Response in higher risk disease also requires improvement in bone marrow blasts. Standardized criteria by the International Working Group are available to assess response to treatment in MDS and are particularly useful to allow comparisons between drug trials,[74] with new hematologic response criteria recently proposed.[75]

Supportive Care

Chronic blood cytopenia is a principal characteristic of MDS. Therapies aimed at alleviating problems related to anemia, neutropenia, and thrombocytopenia are an essential component of management. Bacterial infections require aggressive treatment with antibiotics. Platelet transfusions are administered for episodes of bleeding or for prophylaxis in patients with severe thrombocytopenia. Transfusion thresholds at MDACC include a hemoglobin level of 8 g/dL (unless the patient is otherwise symptomatic) and a platelet count of less than 10 K/UL (unless there is evidence of bleeding). These transfusion thresholds have been challenged by the 2020 COVID-19 pandemia because of a lack of donors. Additional hemostatic support with the use of antifibrinolytic agents may be considered for problematic mucosal bleeding or for surgical procedures. The role of prophylactic antibiotics is less established in neutropenic patients. It is our practice at MDACC to use triple therapy (antibacterial with a fluoroquinolone, antiviral, and antifungal) in all patients with severe neutropenia who are receiving therapy.

Symptomatic anemia is often the major clinical problem in patients with lower-risk MDS. In this group, RBC transfusions are effective symptomatic therapies, but a prolonged transfusion program may cause problems with transfusion-related hemosiderosis, alloantibody formation, and volume overload in patients with impaired cardiac function. Deposition of iron in body tissues is treated with iron chelation. The efficacy of iron chelation therapy is best demonstrated in thalassemia major, in which regular deferoxamine therapy reduces iron deposition in organs and improves survival.[76] The parenteral administration of deferoxamine is inconvenient, and the development of effective oral iron-chelating drugs, such as deferasirox, has allowed iron chelation to be performed more easily.[77] In MDS, iron chelation was hypothesized to have similar advantages.[78] This was confirmed in the recently published randomized double-blind phase II TELESTO study,[79] which demonstrated an increased event-free survival with oral deferasirox compared with placebo. Iron chelation should start with parenteral deferoxamine or oral deferasirox after 20 to 40 units of RBC have been administered, particularly if there is an expectation of prolonged survival and continued transfusion therapy. Serum ferritin may be used as a guide to chelation therapy, with a ferritin concentration greater than 1000 µg/L typically attained after transfusion of 20 RBC units.[66] Iron chelation therapy should also be considered in younger patients who may be candidates for allogeneic transplantation. An elevated pretransplant ferritin has been associated with a lower overall survival after allogeneic transplantation and an increase in the hepatic transplant complication of veno-occlusive disease.[80]

Hematopoietic Growth Factors

Hematopoietic growth factors are the primary regulators of blood progenitor cell proliferation and are used therapeutically to promote effective hematopoiesis. EPO therapy has been explored as an alternative to RBC transfusion in patients with lower-risk MDS. Various forms of recombinant EPO (rEPO), including epoetin a, epoetin b, and the long-acting darbepoetin, have been studied in different cohorts of patients. Overall, erythroid responses in unselected patients were modest, in the range of 10% to 20%.[81] The best responses were identified in patients with low-risk MDS, a low serum EPO level (<200 IU/L), and no RBC transfusion requirement.[82] In this favorable subgroup of patients with MDS, an erythroid response to rEPO therapy was observed in 40% to 60% of patients.[82] The median duration of response was 2 years, and therapy was associated with improved quality of life.[83] Data suggest that patients who respond to growth factor therapy have better survival than historical control cohorts who received supportive care alone.[82]

EPO in combination with G-CSF is also effective, with response rates of 40% to 50% in selected cohorts.[61,83,84] The combination of these two hematopoietic cytokines appears to offer a synergistic clinical benefit and allow improvements in hemoglobin levels in some patients who fail to respond to EPO monotherapy. The benefit of this combination may be most marked in refractory anemia with ring sideroblasts (RARS) and refractory cytopenia with multilineage dysplasia (RCMD), but this has not been confirmed.[82] Disease transformation is a theoretical risk in patients receiving chronic hematopoietic growth factors, but long-term observations of these patients suggested that these cytokines do not promote leukemic transformation.[82,84] Hematopoietic growth factor therapy should be considered to treat anemia in patients with lower-risk MDS associated with a low serum EPO level. EPO can be initiated as monotherapy with the addition of G-CSF if there is no objective response in 2 to 3 months.

Thrombopoietin has been used to promote platelet production and minimize the bleeding complications related to severe thrombocytopenia. Initial trials with recombinant thrombopoietin were disappointing. New second-generation thrombomimetic agents are now being tested.[85–87] Potential concerns of increased blasts and fibrosis, leading to an elevated risk of progression to AML or death, led to discontinuation of the study drug in a phase II trial, though 5-year follow-up data did not show a difference.[87]

Transforming Growth Factor β Signaling Modulators

More recently, the use of luspatercept, a recombinant fusion protein binding transforming growth factor β

(TGF-β) ligands to decrease SMAD2- and SMAD3 signaling involved in ineffective erythropoiesis of MDS, has been studied.[88,89] A phase II study evaluating luspatercept in patients with lower-risk MDS showed an erythroid response rate of 63%, and 38% of patients had transfusion independence for 8 weeks or longer.[90] The double-blind, randomized, placebo-controlled phase III MEDALIST trial validated the previous observations that luspatercept reduced anemia severity in patients with lower-risk MDS-RS who were transfusion dependent and had disease that was refractory to EPO therapy,[91] leading to its Food and Drug Administration (FDA) approval in 2020. Limitations for the use of luspatercept include the cost of therapy and no clear evidence of improved survival, and longer follow-up times are needed to fully understand the effects of the compound on the natural history of MDS progression.

Lenalidomide

Lenalidomide is a chemical analogue of thalidomide with diverse biological actions that encompass immune modulation and antiangiogenic effects. Selective activity of lenalidomide against MDS associated with an interstitial deletion on the long arm of chromosome 5 was first suggested in a study examining the effects of this drug on anemia in patients with low-risk MDS.[92] Erythroid responses were noted in 56% of the cohort, with the most significant response found in the subgroup with a del(5q) abnormality. This observation was confirmed in a larger multicenter phase II study of lenalidomide.[7] This second trial demonstrated an overall erythroid response in 76% of patients with the del(5q) abnormality. Responses were prolonged and occurred rapidly, with a median time to a hematologic response of 4 to 5 weeks. A cytogenetic response was documented in 73% of patients, with 44% developing complete cytogenetic remission. Cytogenetic responses were observed in patients with the del(5q) abnormality alone and in patients with the del(5q) abnormality associated with additional cytogenetic defects. This clearly demonstrated that the activity of lenalidomide was not limited to patients with the 5q- syndrome but was also observed in patients with low-risk MDS. A randomized trial comparing different doses of lenalidomide versus observation further confirmed the activity of the drug at a dose of 10 mg/day.[93] Although none of these studies were powered to document improvement in survival, a recent analysis indicated that achieving a cytogenetic response with lenalidomide was associated with prolonged survival.[94]

Lenalidomide therapy in MDS is usually started at 10 mg/day. A favorable response is typically characterized by normalization of anemia and cytogenetic response.[7] The most important side effect of therapy with lenalidomide is myelosuppression, which may necessitate dose reduction in patients with persistent thrombocytopenia and neutropenia. Interestingly, the degree of myelosuppression has been associated with response. Thrombocytopenia at diagnosis (platelet count $<100 \times 10^9$/L) has been associated with a worse response to lenalidomide treatment. This may reflect repeated or prolonged treatment interruptions secondary to myelosuppression.

Lenalidomide and thalidomide also demonstrated activity in low-risk MDS without the del(5q) abnormality. Lenalidomide has been studied in 214 patients with low-risk MDS (IPSS low and intermediate-1) and predominantly a normal karyotype.[8] In this cohort, 26% of patients achieved transfusion independence, and 17% developed a reduction in transfusion requirement. The median duration of transfusion independence was 41 weeks, and cytogenetic responses were documented in 19% of patients with karyotypic abnormalities. These results were confirmed in a randomized trial.[95]

Hypomethylating Agents

5-Azacitidine and 5-aza-2′-deoxycytidine (decitabine) are chemically related drugs with a spectrum of activity that includes both lower and higher risk MDS. The mechanism of action of these drugs is uncertain, although both agents reverse abnormal promoter DNA methylation that surrounds the promoter of some tumor-suppressor genes in cancer cells. Aberrant promoter methylation is associated with transcriptional repression, or silencing, and may contribute to the loss of tumor-suppressor gene function in MDS. Decitabine and 5-azacitidine are both cytidine analogues that incorporate into DNA and form covalent bonds with DNA methyltransferase enzymes. Depletion of methyltransferase activity within the cell then causes newly synthesized DNA to be hypomethylated compared with the parent strand. After at least two cycles of cell division, DNA becomes globally hypomethylated with alteration in gene expression within the leukemic cell. Both agents display cytotoxicity at high doses, but hypomethylating activity remains prominent at lower doses. These biochemical changes are an attractive target for drug therapy because normal tissues have little gene promoter methylation, so hypomethylating therapy may have some degree of specificity for the malignant clone.

5-Azacitidine first demonstrated broad-spectrum activity in MDS. Comparison of azacitidine (75 mg/m^2 intravenously or subcutaneously for 7 days every 28 days) with best supportive care in a randomized control trial demonstrated an overall response rate of 48% with azacitidine compared with 5% with supportive care.[96,97] Azacitidine therapy was associated with a prolongation in the time to leukemic transformation and better quality of life. The median time to response

was three cycles, and response rates were independent of MDS classification. Complete responses were observed in relatively few patients, approximately 10%, with most patients experiencing hematologic improvement. A report of a multicenter phase III study of azacitidine in patients with higher risk MDS demonstrated an increase in overall survival of approximately 9 months for patients receiving azacitidine compared with other standard therapies.[98] This was the first drug trial that demonstrated a survival advantage in MDS. A subset analysis of the trial data suggested that azacitidine may have significant activity in MDS associated with abnormalities in chromosome 7, a cytogenetic abnormality associated with a poor outcome.

Decitabine has similar clinical activity to azacitidine and has been studied in various intravenous (IV) dose regimens in predominantly higher risk MDS and AML. Comparison of decitabine (45 mg/m^2 in three divided doses administered for three consecutive days every 6 weeks) with best supportive care in a randomized trial demonstrated an overall response rate of 17%, with complete remissions in 9% of patients with predominantly high-risk MDS.[99] Subgroup analysis revealed that patients who received decitabine had a longer median time to transformation to AML or death if they were treatment naïve or had high-risk MDS. Myelosuppression was the major drug toxicity. Data from this trial may underestimate the efficacy of the drug because a significant proportion of patients on decitabine received a small number of treatment cycles, which may have been insufficient to demonstrate a response. This is supported by previous phase II trial data that suggested decitabine had an overall response rate similar to azacitidine.[100] Subsequent clinical trial development with decitabine has focused on improving response rates by lowering the daily dose and lengthening administration schedules. One such schedule of IV administration of decitabine for 5 days every 4 weeks demonstrated a complete response rate of 39% in a high-risk MDS cohort.[101,102] Improvements in hematopoietic function are often delayed after the initiation of azacitidine or decitabine therapy, and drug treatment should continue for four to six cycles before cessation because of poor response.

Chemical modification of histone proteins by acetylation contributes to the regulation of gene expression and probably interacts with abnormal DNA methylation to cause transcriptional suppression of tumor-suppressor genes. Histone deacetylase (HDAC) inhibitors, such as valproic acid and pracinostat, alter chromatin structure to promote gene transcription, and their combination with HMA demonstrates significant in vitro synergy.[103] Initial clinical drug trials in MDS and AML at MDACC indicated increased clinical activity when combining either decitabine or azacitidine with valproic acid.[104,105] None of the randomized trials investigating a HMA with or without a HDAC inhibitor showed a survival improvement.[106–108]

Guadecitabine (SGI-110) is a next-generation HMA that, unlike decitabine, is relatively resistant to degradation, thus allowing for slow release of its active metabolite decitabine and consequently prolonged exposure time and reduced maximum plasma concentration.[109] A phase I study identified guadecitabine 60 mg/m^2 as the biologically effective dose and 90 mg/m^2 as the maximum tolerated dose,[109] and a phase II study showed better-than-expected outcomes in treatment-naïve patients with MDS compared with the first-generation HMA decitabine and azacitidine.[110]

HMA were previously only available as IV administrations, along with a subcutaneous form of azacitidine. However, oral administration of HMA would enhance patient convenience, avoid injection site reactions, and allow for the evaluation of alternative doses and schedules.[111,112]

The oral bioavailability of decitabine was limited due to its rapid degradation by cytidine deaminase (CDA) in the gut and liver, but simultaneous oral administration with the CDA inhibitor cedazuridine (E7727) resulted in increased bioavailability of oral decitabine and similar pharmacokinetics to IV decitabine.[113] A phase II study showed a similar safety profile and response rates between oral cedazuridine–decitabine (ASTX727) and IV decitabine.[114] Preliminary results from the phase III ASCERTAIN study comparing oral ASTX727 with IV decitabine in patients with higher risk MDS showed equivalent HMA exposure between the two arms, safety findings, and clinical activity,[115] and this led to the FDA approval of oral decitabine and cedazuridine for adult patients with MDS in July 2020.

Cytotoxic Chemotherapy

The relatively poor prognosis associated with higher risk MDS has initiated intensive treatment strategies incorporating high-dose chemotherapy in the same protocols used to treat AML. In higher risk MDS, AML-type treatments produce a complete response rate of about 40% to 60%, but remissions are brief.[116,117] This poor response to high-dose chemotherapy is caused, at least in part, by the relatively greater proportion of patients diagnosed with MDS-EB having poor prognosis cytogenetics involving complex changes of chromosomes 5 and 7. Older adult patients with significant comorbidities tolerate high-dose chemotherapy poorly.

Patients with higher risk MDS have been treated with a variety of intensive chemotherapy regimens at MDACC.[118,119] Studies have examined using intermediate- to high-dose cytosine arabinoside (ara-C) (A) in various combinations with idarubicin (I), cyclophosphamide (C), fludarabine (F), and topotecan (T), as regimens: IA, FA, FAI, TA, and CAT. The overall

complete response rate for these regimens was 55% to 58%. A short antecedent history of any hematologic disorder, a normal karyotype, performance status, age, and treatment in a laminar airflow environment were all predictive of attaining a complete response. This intensive approach was beneficial in some patients because those who developed a complete response within 6 weeks of chemotherapy obtained a survival advantage. However, these regimens were toxic, with a significant treatment-related mortality rate in the first 6 weeks, ranging from 5% with TA to 21% with FAI. Consolidation chemotherapy was used in most cases when a remission was achieved with a regimen containing the drugs used in induction but at a reduced intensity of 50% to 66% of the initial dose. Survival of patients treated with IA and TA therapies were comparable and superior to those patients treated with FA, FAI, and CAT regimens, but prognosis remained poor. Nevertheless, this approach does benefit some younger individuals (younger than 65 years) with a normal karyotype, achieving an encouraging 5-year survival rate of 27% with intensive treatment. For older patients, the TA combination can be considered because it has a relatively low treatment-related mortality rate, and it does not contain anthracycline drugs (relatively contraindicated in the presence of heart disease).

Immunosuppressive Therapy

Immune dysfunction contributes to blood cytopenias in some patients with MDS, producing a clinical overlap with aplastic anemia. Immunosuppressive therapy with antithymocyte globulin (ATG) with or without the addition of cyclosporine has been explored in small numbers of patients with MDS. Response rates of 30% to 50% have been observed in selected cohorts of patients with lower-risk MDS administered a course of ATG, with a minority of patients experiencing prolonged remission.[120–122] Features that may predict a good response to immunosuppressive therapy include younger age, HLA-DR status, shorter duration of RBC transfusions, low-risk IPSS, and bone marrow hypocellularity.[122–124] Selection of appropriate patients for immunosuppression is important because ATG therapy is poorly tolerated in an older population with low-risk MDS.[125]

Hematopoietic Stem Cell Transplantation

In MDS, allo-SCT is potentially curative, but the therapy carries significant risk associated with treatment toxicities, prolonged cytopenias, infections, and graft-versus-host disease. In young patients with suitable donors, the transplant procedure offers the best chance of cure, with a long-term disease-free survival rate of 30% to 50%.[126–130] Given the risks associated with this procedure, patient suitability and timing of the transplant are important issues.

Allogeneic transplantation with myeloablative conditioning has been examined exclusively in younger patients (median age in the mid-30s) in most studies. Patients with lower-risk disease have experienced the best survival rate. However, this is also the subgroup of patients predicted to experience prolonged survival without aggressive therapies. This procedure is associated with a significant treatment-related mortality rate of up to 30% to 50% in some studies.[128,129] Relapse after transplantation occurs in approximately 20%, and the relapsed disease has a relatively poor response to donor lymphocyte infusion.[128,129,131] Increased risk of allogeneic transplantation mortality in MDS is associated with older age, poor-risk cytogenetics (particularly abnormalities of chromosome 7 or a complex karyotype), the presence of excess blasts in the bone marrow, and longer duration of disease.[132,133] Patients with treatment-related MDS also have a poor transplant outcome, but this is related to the frequency of high-risk cytogenetic changes.[133,134]

The development of nonmyeloablative allogeneic transplantation with reduced-intensity conditioning has allowed allogeneic transplantation to be considered in older patients with MDS and in patients whose comorbidities or organ dysfunction would exclude them from myeloablative treatment.[135] This procedure has reduced transplant-related mortality, the major problem limiting the availability of this potentially curative therapy to older patients. This therapy aims to minimize organ toxicity related to initial chemotherapy or radiation therapy and allow stable engraftment of donor cells that provide the curative potential associated with the graft-versus-leukemia effect. Comparison of reduced-intensity conditioning transplantation with standard myeloablative conditioning showed reduced transplant-related mortality but increased relapse rate, resulting in comparable rates of overall survival between the two transplantation strategies.[132,136–138]

Statistical modeling based on historical allogeneic transplantation outcomes for matched sibling transplantation suggested that the maximal overall survival is achieved by different transplant strategies in different MDS risk groups.[139] Patients with lower-risk disease maximize overall survival by delaying transplantation after diagnosis until evidence of disease progression but before the development of overt acute leukemia. This delayed transplant approach provided the greatest survival benefit to younger patients (younger than 40 years).

Specific features of disease progression have not been defined, but evidence of new cytogenetic

abnormalities, progressive cytopenias, and increasing blast percentage in the bone marrow are suggested as potential triggers for transplantation. Patients with higher risk disease should ideally receive the transplant as soon as possible after diagnosis. The presence of bone marrow fibrosis delays engraftment in allogeneic transplantation, and its presence is an additional risk factor in transplant outcome in higher risk MDS. In this group, fibrosis considerably increases transplantation risk.

Early consideration of transplantation is suggested in a younger patient with significant MDS-associated fibrosis.[134] The outcomes of patients older than 60 years of age with MDS treated with either reduced-intensity transplantation or HMA were studied.[9] The results of this analysis indicated that transplant should not be considered as first-line therapy in lower-risk MDS. Of interest, in higher risk MDS, it appears that there is a benefit toward transplant compared with HMA-based therapy, but survival curves cross significantly later than after 24 months of therapy. This indicated that there is probably a specific group of patients, not yet defined, that derives the maximal benefit from transplantation.

Emerging Therapeutics

Other Oral Hypomethylating Agents

The bioavailability and safety of oral azacitidine (CC-486) was initially evaluated an open-label pharmacokinetic study of patients with MDS, AML, or solid tumors.[111] In a phase I study in patients with MDS, CMML, and AML, oral azacitidine demonstrated biologic and clinical activity with extended dosing schedules showing sustained epigenetic effects.[112,140,141] Its use in lower-risk MDS is being further investigated.[142–144] Furthermore, ASTX030, an oral combination of azacitidine and cedazuridine, is currently being researched after showing the same efficacy as parenteral azacitidine in mouse models.[145]

Immunotherapy

The PD-1 axis is expressed in patients with MDS, which may allow for the development of new forms of therapy and combinations using inhibitors of this pathway.[146] Single-agent pembrolizumab (anti–PD-1 antibody), nivolumab (anti–PD-1 antibody), and ipilimumab (anti–CTLA-4 antibody) did not show significant responses but had acceptable toxicity profiles.[147,148] Updated results from ongoing phase II studies investigating the combination of azacitidine with pembrolizumab, nivolumab, or ipilimumab indicate that combination therapy is safe and well tolerated with antitumor activity.[148,149] Azacitidine in conjunction with double immune checkpoint inhibitor blockade with nivolumab and ipilimumab has also shown a tolerable safety profile and clinical activity.[150] The combination of HMA with anti–PD-L1 antibodies has also been investigated.[151,152]

Recently, T-cell immunoglobulin mucin-3 (TIM-3), an inhibitory immune checkpoint receptor expressed on AML cells, is being studied as a potential therapeutic target with the combination of the anti-TIM-3 antibody MGB453 and HMA.[153,154] Furthermore, CD47 expression on blasts from lower-risk patients with MDS was found to be similar to normal cells, but increased expression was observed in higher risk patients with MDS,[155] leading to the hypothesis that increased CD47 expression could represent progression or transformation.[156] The use of magrolimab, an anti-CD47 antibody, in patients with MDS is currently being explored; data recently presented include an overall response rate of 92% with a complete response rate of 50%.[157]

Venetoclax

Venetoclax is a BH3-mimetic that inhibits the antiapoptotic Bcl-2 protein, leading to programmed cell death.[158] Preclinical studies show synergy between venetoclax and HMA in higher risk MDS and AML.[159,160] A phase Ib study evaluating azacitidine and venetoclax in treatment-naïve patients with higher risk MDS showed that combination therapy had a tolerable safety profile and potential efficacy.[161] Multiple studies evaluating different combinations of therapies with venetoclax are underway.

Targeted Therapies

With the incorporation of molecular and genomic analysis into the diagnostic bone marrow aspiration or biopsy, the use of therapies that target particular mutations is being studied. Many of these therapeutic targets have been studied in AML, and clinical trials are underway for their potential role in the treatment of MDS. Current genomic targets under investigation include *TP53*, *IDH2*, *IDH1*, and *FLT3*.

TP53 mutations are one of the most frequently occurring mutations in myeloid malignancies and often associated with complex karyotype and poor prognoses.[31] APR-246 covalently binds to p53 and restores wild-type proapoptotic activity.[162] A dose escalation phase 1b clinical trial showed the combination of azacitidine and APR-246 had manageable nausea and transient neurologic adverse events,[163] and a dose expansion phase II trial showed an overall response rate of 87% in patients with MDS and

oligoblastic AML.[164] Similarly, our French colleagues conducted a similar phase II trial with azacitidine and APR-246 showing a response rate of 66%.[165] A randomized phase III study of frontline azacitidine with or without APR-246 in *TP53*-mutant MDS is underway.

Although *IDH2* and *IDH1* mutations are less frequently observed in MDS,[166,167] studies involving targeted inhibitors are underway. Enasidenib (AG-221) is a selective oral inhibitor of mutant IDH2 enzyme that is FDA approved in patients with relapsed or refractory *IDH2*-mutated AML with response rates of approximately 40%.[168] Preliminary results from a phase II study of enasidenib in treatment-naïve patients with higher risk *IDH2*-mutated MDS showed a response rate of 85%.[169] Ivosidenib (AG-120) is an oral targeted inhibitor of mutant IDH1 enzyme. Studies in *IDH1*-mutant AML have shown transfusion independence, durable remissions, and some molecular remissions.[170,171] Very few patients with MDS have been treated with ivosidenib, but further exploration of this genomic targeted is necessary.

FLT3 mutations are rare in patients with MDS but can occur in 15% to 30% of patients who have failed HMA therapy.[172,173] A phase 2 study showed significant activity of the addition of sorafenib, a FLT3 inhibitor, to azacitidine in patients with HMA failure.[174] Several small studies using second- and third-generation FLT3 inhibitors in MDS are underway.[73]

SPECIFIC CLINICAL SITUATIONS

Despite the clinical activity of several agents described earlier, most patients with MDS will eventually succumb to their disease. This emphasizes the need to develop better strategies, both up front and in patients who have failed prior therapies.

Patients with Lower-Risk Disease and Poor Prognosis

It is now demonstrated that the prognosis of patients with lower-risk MDS is very heterogeneous, with a significant subset of patients having poor prognosis.[4] Because most of these patients decease as a consequence of MDS, introducing therapy early in this selected group of patients may help. This has significant implications not only for the role of allo-SCT in MDS but also for the incorporation of disease-modifying strategies. We have studied the role of very low-dose or oral schedules of HMA in this setting.[142,143,175,176] Randomized phase III trials are being conducted to investigate the impact of these interventions on survival.[144]

Failure of Hypomethylating Agents

One of the major problems is the treatment of patients who have failed therapy with HMA. Two different scenarios exist: primary (when the patient progresses while on HMA therapy without experiencing response) and secondary (when the patient has an initial response but progresses later in the course of treatment) HMA failure.[177] The survival of patients with lower-risk disease and hypomethylating failure is less than 17 months.[12] Data from MDACC indicated that the prognosis is very poor for patients with higher risk disease and hypomethylating failure with a median survival of less than 5 months. Currently, no therapy has shown significant activity for patients with HMA failure. In general, this group of patients is refractory to most conventional antileukemia agents available, such as cytarabine. These patients should be treated with investigational new agents, considered for allo-SCT as soon as possible, or both. Agents currently being investigated include guadecitabine, immunotherapy, venetoclax, targeted therapy, and rigosertib, among others.

The next-generation HMA guadecitabine has been shown to have activity in patients who have failed decitabine and azacitidine in a phase II trial,[178] leading to an ongoing phase III ASTRAL-3 study of single-agent guadecitabine. Its use in combination with the immune checkpoint inhibitor atezolizumab was found to be safe in patients with relapsed or refractory MDS,[179] and a phase II study is ongoing. Although investigative efforts into various immune checkpoint inhibitors with and without HMA therapy have not yielded significant survival advantages, single-agent ipilimumab had a 30% response rate in patients who previously failed HMA.[148] Further studies with immunotherapy in patients with relapsed or refractory MDS are warranted.

Furthermore, the use of venetoclax as monotherapy or in combination with azacitidine is undergoing investigation. A phase Ib study showed a response rate of 40% with venetoclax and azacitidine with only modest clinical activity observed with single-agent venetoclax,[180] and multiple phase II studies are underway to further explore this therapeutic option. Regarding targeted therapy options for *IDH2*- or *IDH1*-mutant MDS that were previously discussed, multiple studies evaluating enasidenib, ivosidenib, and ivosidenib with nivolumab in the setting of relapsed or refractory MDS are underway.[169,181,182]

Additional investigational agents of interest include telaglenastat (a glutaminase inhibitor), H3B-8800 (a splicing modulator), and various adjunct therapies to HMA. Recent studies with rigosertib have failed to demonstrate improvement in survival in patients with higher risk disease and primary HMA failure.

Total Therapy Incorporating Allogeneic Stem Cell Transplantation

Traditionally, therapy for MDS is viewed as a dichotomy between candidates for allo-SCT and those who are not candidates, and the need for bridge therapy before allo-SCT remains controversial.[183] Additionally, we also observe very high relapse rates after transplant in specific subsets of patients, such as those with *TP53* mutations or complex cytogenetics.[184] The introduction of powerful new combinations including APR-247, magrolimab, and venetoclax, argues for total therapy that results in minimal residual disease negativity pre-allo-SCT followed by posttransplant maintenance therapy with HMA or targeted approaches, and further investigation is warranted.

MD ANDERSON PRACTICE TIPS

- Analysis of gene mutations using next-generation sequencing assays is important in MDS. A small fraction of patients with MDS carry an NPM1 mutation. These patients can be cured with AML-like therapy followed by allo-SCT.
- Low-risk patients with diploid cytogenetics without thrombocytopenia and anemia, as sole cytopenia, can respond to lenalidomide.
- Around 20% of patients with higher risk MDS failure carry a Flt-3 mutation. Usually, these patients have leukocytosis. These patients can respond to the combination of HMA and Flt-3 inhibitor.
- Patients with mutations on IDH2 and IDH1 (~15% of patients) respond to IDH inhibitors as single agents or in combination with HMAs.
- A subset of patients with higher risk HMA failure have diploid cytogenetics. These patients can respond to combinations of lower doses of nucleoside analogues (clofarabine, cladribine) with low-dose ara-C.
- In patients with higher risk disease, we attempt to proceed with allo-SCT at the time of best response (morphologic, cytogenetic, molecular) in an attempt to minimize relapse posttransplantation.

REFERENCES

1. Naqvi K, Jabbour E, Bueso-Ramos C, et al. Implications of discrepancy in morphologic diagnosis of myelodysplastic syndrome between referral and tertiary care centers. *Blood.* 2011;118(17):4690-4693.
2. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood.* 1997;89(6):2079-2088.
3. Malcovati L, Germing U, Kuendgen A, et al. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. *J Clin Oncol.* 2007;25(23):3503-3510.
4. Garcia-Manero G, Shan J, Faderl S, et al. A prognostic score for patients with lower risk myelodysplastic syndrome. *Leukemia.* 2008;22(3):538-543.
5. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood.* 2012;120(12):2454-2465.
6. Benton CB, Khan M, Sallman D, et al. Prognosis of patients with intermediate risk IPSS-R myelodysplastic syndrome indicates variable outcomes and need for models beyond IPSS-R. *Am J Hematol.* 2018;93(10):1245-1253.
7. List A, Dewald G, Bennett J, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *N Engl J Med.* 2006;355(14):1456-1465.
8. Raza A, Reeves JA, Feldman EJ, et al. Phase 2 study of lenalidomide in transfusion-dependent, low-risk, and intermediate-1 risk myelodysplastic syndromes with karyotypes other than deletion 5q. *Blood.* 2008;111(1):86-93.
9. Koreth J, Pidala J, Perez WS, et al. Role of reduced-intensity conditioning allogeneic hematopoietic stem-cell transplantation in older patients with de novo myelodysplastic syndromes: an international collaborative decision analysis. *J Clin Oncol.* 2013;31(21):2662-2670.
10. Jabbour EJ, Garcia-Manero G, Strati P, et al. Outcome of patients with low-risk and intermediate-1-risk myelodysplastic syndrome after hypomethylating agent failure: a report on behalf of the MDS Clinical Research Consortium. *Cancer.* 2015;121(6):876-882.
11. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. *J Clin Oncol.* 2010;28(4):562-569.
12. Jabbour E, Garcia-Manero G, Batty N, et al. Outcome of patients with myelodysplastic syndrome after failure of decitabine therapy. *Cancer.* 2010;116(16):3830-3834.
13. Ma X, Does M, Raza A, Mayne ST. Myelodysplastic syndromes: incidence and survival in the United States. *Cancer.* 2007;109(8):1536-1542.
14. Rollison DE, Howlader N, Smith MT, et al. Epidemiology of myelodysplastic syndromes and chronic myeloproliferative disorders in the United States, 2001-2004, using data from the NAACCR and SEER programs. *Blood.* 2008;112(1):45-52.
15. Matsuda A, Germing U, Jinnai I, et al. Difference in clinical features between Japanese and German patients with refractory anemia in myelodysplastic syndromes. *Blood.* 2005;106(8):2633-2640.
16. Morel P, Hebbar M, Lai JL, et al. Cytogenetic analysis has strong independent prognostic value in de novo myelodysplastic syndromes and can be incorporated in a new scoring system: a report on 408 cases. *Leukemia.* 1993;7(9):1315-1323.
17. Chen B, Zhao WL, Jin J, et al. Clinical and cytogenetic features of 508 Chinese patients with myelodysplastic syndrome and comparison with those in Western countries. *Leukemia.* 2005;19(5):767-775.
18. Poppe B, Van Limbergen H, Van Roy N, et al. Chromosomal aberrations in Bloom syndrome patients with myeloid malignancies. *Cancer Genet Cytogenet.* 2001;128(1):39-42.
19. Luna-Fineman S, Shannon KM, Atwater SK, et al. Myelodysplastic and myeloproliferative disorders of childhood: a study of 167 patients. *Blood.* 1999;93(2):459-466.
20. Allan JM, Wild CP, Rollinson S, et al. Polymorphism in glutathione S-transferase P1 is associated with susceptibility to chemotherapy-induced leukemia. *Proc Natl Acad Sci U S A.* 2001;98(20):11592-11597.
21. Felix CA, Walker AH, Lange BJ, et al. Association of CYP3A4 genotype with treatment-related leukemia. *Proc Natl Acad Sci U S A.* 1998;95(22):13176-13181.
22. Larson RA, Wang Y, Banerjee M, et al. Prevalence of the inactivating 609C-->T polymorphism in the NAD(P)H:quinone oxidoreductase (NQO1) gene in patients with primary and therapy-related myeloid leukemia. *Blood.* 1999;94(2):803-807.
23. Descatha A, Jenabian A, Conso F, Ameille J. Occupational exposures and haematological malignancies: overview on human recent data. *Cancer Causes Control.* 2005;16(8):939-953.
24. West RR, Stafford DA, Farrow A, Jacobs A. Occupational and environmental exposures and myelodysplasia: a case-control study. *Leuk Res.* 1995;19(2):127-139.
25. Rigolin GM, Cuneo A, Roberti MG, et al. Exposure to myelotoxic agents and myelodysplasia: case-control study and correlation with clinicobiological findings. *Br J Haematol.* 1998;103(1):189-197.
26. Nagata C, Shimizu H, Hirashima K, et al. Hair dye use and occupational exposure to organic solvents as risk factors for myelodysplastic syndrome. *Leuk Res.* 1999;23(1):57-62.
27. Kantarjian HM, Keating MJ, Walters RS, et al. Therapy-related leukemia and myelodysplastic syndrome: clinical, cytogenetic, and prognostic features. *J Clin Oncol.* 1986;4(12):1748-1757.
28. Josting A, Wiedenmann S, Franklin J, et al. Secondary myeloid leukemia and myelodysplastic syndromes in patients treated for Hodgkin's disease: a report from the German Hodgkin's Lymphoma Study Group. *J Clin Oncol.* 2003;21(18):3440-3446.
29. Traweek ST, Slovak ML, Nademanee AP, et al. Clonal karyotypic hematopoietic cell abnormalities occurring after autologous bone marrow transplantation for Hodgkin's disease and non-Hodgkin's lymphoma. *Blood.* 1994;84(3):957-963.
30. Quintas-Cardama A, Daver N, Kim H, et al. A prognostic model of therapy-related myelodysplastic syndrome for predicting survival and transformation to acute myeloid leukemia. *Clin Lymphoma Myeloma Leuk.* 2014;14(5):401-410.
31. Bejar R, Stevenson K, Abdel-Wahab O, et al. Clinical effect of point mutations in myelodysplastic syndromes. *N Engl J Med.* 2011;364(26):2496-2506.
32. Busque L, Patel JP, Figueroa ME, et al. Recurrent somatic TET2 mutations in normal elderly individuals with clonal hematopoiesis. *Nat Genet.* 2012;44(11):1179-1181.
33. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. *N Engl J Med.* 2014;371(26):2488-2498.
34. Genovese G, Kahler AK, Handsaker RE, et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. *N Engl J Med.* 2014;371(26):2477-2487.
35. Takahashi K, Wang F, Kantarjian H, et al. Preleukaemic clonal haemopoiesis and risk of therapy-related myeloid neoplasms: a case-control study. *Lancet Oncol.* 2017;18(1):100-111.
36. Gillis NK, Ball M, Zhang Q, et al. Clonal haemopoiesis and therapy-related myeloid malignancies in elderly patients: a proof-of-concept, case-control study. *Lancet Oncol.* 2017;18(1):112-121.
37. Jaiswal S, Natarajan P, Silver AJ, et al. Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease. *N Engl J Med.* 2017;377(2):111-121.

38. Kwok B, Hall JM, Witte JS, et al. MDS-associated somatic mutations and clonal hematopoiesis are common in idiopathic cytopenias of undetermined significance. *Blood.* 2015;126(21):2355-2361.
39. Malcovati L, Gallì A, Travaglino E, et al. Clinical significance of somatic mutation in unexplained blood cytopenia. *Blood.* 2017;129(25):3371-3378.
40. Hansen JW, Westman MK, Sjö LD, et al. Mutations in idiopathic cytopenia of undetermined significance assist diagnostics and correlate to dysplastic changes. *Am J Hematol.* 2016;91(12):1234-1238.
41. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood.* 2016;127(20):2391-2405.
42. Swerdlow SH, Campo E, Harris NL, Pileri SA. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.* International Agency for Research on Cancer; 2017.
43. Valent P, Horny HP, Bennett JM, et al. Definitions and standards in the diagnosis and treatment of the myelodysplastic syndromes: consensus statements and report from a working conference. *Leuk Res.* 2007;31(6):727-736.
44. Bain BJ. The bone marrow aspirate of healthy subjects. *Br J Haematol.* 1996;94(1):206-209.
45. Haase D, Germing U, Schanz J, et al. New insights into the prognostic impact of the karyotype in MDS and correlation with subtypes: evidence from a core dataset of 2124 patients. *Blood.* 2007;110(13):4385-4395.
46. Schanz J, Tuchler H, Sole F, et al. New comprehensive cytogenetic scoring system for primary myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia after MDS derived from an international database merge. *J Clin Oncol.* 2012;30(8):820-829.
47. Pedersen-Bjergaard J, Pedersen M, Roulston D, Philip P. Different genetic pathways in leukemogenesis for patients presenting with therapy-related myelodysplasia and therapy-related acute myeloid leukemia. *Blood.* 1995;86(9):3542-3552.
48. Rowley JD, Golomb HM, Vardiman JW. Nonrandom chromosome abnormalities in acute leukemia and dysmyelopoietic syndromes in patients with previously treated malignant disease. *Blood.* 1981;58(4):759-767.
49. Shen L, Kantarjian H, Guo Y, et al. DNA methylation predicts survival and response to therapy in patients with myelodysplastic syndromes. *J Clin Oncol.* 2010;28(4):605-613.
50. Sokal G, Michaux JL, Van Den Berghe H, et al. A new hematologic syndrome with a distinct karyotype: the 5 q--chromosome. *Blood.* 1975;46(4):519-533.
51. Pellagatti A, Jadersten M, Forsblom AM, et al. Lenalidomide inhibits the malignant clone and up-regulates the SPARC gene mapping to the commonly deleted region in 5q- syndrome patients. *Proc Natl Acad Sci U S A.* 2007;104(27):11406-11411.
52. Liu TX, Becker MW, Jelinek J, et al. Chromosome 5q deletion and epigenetic suppression of the gene encoding alpha-catenin (CTNNA1) in myeloid cell transformation. *Nat Med.* 2007;13(1):78-83.
53. Ebert BL, Pretz J, Bosco J, et al. Identification of RPS14 as a 5q- syndrome gene by RNA interference screen. *Nature.* 2008;451(7176):335-339.
54. Starczynowski DT, Kuchenbauer F, Argiropoulos B, et al. Identification of miR-145 and miR-146a as mediators of the 5q- syndrome phenotype. *Nat Med.* 2010;16(1):49-58.
55. Lai JL, Preudhomme C, Zandecki M, et al. Myelodysplastic syndromes and acute myeloid leukemia with 17p deletion. An entity characterized by specific dysgranulopoiesis and a high incidence of P53 mutations. *Leukemia.* 1995;9(3):370-381.
56. Gibbons RJ, Pellagatti A, Garrick D, et al. Identification of acquired somatic mutations in the gene encoding chromatin-remodeling factor ATRX in the alpha-thalassemia myelodysplasia syndrome (ATMDS). *Nat Genet.* 2003;34(4):446-449.
57. Maciejewski JP, Mufti GJ. Whole genome scanning as a cytogenetic tool in hematologic malignancies. *Blood.* 2008;112(4):965-974.
58. Heinrichs S, Kulkarni RV, Bueso-Ramos CE, et al. Accurate detection of uniparental disomy and microdeletions by SNP array analysis in myelodysplastic syndromes with normal cytogenetics. *Leukemia.* 2009;23(9):1605-1613.
59. Dunbar AJ, Gondek LP, O'Keefe CL, et al. 250K single nucleotide polymorphism array karyotyping identifies acquired uniparental disomy and homozygous mutations, including novel missense substitutions of c-Cbl, in myeloid malignancies. *Cancer Res.* 2008;68(24):10349-10357.
60. Papaemmanuil E, Gerstung M, Malcovati L, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. *Blood.* 2013;122(22):3616-3627; quiz 3699.
61. Gerstung M, Pellagatti A, Malcovati L, et al. Combining gene mutation with gene expression data improves outcome prediction in myelodysplastic syndromes. *Nat Commun.* 2015;6:5901.
62. Matsui WH, Brodsky RA, Smith BD, et al. Quantitative analysis of bone marrow CD34 cells in aplastic anemia and hypoplastic myelodysplastic syndromes. *Leukemia.* 2006;20(3):458-462.
63. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. *Br J Haematol.* 1982;51(2):189-199.
64. Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. *Blood.* 2002;100(7):2292-2302.
65. Howe RB, Porwit-MacDonald A, Wanat R, et al. The WHO classification of MDS does make a difference. *Blood.* 2004;103(9):3265-3270.
66. Malcovati L, Porta MG, Pascutto C, et al. Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making. *J Clin Oncol.* 2005;23(30):7594-7603.
67. Dayyani F, Conley AP, Strom SS, et al. Cause of death in patients with lower-risk myelodysplastic syndrome. *Cancer.* 2010;116(9):2174-2179.
68. Kantarjian H, O'Brien S, Ravandi F, et al. Proposal for a new risk model in myelodysplastic syndrome that accounts for events not considered in the original International Prognostic Scoring System. *Cancer.* 2008;113(6):1351-1361.
69. Buesche G, Teoman H, Wilczak W, et al. Marrow fibrosis predicts early fatal marrow failure in patients with myelodysplastic syndromes. *Leukemia.* 2008;22(2):313-322.
70. Naqvi K, Garcia-Manero G, Sardesai S, et al. Association of comorbidities with overall survival in myelodysplastic syndrome: development of a prognostic model. *J Clin Oncol.* 2011;29(16):2240-2246.
71. Naqvi K, Sasaki K, Montalban-Bravo G, et al. Clonal hematopoiesis of indeterminate potential-associated mutations and risk of comorbidities in patients with myelodysplastic syndrome. *Cancer.* 2019;125(13):2233-2241.
72. Daver N, Naqvi K, Jabbour E, et al. Impact of comorbidities by ACE-27 in the revised-IPSS for patients with myelodysplastic syndromes. *Am J Hematol.* 2014;89(5):509-516.
73. Garcia-Manero G, Chien K, Montalban-Bravo G. Myelodysplastic syndromes: 2021 update on diagnosis, risk-stratification and management. *Am J Hematol.* 2020;95(11):1399-1420..
74. Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood.* 2006;108(2):419-425.
75. Platzbecker U, Fenaux P, Adès L, et al. Proposals for revised IWG 2018 hematological response criteria in patients with MDS included in clinical trials. *Blood.* 2019;133(10):1020-1030.
76. Brittenham GM, Griffith PM, Nienhuis AW, et al. Efficacy of deferoxamine in preventing complications of iron

overload in patients with thalassemia major. *N Engl J Med.* 1994;331(9):567-573.
77. Neufeld EJ. Oral chelators deferasirox and deferiprone for transfusional iron overload in thalassemia major: new data, new questions. *Blood.* 2006;107(9):3436-3441.
78. Jensen PD, Heickendorff L, Pedersen B, et al. The effect of iron chelation on haemopoiesis in MDS patients with transfusional iron overload. *Br J Haematol.* 1996;94(2):288-299.
79. Angelucci E, Li J, Greenberg P, et al. Iron chelation in transfusion-dependent patients with low- to intermediate-1-risk myelodysplastic syndromes: a randomized trial. *Ann Intern Med.* 2020;172(8):513-522.
80. Armand P, Kim HT, Cutler CS, et al. Prognostic impact of elevated pretransplantation serum ferritin in patients undergoing myeloablative stem cell transplantation. *Blood.* 2007;109(10):4586-4588.
81. Hellstrom-Lindberg E. Efficacy of erythropoietin in the myelodysplastic syndromes: a meta-analysis of 205 patients from 17 studies. *Br J Haematol.* 1995;89(1):67-71.
82. Park S, Grabar S, Kelaidi C, et al. Predictive factors of response and survival in myelodysplastic syndrome treated with erythropoietin and G-CSF: the GFM experience. *Blood.* 2008;111(2):574-582.
83. Hellstrom-Lindberg E, Gulbrandsen N, Lindberg G, et al. A validated decision model for treating the anaemia of myelodysplastic syndromes with erythropoietin + granulocyte colony-stimulating factor: significant effects on quality of life. *Br J Haematol.* 2003;120(6):1037-1046.
84. Jadersten M, Montgomery SM, Dybedal I, et al. Long-term outcome of treatment of anemia in MDS with erythropoietin and G-CSF. *Blood.* 2005;106(3):803-811.
85. Kantarjian H, Fenaux P, Sekeres MA, et al. Safety and efficacy of romiplostim in patients with lower-risk myelodysplastic syndrome and thrombocytopenia. *J Clin Oncol.* 2010;28(3):437-444.
86. Giagounidis A, Mufti GJ, Fenaux P, et al. Results of a randomized, double-blind study of romiplostim versus placebo in patients with low/intermediate-1-risk myelodysplastic syndrome and thrombocytopenia. *Cancer.* 2014;120(12):1838-1846.
87. Kantarjian HM, Fenaux P, Sekeres MA, et al. Long-term follow-up for up to 5 years on the risk of leukaemic progression in thrombocytopenic patients with lower-risk myelodysplastic syndromes treated with romiplostim or placebo in a randomised double-blind trial. *Lancet Haematol.* 2018;5(3):e117-e126.
88. Zhou L, Nguyen AN, Sohal D, et al. Inhibition of the TGF-β receptor I kinase promotes hematopoiesis in MDS. *Blood.* 2008;112(8):3434-3443.
89. Bataller A, Montalban-Bravo G, Soltysiak KA, Garcia-Manero G. The role of TGFβ in hematopoiesis and myeloid disorders. *Leukemia.* 2019;33(5):1076-1089.
90. Platzbecker U, Germing U, Götze KS, et al. Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): a multicentre, open-label phase 2 dose-finding study with long-term extension study. *Lancet Oncol.* 2017;18(10):1338-1347.
91. Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. *N Engl J Med.* 2020;382(2):140-151.
92. List A, Kurtin S, Roe DJ, et al. Efficacy of lenalidomide in myelodysplastic syndromes. *N Engl J Med.* 2005;352(6):549-557.
93. Fenaux P, Giagounidis A, Selleslag D, et al. A randomized phase 3 study of lenalidomide versus placebo in RBC transfusion-dependent patients with low-/intermediate-1-risk myelodysplastic syndromes with del5q. *Blood.* 2011;118(14):3765-3776.
94. List AF, Bennett JM, Sekeres MA, et al. Extended survival and reduced risk of AML progression in erythroid-responsive lenalidomide-treated patients with lower-risk del(5q) MDS. *Leukemia.* 2014;28(5):1033-1040.
95. Santini V, Almeida A, Giagounidis A, et al. Efficacy and safety of lenalidomide (LEN) versus placebo (PBO) in RBC-transfusion dependent (TD) patients (Pts) with IPSS low/intermediate (Int-1)-risk myelodysplastic syndromes (MDS) without Del(5q) and unresponsive or refractory to erythropoiesis-stimulating agents (ESAs): results from a randomized phase 3 study (CC-5013-MDS-005). *Blood.* 2014;124(21):409-409.
96. Silverman LR, Demakos EP, Peterson BL, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study o the cancer and leukemia group B. *J Clin Oncol.* 2002;20(10):2429-2440.
97. Silverman LR, McKenzie DR, Peterson BL, et al. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. *J Clin Oncol.* 2006;24(24):3895-3903.
98. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol.* 2009;10(3):223-232.
99. Kantarjian H, Issa JP, Rosenfeld CS, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. *Cancer.* 2006;106(8):1794-1803.
100. Wijermans P, Lubbert M, Verhoef G, et al. Low-dose 5-aza-2'-deoxycytidine, a DNA hypomethylating agent, for the treatment of high-risk myelodysplastic syndrome: a multicenter phase II study in elderly patients. *J Clin Oncol.* 2000;18(5):956-962.
101. Issa JP, Garcia-Manero G, Giles FJ, et al. Phase 1 study of low-dose prolonged exposure schedules of the hypomethylating agent 5-aza-2'-deoxycytidine (decitabine) in hematopoietic malignancies. *Blood.* 2004;103(5):1635-1640.
102. Kantarjian H, Oki Y, Garcia-Manero G, et al. Results of a randomized study of 3 schedules of low-dose decitabine in higher-risk myelodysplastic syndrome and chronic myelomonocytic leukemia. *Blood.* 2007;109(1):52-57.
103. Cameron EE, Bachman KE, Myohanen S, et al. Synergy of demethylation and histone deacetylase inhibition in the re-expression of genes silenced in cancer. *Nat Genet.* 1999;21(1):103-107.
104. Garcia-Manero G, Kantarjian HM, Sanchez-Gonzalez B, et al. Phase 1/2 study of the combination of 5-aza-2'-deoxycytidine with valproic acid in patients with leukemia. *Blood.* 2006;108(10):3271-3279.
105. Soriano AO, Yang H, Faderl S, et al. Safety and clinical activity of the combination of 5-azacytidine, valproic acid, and all-trans retinoic acid in acute myeloid leukemia and myelodysplastic syndrome. *Blood.* 2007;110(7):2302-2308.
106. Prebet T, Sun Z, Figueroa ME, et al. Prolonged administration of azacitidine with or without entinostat for myelodysplastic syndrome and acute myeloid leukemia with myelodysplasia-related changes: results of the US Leukemia Intergroup trial E1905. *J Clin Oncol.* 2014;32(12):1242-1248.
107. Issa JP, Garcia-Manero G, Huang X, et al. Results of phase 2 randomized study of low-dose decitabine with or without valproic acid in patients with myelodysplastic syndrome and acute myelogenous leukemia. *Cancer.* 2015;121(4):556-561.
108. Garcia-Manero G, Montalban-Bravo G, Berdeja JG, et al. Phase 2, randomized, double-blind study of pracinostat in combination with azacitidine in patients with untreated, higher-risk myelodysplastic syndromes. *Cancer.* 2017;123(6):994-1002.
109. Issa J-PJ, Roboz G, Rizzieri D, et al. Safety and tolerability of guadecitabine (SGI-110) in patients with myelodysplastic syndrome and acute myeloid leukaemia: a multicentre, randomised, dose-escalation phase 1 study. *Lancet Oncol.* 2015;16(9):1099-1110.
110. Garcia-Manero G, Sasaki K, Montalban-Bravo G, et al. Final report of a phase II study of guadecitabine (SGI-110) in patients

(pts) with previously untreated myelodysplastic syndrome (MDS). *Blood.* 2018;132(suppl 1):232.
111. Garcia-Manero G, Stoltz M, Ward M, et al. A pilot pharmacokinetic study of oral azacitidine. *Leukemia.* 2008;22(9):1680-1684.
112. Garcia-Manero G, Gore SD, Cogle CR, et al. Evaluation of oral azacitidine using extended treatment schedules: a phase I study. 2010;116(21):603.
113. Savona MR, Odenike O, Amrein PC, et al. An oral fixed-dose combination of decitabine and cedazuridine in myelodysplastic syndromes: a multicentre, open-label, dose-escalation, phase 1 study. *Lancet Haematol.* 2019;6(4):e194-e203.
114. Garcia-Manero G, Griffiths EA, Roboz GJ, et al. A phase 2 dose-confirmation study of oral ASTX727, a combination of oral decitabine with a cytidine deaminase inhibitor (CDAi) cedazuridine (E7727), in subjects with myelodysplastic syndromes (MDS). *Blood.* 2017;130(suppl 1):4274.
115. Garcia-Manero G, McCloskey J, Griffiths EA, et al. Pharmacokinetic exposure equivalence and preliminary efficacy and safety from a randomized cross over phase 3 study (ASCERTAIN study) of an oral hypomethylating agent ASTX727 (cedazuridine/decitabine) compared to IV decitabine. *Blood.* 2019;134(suppl 1):846.
116. Wattel E, De Botton S, Luc Lai J, et al. Long-term follow-up of de novo myelodysplastic syndromes treated with intensive chemotherapy: incidence of long-term survivors and outcome of partial responders. *Br J Haematol.* 1997;98(4):983-991.
117. Bernasconi C, Alessandrino EP, Bernasconi P, et al. Randomized clinical study comparing aggressive chemotherapy with or without G-CSF support for high-risk myelodysplastic syndromes or secondary acute myeloid leukaemia evolving from MDS. *Br J Haematol.* 1998;102(3):678-683.
118. Kantarjian H, Beran M, Cortes J, et al. Long-term follow-up results of the combination of topotecan and cytarabine and other intensive chemotherapy regimens in myelodysplastic syndrome. *Cancer.* 2006;106(5):1099-1109.
119. Beran M, Shen Y, Kantarjian H, et al. High-dose chemotherapy in high-risk myelodysplastic syndrome: covariate-adjusted comparison of five regimens. *Cancer.* 2001;92(8):1999-2015.
120. Molldrem JJ, Caples M, Mavroudis D, et al. Antithymocyte globulin for patients with myelodysplastic syndrome. *Br J Haematol.* 1997;99(3):699-705.
121. Killick SB, Mufti G, Cavenagh JD, et al. A pilot study of antithymocyte globulin (ATG) in the treatment of patients with "low-risk" myelodysplasia. *Br J Haematol.* 2003;120(4):679-684.
122. Lim ZY, Killick S, Germing U, et al. Low IPSS score and bone marrow hypocellularity in MDS patients predict hematological responses to antithymocyte globulin. *Leukemia.* 2007;21(7):1436-1441.
123. Sauntharajah Y, Nakamura R, Nam JM, et al. HLA-DR15 (DR2) is overrepresented in myelodysplastic syndrome and aplastic anemia and predicts a response to immunosuppression in myelodysplastic syndrome. *Blood.* 2002;100(5):1570-1574.
124. Sauntharajah Y, Nakamura R, Wesley R, et al. A simple method to predict response to immunosuppressive therapy in patients with myelodysplastic syndrome. *Blood.* 2003;102(8):3025-3027.
125. Steensma DP, Dispenzieri A, Moore SB, et al. Antithymocyte globulin has limited efficacy and substantial toxicity in unselected anemic patients with myelodysplastic syndrome. *Blood.* 2003;101(6):2156-2158.
126. Arnold R, de Witte T, van Biezen A, et al. Unrelated bone marrow transplantation in patients with myelodysplastic syndromes and secondary acute myeloid leukemia: an EBMT survey. European Blood and Marrow Transplantation Group. *Bone Marrow Transplant.* 1998;21(12):1213-1216.
127. Runde V, de Witte T, Arnold R, et al. Bone marrow transplantation from HLA-identical siblings as first-line treatment in patients with myelodysplastic syndromes: early transplantation is associated with improved outcome. Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant.* 1998;21(3):255-261.
128. Sierra J, Perez WS, Rozman C, et al. Bone marrow transplantation from HLA-identical siblings as treatment for myelodysplasia. *Blood.* 2002;100(6):1997-2004.
129. Castro-Malaspina H, Harris RE, Gajewski J, et al. Unrelated donor marrow transplantation for myelodysplastic syndromes: outcome analysis in 510 transplants facilitated by the National Marrow Donor Program. *Blood.* 2002;99(6):1943-1951.
130. Deeg HJ, Storer B, Slattery JT, et al. Conditioning with targeted busulfan and cyclophosphamide for hemopoietic stem cell transplantation from related and unrelated donors in patients with myelodysplastic syndrome. *Blood.* 2002;100(4):1201-1207.
131. Campregher PV, Gooley T, Scott BL, et al. Results of donor lymphocyte infusions for relapsed myelodysplastic syndrome after hematopoietic cell transplantation. *Bone Marrow Transplant.* 2007;40(10):965-971.
132. Martino R, Iacobelli S, Brand R, et al. Retrospective comparison of reduced-intensity conditioning and conventional high-dose conditioning for allogeneic hematopoietic stem cell transplantation using HLA-identical sibling donors in myelodysplastic syndromes. *Blood.* 2006;108(3):836-846.
133. Armand P, Kim HT, DeAngelo DJ, et al. Impact of cytogenetics on outcome of de novo and therapy-related AML and MDS after allogeneic transplantation. *Biol Blood Marrow Transplant.* 2007;13(6):655-664.
134. Chang C, Storer BE, Scott BL, et al. Hematopoietic cell transplantation in patients with myelodysplastic syndrome or acute myeloid leukemia arising from myelodysplastic syndrome: similar outcomes in patients with de novo disease and disease following prior therapy or antecedent hematologic disorders. *Blood.* 2007;110(4):1379-1387.
135. Giralt S, Thall PF, Khouri I, et al. Melphalan and purine analog-containing preparative regimens: reduced-intensity conditioning for patients with hematologic malignancies undergoing allogeneic progenitor cell transplantation. *Blood.* 2001;97(3):631-637.
136. Scott BL, Sandmaier BM, Storer B, et al. Myeloablative vs nonmyeloablative allogeneic transplantation for patients with myelodysplastic syndrome or acute myelogenous leukemia with multilineage dysplasia: a retrospective analysis. *Leukemia.* 2006;20(1):128-135.
137. Sorror ML, Sandmaier BM, Storer BE, et al. Comorbidity and disease status based risk stratification of outcomes among patients with acute myeloid leukemia or myelodysplasia receiving allogeneic hematopoietic cell transplantation. *J Clin Oncol.* 2007;25(27):4246-4254.
138. Kroger N, Iacobelli S, Franke GN, et al. Dose-reduced versus standard conditioning followed by allogeneic stem-cell transplantation for patients with myelodysplastic syndrome: a prospective randomized phase III study of the EBMT (RICMAC trial). *J Clin Oncol.* 2017;35(19):2157-2164.
139. Cutler CS, Lee SJ, Greenberg P, et al. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: delayed transplantation for low-risk myelodysplasia is associated with improved outcome. *Blood.* 2004;104(2):579-585.
140. Garcia-Manero G, Gore SD, Cogle C, et al. Phase I study of oral azacitidine in myelodysplastic syndromes, chronic myelomonocytic leukemia, and acute myeloid leukemia. *J Clin Oncol.* 2011;29(18):2521-2527.
141. Laille E, Shi T, Garcia-Manero G, et al. Pharmacokinetics and pharmacodynamics with extended dosing of CC-486 in patients with hematologic malignancies. *PLoS One.* 2015;10(8):e0135520.

142. Garcia-Manero G, Gore SD, Kambhampati S, et al. Safety and efficacy of oral azacitidine (CC-486) administered in extended treatment schedules to patients with lower-risk myelodysplastic syndromes. *Blood.* 2012;120(21):424-424.
143. Garcia-Manero G, Gore SD, Kambhampati S, et al. Efficacy and safety of extended dosing schedules of CC-486 (oral azacitidine) in patients with lower-risk myelodysplastic syndromes. *Leukemia.* 2016;30(4):889-896.
144. Garcia-Manero G, Almeida A, Giagounidis A, et al. Design and rationale of the QUAZAR Lower-Risk MDS (AZA-MDS-003) trial: a randomized phase 3 study of CC-486 (oral azacitidine) plus best supportive care vs placebo plus best supportive care in patients with IPSS lower-risk myelodysplastic syndromes and poor prognosis due to red blood cell transfusion-dependent anemia and thrombocytopenia. *BMC Hematol.* 2016;16:12.
145. Ramsey HE, Oganesian A, Gorska AE, et al. Oral azacitidine and cedazuridine approximate parenteral azacitidine efficacy in murine model. *Target Oncol.* 2020;15(2):231-240.
146. Yang H, Bueso-Ramos C, DiNardo C, et al. Expression of PD-L1, PD-L2, PD-1 and CTLA4 in myelodysplastic syndromes is enhanced by treatment with hypomethylating agents. *Leukemia.* 2014;28(6):1280-1288.
147. Garcia-Manero G, Tallman MS, Martinelli G, et al. Pembrolizumab, a PD-1 inhibitor, in patients with myelodysplastic syndrome (MDS) after failure of hypomethylating agent treatment. *Blood.* 2016;128(22):345-345.
148. Garcia-Manero G, Sasaki K, Montalban-Bravo G, et al. A phase II study of nivolumab or ipilimumab with or without azacitidine for patients with myelodysplastic syndrome (MDS). *Blood.* 2018;132(suppl 1):465.
149. Chien KS, Borthakur GM, Naqvi K, et al. Updated preliminary results from a phase II study combining azacitidine and pembrolizumab in patients with higher-risk myelodysplastic syndrome. *Blood.* 2019;134(suppl 1):4240.
150. Garcia-Manero G, Montalban-Bravo G, Sasaki K, et al. Double immune checkpoint inhibitor blockade with nivolumab and ipilimumab with or without azacitidine in patients with myelodysplastic syndrome (MDS). *Blood.* 2018;132(suppl 1):1831.
151. Zeidan AM, Cavenagh J, Voso MT, et al. Efficacy and safety of azacitidine (AZA) in combination with the anti-PD-L1 durvalumab (durva) for the front-line treatment of older patients (pts) with acute myeloid leukemia (AML) who are unfit for intensive chemotherapy (IC) and pts with higher-risk myelodysplastic syndromes (HR-MDS): results from a large, international, randomized phase 2 Study. *Blood.* 2019;134(suppl 1):829.
152. Gerds AT, Scott BL, Greenberg PL, et al. PD-L1 Blockade with atezolizumab in higher-risk myelodysplastic syndrome: an initial safety and efficacy analysis. *Blood.* 2018;132(suppl 1):466.
153. Asayama T, Tamura H, Ishibashi M, et al. Functional expression of Tim-3 on blasts and clinical impact of its ligand galectin-9 in myelodysplastic syndromes. *Oncotarget.* 2017;8(51):88904-88917.
154. Borate U, Esteve J, Porkka K, et al. Phase Ib study of the anti-TIM-3 antibody MBG453 in combination with decitabine in patients with high-risk myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). *Blood.* 2019;134(suppl 1):570.
155. Pang WW, Pluvinage JV, Price EA, et al. Hematopoietic stem cell and progenitor cell mechanisms in myelodysplastic syndromes. *Proc Natl Acad Sci U S A.* 2013;110(8):3011-3016.
156. Chao MP, Takimoto CH, Feng DD, et al. Therapeutic targeting of the macrophage immune checkpoint CD47 in myeloid malignancies. *Front Oncol.* 2019;9:1380.
157. Sallman DA, Asch AS, Al Malki MM, et al. The first-in-class anti-CD47 antibody magrolimab (5F9) in combination with azacitidine is effective in MDS and AML patients: ongoing phase 1b results. *Blood.* 2019;134(suppl 1):569.
158. Pan R, Hogdal LJ, Benito JM, et al. Selective BCL-2 inhibition by ABT-199 causes on-target cell death in acute myeloid leukemia. *Cancer Discov.* 2014;4(3):362-375.
159. Jilg S, Reidel V, Muller-Thomas C, et al. Blockade of BCL-2 proteins efficiently induces apoptosis in progenitor cells of high-risk myelodysplastic syndromes patients. *Leukemia.* 2016;30(1):112-123.
160. DiNardo CD, Pratz K, Pullarkat V, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. *Blood.* 2019;133(1):7-17.
161. Wei AH, Garcia JS, Borate U, et al. A phase 1b study evaluating the safety and efficacy of venetoclax in combination with azacitidine in treatment-naïve patients with higher-risk myelodysplastic syndrome. *Blood.* 2019;134(suppl 1):568.
162. Rokaeus N, Shen J, Eckhardt I, et al. PRIMA-1(MET)/APR-246 targets mutant forms of p53 family members p63 and p73. *Oncogene.* 2010;29(49):6442-6451.
163. Sallman DA, DeZern AE, Steensma DP, et al. Phase 1b/2 combination study of APR-246 and azacitidine (AZA) in patients with TP53 mutant myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). *Blood.* 2018;132(suppl 1):3091.
164. Sallman DA, DeZern AE, Garcia-Manero G, et al. Phase 2 results of APR-246 and azacitidine (AZA) in patients with TP53 mutant myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia (AML). *Blood.* 2019;134(suppl 1):676.
165. Cluzeau T, Sebert M, Rahmé R, et al. APR-246 Combined with azacitidine (AZA) in TP53 mutated myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML): a phase 2 study by the Groupe Francophone Des Myélodysplasies (GFM). *Blood.* 2019;134(suppl 1):677.
166. Patnaik MM, Hanson CA, Hodnefield JM, et al. Differential prognostic effect of IDH1 versus IDH2 mutations in myelodysplastic syndromes: a Mayo Clinic study of 277 patients. *Leukemia.* 2012;26(1):101-105.
167. Medeiros BC, Fathi AT, DiNardo CD, et al. Isocitrate dehydrogenase mutations in myeloid malignancies. *Leukemia.* 2017;31(2):272-281.
168. Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. *Blood.* 2017;130(6):722-731.
169. Richard-Carpentier G, DeZern AE, Takahashi K, et al. Preliminary results from the phase II study of the IDH2-inhibitor enasidenib in patients with high-risk IDH2-mutated myelodysplastic syndromes (MDS). *Blood.* 2019;134(suppl 1):678.
170. DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. *N Engl J Med.* 2018;378(25):2386-2398.
171. Roboz GJ, DiNardo CD, Stein EM, et al. Ivosidenib induces deep durable remissions in patients with newly diagnosed IDH1-mutant acute myeloid leukemia. *Blood.* 2020;135(7):463-471.
172. Daver N, Strati P, Jabbour E, et al. FLT3 mutations in myelodysplastic syndrome and chronic myelomonocytic leukemia. *Am J Hematol.* 2013;88(1):56-59.
173. Takahashi K, Jabbour E, Wang X, et al. Dynamic acquisition of FLT3 or RAS alterations drive a subset of patients with lower risk MDS to secondary AML. *Leukemia.* 2013;27(10):2081-2083.
174. Ravandi F, Alattar ML, Grunwald MR, et al. Phase 2 study of azacytidine plus sorafenib in patients with acute myeloid leukemia and FLT-3 internal tandem duplication mutation. *Blood.* 2013;121(23):4655-4662.
175. Garcia-Manero G, Jabbour E, Borthakur G, et al. Randomized open-label phase II study of decitabine in patients with low- or intermediate-risk myelodysplastic syndromes. *J Clin Oncol.* 2013;31(20):2548-2553.

176. Jabbour E, Short NJ, Montalban-Bravo G, et al. Randomized phase 2 study of low-dose decitabine vs low-dose azacitidine in lower-risk MDS and MDS/MPN. *Blood.* 2017;130(13):1514-1522.
177. Santini V. How I treat MDS after hypomethylating agent failure. *Blood.* 2019;133(6):521-529.
178. Garcia-Manero G, Roboz G, Walsh K, et al. Guadecitabine (SGI-110) in patients with intermediate or high-risk myelodysplastic syndromes: phase 2 results from a multicentre, open-label, randomised, phase 1/2 trial. *Lancet Haematol.* 2019;6(6):e317-e327.
179. O'Connell CL, Kropf PL, Punwani N, et al. Phase I results of a multicenter clinical trial combining guadecitabine, a DNA methyltransferase inhibitor, with atezolizumab, an immune checkpoint inhibitor, in patients with relapsed or refractory myelodysplastic syndrome or chronic myelomonocytic leukemia. *Blood.* 2018;132(suppl 1):1811.
180. Zeidan AM, Pollyea DA, Garcia JS, et al. A phase 1b study evaluating the safety and efficacy of venetoclax as monotherapy or in combination with azacitidine for the treatment of relapsed/refractory myelodysplastic syndrome. *Blood.* 2019;134(suppl 1):565.
181. Foran JM, DiNardo CD, Watts JM, et al. Ivosidenib (AG-120) in patients with IDH1-mutant relapsed/refractory myelodysplastic syndrome: updated enrollment of a phase 1 dose escalation and expansion study. *Blood.* 2019;134(suppl 1):4254.
182. Chandhok NS, Wei W, Halene S, Prebet T. Ivo-Nivo: a phase II study of the IDH1 inhibitor ivosidenib (AG-120) in combination with the checkpoint blockade inhibitor nivolumab for patients with IDH1 mutated relapsed/refractory AML and high risk MDS. *Blood.* 2019;134(suppl 1):1374.
183. Oran B, Popat U, Andersson B, Champlin R. Allogeneic hematopoietic stem cell transplantation for myelodysplastic syndromes. *Clin Lymphoma Myeloma Leuk.* 2013;13(suppl 2):S282-S288.
184. Lindsley RC, Saber W, Mar BG, et al. Prognostic mutations in myelodysplastic syndrome after stem-cell transplantation. *N Engl J Med.* 2017;376(6):536-547.

This page intentionally left blank

6 Philadelphia Chromosome-Negative Myeloproliferative Neoplasms

Prithviraj Bose
Lucia Masarova
Hesham M. Amin
Srdan Verstovsek

KEY CONCEPTS

- Polycythemia vera (PV) is the most common of the Ph-negative myeloproliferative neoplasms (MPNs). Virtually all cases are driven by activating *JAK2* mutations, and elevation of all three cell counts is typical. Life expectancy is good but shorter than that of an age- and sex-matched population. Thrombosis is the major clinical concern, and prevention of the same is the principal goal of therapy. PV can progress to myelofibrosis (MF) or transform to acute myeloid leukemia (AML). All patients need aspirin unless it is contraindicated. Low-risk patients are typically treated with phlebotomy, whereas high-risk patients need cytoreductive therapy. The target hematocrit level for all patients is to be less than 45%. Leukocytosis is clearly associated with mortality and leukemic transformation; its relationship with thrombotic risk is less certain. Hydroxyurea (HU) and interferon (IFN) are both reasonable frontline options for cytoreductive therapy; ruxolitinib is approved for use after failure of HU.
- Essential thrombocythemia (ET) is the most indolent of the classic Ph-negative MPNs. Careful distinction of ET from prefibrotic primary myelofibrosis (pre-PMF) is necessary. Life expectancy in ET is the same as, or only slightly lower than, that of an age- and sex-matched population. Driver mutations in *JAK2* underlie approximately half the cases, with *CALR* and *MPL* mutations accounting for most of the remainder. ET can progress to MF and rarely transform to AML. Thrombosis and bleeding are the main clinical concerns, and the goal of therapy is to mitigate these risks. Patients are risk stratified for thrombosis by age, *JAK2* mutation status, thrombosis history, and cardiovascular risk factors. The platelet count does not correlate with thrombotic risk. HU or IFN are the cytoreductive agents of choice; anagrelide is commonly used as a second-line therapy. Aspirin is generally recommended, but should be avoided in the presence of acquired von Willebrand disease.
- Myelofibrosis can be primary (PMF) or arise as a complication of PV or ET (post-PV/ET MF). Overt MF is usually characterized by anemia, splenomegaly, a variety of symptoms, leukoerythroblastosis, and markedly reduced survival compared with PV and ET. Pre-PMF is more indolent but carries a worse prognosis than ET. The distribution of driver mutations in PMF is generally similar to that in ET, but mutations in "nondriver" genes are much more common. The risk of leukemic transformation is much higher in MF than in ET or PV. Accurate prognosis for patients with MF is critical for decisions about stem cell transplant (SCT) and depends on several clinical and genomic factors. JAK inhibitors represent the cornerstone of therapy; in some patients, anemia-directed therapy with or without JAK inhibitors may be appropriate.
- Chronic eosinophilic disorders/hypereosinophilic syndromes (CED/HES) are heterogeneous disorders characterized by hypereosinophilia in the blood and possible eosinophilic organ infiltrations. Diagnosis requires exclusion of secondary causes. Evaluation for end-organ damage is always needed. Primary CED/HES include myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRα*, *PDGFRβ*, *FGFR1*, or with *PCM1-JAK2*. Patients might have various nonspecific symptoms or serious organ involvement (gastrointestinal system, heart, skin, lungs). *PDGFRα/β* rearrangements are sensitive to the tyrosine kinase inhibitor imatinib, and these patients have favorable life expectancy. Secondary agents commonly used are steroids, IFN, HU, and, less frequently, chemotherapy. Patients with *FGFR1* rearrangement usually have aggressive disease with rapid progression to acute leukemia. Stem cell transplantation is needed for long-term survival. The novel tyrosine kinase inhibitor pemigatinib is being evaluated in clinical trials as of this writing and showing optimistic results.

- Chronic neutrophilic leukemia (CNL) is a very rare, atypical MPN characterized by overproduction of mature neutrophils and the presence of *CSF3R* mutation in nearly all patients. Patients have various, mostly nonspecific constitutional symptoms. The presence of *CSF3R* mutation with neutrophilia is pathognomonic for diagnosis. CNL usually has an aggressive course, with a median survival of approximately 2 years and the tendency to progress to acute leukemia. There are no standard therapies. Cytoreduction therapy, such as HU; IFN; or cladribine-based chemotherapy are used most often. The JAK inhibitor ruxolitinib is being explored in clinical trials. All patients with CNL be considered for stem cell transplantation.
- Systemic mastocytosis (SM) is a heterogeneous group of diseases characterized by clonal expansion of malignant mast cells and their accumulation in various organs. KIT^{D618V} mutation occurs in more than 90% of the patients. The most important step in prognosis is evaluation for organ damage (C findings), which defines an aggressive subtype of SM. Clinical presentation is mostly driven by release of vasoactive mediations from mast cells (such as itching, flushing, diarrhea, and others). Patients with indolent SM have a normal life expectancy, but those with the aggressive form have significantly decreased survival rates. Higher age, advanced clinical features (eg, anemia, thrombocytopenia, leukocytosis), and the presence of mutations in *SRSF2, ASXL1*, or *RUNX1* predict inferior outcome. In addition to symptom relief, the goals of therapy for aggressive SM are reduction of disease burden and prevention of organ damage. The multikinase inhibitor, midostaurin, represents the only approved targeted therapy. Avapritinib is a promising agent being evaluated in clinical trials as of this writing.

INTRODUCTION

The field of myeloproliferative disorders (MPDs) has evolved considerably since the sentinel observations made by William Dameshek in 1951. He commented in an editorial in the journal *Blood:* "To put together such apparently dissimilar diseases as chronic granulocytic leukemia, polycythemia, myeloid metaplasia and di Guglielmo's syndrome may conceivably be without foundation, but for the moment at least, this may prove useful and even productive. What more can one ask of a theory?"[1]

The central feature among the MPDs, now termed myeloproliferative *neoplasms* (MPNs), is effective clonal myeloproliferation without dysplasia. Other features shared by most MPNs include involvement of a multipotent hematopoietic stem/progenitor cell; marrow hypercellularity; predisposition to thrombosis, hemorrhage, and marrow fibrosis; and phenotypic "driver" mutations in tyrosine kinases (TKs), eg, JAK2 (Janus kinase 2)[2–5] and c-KIT[6]; or other cellular proteins that affect JAK-signal transducer and activator of transcription (STAT) signaling (eg, the thrombopoietin receptor c-MPL[7,8] and the endoplasmic reticulum chaperone CALR.)[9,10] When the concept of MPDs was first proposed, it consisted of five disorders: chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), chronic idiopathic myelofibrosis (CIMF), and erythroleukemia. Over the years, erythroleukemia was reclassified under acute myeloid leukemia (AML), and CIMF was renamed primary myelofibrosis (PMF). Prefibrotic (pre-) and overt PMF are now recognized as distinct entities in the most recent 2016 revision to the World Health Organization (WHO) classification of myeloid neoplasms.[11] Also included under the broad heading of MPNs are atypical MPNs, namely, chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia (CEL), and MPN-unclassifiable (MPN-U) (Table 6–1). The MPNs are, in turn, classified among the five categories of myeloid neoplasms, the others being: (1) AML; (2) myelodysplastic syndromes (MDS); (3) MDS/MPN "overlap" syndromes, which include chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia (JMML), atypical CML (aCML), *BCR-ABL* negative, MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T), and MDS/MPN-unclassifiable (MDS/MPN-U); and (4) mastocytosis, which is no longer grouped together with MPNs. There is also a separate WHO category for myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRα*, *PDGFRβ*, or *FGFR1*, or with *PCM1-JAK2*. Major changes to the WHO diagnostic criteria for PV were introduced in the 2016 revision, and are discussed below. CML, characterized by a balanced, reciprocal translocation between chromosomes 9q34 and 22q11, termed the "Philadelphia chromosome" (Ph), resulting in the BCR-ABL fusion protein that drives the disease, is discussed elsewhere. Here, we discuss the classic, Ph-negative (Ph-) MPNs (PV, ET, and PMF), as well as CEL, myeloid/lymphoid neoplasms with eosinophilia (MLN-Eo), CNL, and systemic mastocytosis, in which important advances have been made both in our understanding of its pathophysiology and its clinical management.

Table 6–1 2016 World Health Organization Classification Scheme for Myeloid Neoplasms

1.	Acute myeloid leukemia
2.	Myelodysplastic syndromes (MDS)
3.	Myeloproliferative neoplasms (MPNs)
	3.1 Chronic myeloid leukemia (CML), *BCR-ABL1*+
	3.2 Polycythemia vera (PV)
	3.3 Essential thrombocythemia (ET)+
32.	3.4 Primary myelofibrosis (PMF)
	• Prefibrotic primary myelofibrosis (pre-PMF)
	• Overt primary myelofibrosis (overt PMF)
	3.5 Chronic neutrophilic leukemia (CNL)
	3.6 Chronic eosinophilic leukemia, not otherwise specified (CEL)
	3.7 MPNs, unclassifiable
4.	MDS/MPN "overlap" syndromes
	4.1 Chronic myelomonocytic leukemia (CMML)
	4.2 Juvenile myelomonocytic leukemia (JMML)
	4.3 Atypical chronic myeloid leukemia (aCML), *BCR-ABL*$^-$
	4.4 MDS/MPN, unclassifiable (MDS/MPN-U)
	4.5 MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
5.	Myeloid/lymphoid neoplasms associated with eosinophilia and abnormalities of *PDGFRα*, *PDGFRβ*, *FGFR1*, or with *PCM1-JAK2*
	5.1 Myeloid neoplasms with *PDGFRα* rearrangement
	5.2 Myeloid neoplasms with *PDGFRβ* rearrangement
	5.3 Myeloid neoplasms with *FGFR1* rearrangement (8p11 syndrome)
	5.4 *Provisional entity*: Myeloid/lymphoid neoplasms with *PCM1-JAK2*

Data from Arber DA, Orazi A, Hasserjian R, et al: The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia, *Blood* 2016 May 19;127(20):2391-2405.

POLYCYTHEMIA VERA

PV is a clonal disorder characterized by the accumulation of phenotypically normal red cells, granulocytes, and platelets. The word *polycythemia* is composed of the Greek words *poly* ("many"), *cyt* ("cells"), and *hemia* ("blood"), indicating the presence of too many blood cells (red, white, and platelets). The term *vera* is from the Latin word meaning true, making a distinction between PV and a host of other conditions that can result in an increase in the number of red blood cells (RBCs). The central feature of the disease is elevated red cell mass (RCM), associated with a predisposition to thrombosis. PV occurs mainly in older adults. The annual incidence of PV is around 1 case per 100,000 population,[12] and the US prevalence has been estimated to be 44 to 57 individuals per 100,000.[13] In a large observational study of 1638 patients with PV, the median age at diagnosis was 62.1 years, and only 4% of the patients were younger than 40 years.[14] The median survival is long, approximately 18.9 years (although inferior to that of the age- and sex-matched general population), as found in an international study of 1545 patients that used a more contemporary (2008 WHO) definition of PV.[15] However, other studies from referral centers with more complete follow-up have reported the median survival of patients with PV to be shorter, around 13.5 years.[16]

The JAK-STAT pathway has been known to play an important role in hematopoiesis, which is mediated in part by erythropoietin (Epo) and thrombopoietin (Tpo) via their cognate receptors. In 2005, four different groups identified an activating mutation in the *JAK2* gene in as many as 97% of patients with PV.[2–5] The JAK proteins are bound to the cytoplasmic domains of type I cytokine receptors (eg, the Epo and Tpo receptors), and the binding of cytokines or growth factors (eg, Epo and Tpo) to their cell-surface receptors induces dimerization and phosphorylation of the JAKs. The activated JAK then phosphorylates the cytoplasmic domains of

the cytokine receptors. STATs bind to these phosphorylated receptor sites and in turn are phosphorylated by the JAKs. These phosphorylated and activated STAT molecules regulate the transcription of the target genes in the nucleus. JAK2 has two domains: JH1 (the active kinase domain) and JH2 (the "pseudokinase" domain that autoinhibits the kinase domain). The most common mutation in PV (and in all 3 classic, Ph- MPNs) is a guanine-to-thymine substitution in exon 14, resulting in a valine-to-phenylalanine substitution at position 617 (*JAK2*V617F). This gain-of-function mutation, which renders JAK2 constitutively active, results in Epo-independent proliferation of erythroid precursors. The pathologic nature of this mutation has been illustrated by many studies, and *JAK2*V617F knockin mouse models resembling human PV have been created, showing that the mutation in hematopoietic stem cells is sufficient to initiate the disease.[17] In contrast to wild-type JAK2, mutated JAK2 allows for the Epo-independent growth of cell lines in culture.[3–5] The *JAK2*V617F mutation is present in approximately 95% to 97% of patients with PV and is not present in secondary polycythemia. Mutations in exon 12 of *JAK2* have been identified in most of the remaining patients with PV who are negative for the *JAK2*V617F mutation.[18] Therefore, with current sensitive testing, virtually all patients with PV should have mutations in either exon 14 or exon 12 of *JAK2*. Very recently, recurrent indels in exon 13 of the *JAK2* gene, also affecting the JH2 domain, have been described as giving rise to a novel MPN with features of both PV and CEL.[19] Loss-of-function mutations in *LNK*, a physiologic-negative regulator of *JAK2*, have been implicated in some cases of *JAK2*–wild type erythropoiesis.[20]

Clinical Features

Presenting symptoms include vasomotor manifestations such as headache, dizziness, trouble concentrating, blurry vision, tinnitus, erythromelalgia, and acral paresthesias, as well as constitutional symptoms such as fatigue, pruritus (especially after a hot shower or bath), bone and muscle aches, fever, weight loss, and drenching night sweats.[21] In an internet-based survey of 405 patients with PV, the most frequently reported constitutional symptoms were fatigue (85%), itching (65%), night sweats (49%), and bone pain (43%).[22] Thrombosis and hemorrhage are the most common serious complications. Palpable splenomegaly is found in about 40% of patients and may cause abdominal discomfort and/or early satiety.[21] The peripheral blood picture is typically one of "pancytosis." Thrombocytosis can be associated with ocular migraine and erythromelalgia (burning pain in the feet or hands associated with warmth and erythema). Some patients are asymptomatic and are diagnosed after abnormal findings on a routine blood examination. The bone marrow (BM) is typically hypercellular with panmyelosis and megakaryocyte pleomorphism.[11] Cytogenetic abnormalities are relatively infrequent but adversely affect survival.[15]

Thrombosis

Thrombosis is the most serious complication of PV (Table 6–2) and is a presenting manifestation in 15% to 20% of patients.[23,24] In a study of 1213 patients with PV, thrombosis (arterial and venous combined) occurred in 41% of patients overall (64% of thrombotic events occurred at presentation or before diagnosis and 36% occurred during follow-up).[23] In a more recent study of 1545 patients diagnosed using 2008 WHO diagnostic criteria, thrombosis occurred in 23.4% of patients at or before diagnosis and in 21% during follow-up.[15,25] Arterial thrombosis was more common overall than venous thrombosis, and was predicted by prior arterial events and hypertension, whereas venous thrombosis was predicted by prior venous events and age of 65 years or older. Ischemic stroke and transient ischemic attacks accounted for the majority of arterial thromboses at diagnosis.[23,25] The overall incidence of thrombotic events has been estimated at 2.62% to 4.4% of patients per year.[23,25,26] The rate of thrombotic events increases with age (1.8/100 patients per year for those <40 years to 5.1/100 patients per year for those >70 years).[23] Older age and a history of thrombosis are the two best established risk factors for thrombosis.[23,25] In the Polycythemia Vera Study Group studies, one third of the individuals who survived the initial thrombotic event had recurrent thrombosis.[27] Budd-Chiari syndrome (BCS) can be a presenting manifestation of PV. PV is the underlying cause in 50% of patients with BCS,[28] and the *JAK2* mutation has been found in 40% to 58% of patients with BCS.[29] Leukocytosis (white blood cells [WBCs] $>11 \times 10^9$/L or $>15 \times 10^9$/L)[30,31] has been found to be a risk factor for thrombosis in some, but not all, studies.[32,33]

Disease Evolution, Causes of Death, and Prognostic Models

Progression to myelofibrosis (MF; termed post-PV MF) and transformation to AML are the two major late complications of PV. Post-PV MF develops in 4.9% to 6% of patients with PV at 10 years and 6% to 14% at 15 years,[34] and is characterized by clinical features similar to PMF (anemia, serum lactate dehydrogenase elevation, leukoerythroblastosis, and progressive splenomegaly). Major diagnostic criteria include a history of PV and grade 2 or higher fibrosis in the BM.[35] Passamonti et al developed the Myelofibrosis Secondary to PV or ET Prognostic Model (MYSEC-PM) for prediction of overall survival (OS) and leukemia-free survival

Table 6–2 Thrombosis and Bleeding in Polycythemia Vera (at Diagnosis and at Follow-Up)

	At Diagnosis				At Follow-Up				
Study	No. of Patients	Asymptomatic	Major Thrombosis (%) (Arterial %, Venous %)	Bleeding (%)	Major Thrombosis (%) (Arterial %, Venous %)	Bleeding (%)	Major Thrombosis Rate	Deaths From Thrombosis (%)	Deaths From Bleeding (%)
PVSG01	431	NR	13.9 (61, 39)	14.9	27.6 (NR, NR)	2.7		31	5
Groupo Italiano Studio Policitemia (GISP)	1,213	NR	34 (67, 33)	NR	19 (63, 37)	NR	3.4%/y	29.7	2.6
ECLAP	1,638	NR	36 (75, 25)	8.1	10.3 (70, 30)	7.1	4.4%/y	26	3.7
Passamonti (2000[a])	163	37	34 (64, 36)	3	18 (80, 20)	NR		19	6
CYTO-PV	365	NR	25 (60, 40)	4.9	7.4 (56, 44)	1.9	2.7%/y	44	NR
IWG-MRT	1,545	NR	23 (68, 32)	4.2	21 (57, 43)	4.2	2.6%/y	21	1.4

[a]Data from Passamonti F, Brusamolino E, Lazzarino M, et al. Efficacy of pipobroman in the treatment of polycythemia vera: long-term results in 163 patients, *Haematologica* 2000 Oct;85(10):1011-1018.



(LFS) based on a cohort of 685 molecularly annotated patients with post-PV or post-ET MF.[36] In this cohort, the median OS for patients with post-PV MF was 8.1 years. PV transforms to blast phase (leukemic transformation) in 2.3% to 14.4% of patients at 10 years and 5.5% to 18.7% of patients at 15 years.[34] In the European Collaboration on Low-Dose Aspirin in Polycythemia Vera (ECLAP) study, AML/MDS developed from the diagnosis of PV in 22 of the 1638 patients (1.3%) after a median of 8.4 years. Older age and exposure to chemotherapy (^{32}P, busulfan, and pipobroman; $P = .002$), but not hydroxyurea (HU) alone, were associated with an increased risk of AML.[14] Very-long-term follow-up (median, 16.3 years) of the French Polycythemia Study Group study comparing HU with pipobroman in 285 patients also found a much higher cumulative incidence of AML/MDS in the pipobroman group.[37] In a prospective study of 338 PV patients, post-PV MF developed in 8 patients and AML developed in 10 after a median of 3.2 years. *JAK2*V617F allele burden was significantly related to the risk of development of MF but not AML.[32] Very recently, a retrospective study of 520 PV patients seen at 10 US centers found that persistent leukocytosis was significantly associated with disease evolution to MF, MDS, or AML.[33]

The most common causes of death in PV are thrombotic complications and leukemic transformation. In a study of 1213 patients, the most frequent fatal complications were thrombosis (30%) and cancer (15% acute leukemia, 15% other cancers).[23] In the ECLAP study (N = 1638), the most common causes of death were cardiovascular complications, leukemic transformation, and solid tumors in 45%, 13%, and 19.5%, respectively.[26] In the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) study (N = 1545), the most common causes of death were cancer (36% acute leukemia, 36% other cancers) and thrombotic complications (32%).[15] A prognostic model developed from this study included age (57–66 or ≥67 years), leukocytosis (≥15 × 10^9/L), and venous thrombosis as independent predictors of worse survival. Independent risk factors for shorter LFS included older age, abnormal karyotype, and leukocyte count ≥15 × 10^9/L. This study confirmed the associations of chlorambucil, pipobroman and ^{32}P, but not HU or busulfan, with leukemic transformation. A nested case control study from Sweden also found high exposures to ^{32}P and alkylating agents, but not HU, to be associated with significantly higher risks of transformation to AML/MDS.[38] More recently, targeted deep sequencing efforts have identified mutations in *ASXL1, SRSF2*, and *IDH2* as prognostically adverse in PV.[39] The mutation-enhanced International Prognostic Scoring System for PV integrates clinical and molecular information into a three-tiered (low, intermediate, and high risk) system to predict OS in PV built on hazard ratio–based points allocation to age more than 67 years, *SRSF2* mutation, leukocyte count ≥15 × 10^9/L, and thrombosis history.[40]

Diagnosis

The 2016 revision to the WHO classification of myeloid neoplasms and acute leukemia[11] saw major changes to the diagnostic criteria for PV (Table 6–3). These include lowering of the hemoglobin (Hgb) and hematocrit (Hct) cutoffs for diagnosis, largely based on the recognition that individuals with so-called "masked" PV (mPV) have worse outcomes,[41,42] at least in part because of less recognition and treatment,[43] and elevation of BM biopsy changes characteristic of PV to a major criterion, although BM biopsy is not required for diagnosis in cases that fulfill the 2008 WHO criteria for Hgb (>18.5 g/dL in men and >16.5 g/dL women) or Hct (>55.5% in men and >49.5% in women), are *JAK2*-mutated, and have a low serum Epo level. Compared with the Polycythemia Vera Study Group criteria, for which RCM measurement was mandatory, the WHO criteria have placed less reliance on direct RCM measurement and established Hgb and Hct cutoffs (Hgb >16.5 g/dL in men and >16 g/dL in women; Hct >49%

Table 6–3 2016 World Health Organization Diagnostic Criteria for Polycythemia Vera

Major criteria
• Hgb >16.5 g/dL in men and Hgb >16 g/dL in women or Hct >49% in men and Hct >48% in women, or other evidence of increased red cell mass
• Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleiomorphic, mature megakaryocytes (differences in size)
• Presence of *JAK2*V617F or *JAK2* exon 12 mutation
Minor criterion
• Subnormal serum erythropoietin level
Diagnosis: All 3 major criteria, or the first 2 major criteria and the minor criterion

Reproduced with permission from Arber DA, Orazi A, Hasserjian R, et al: The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia, *Blood* 2016 May 19;127(20):2391-2405.
Hgb, hemoglobin; Hct, hematocrit.

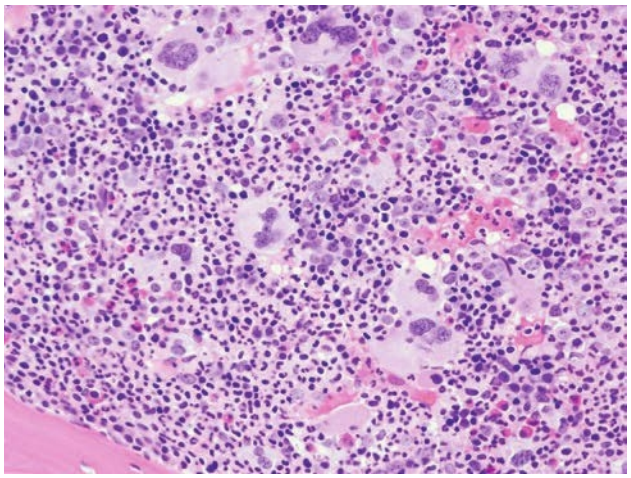


FIGURE 6–1 Bone marrow biopsy from a patient with PV shows remarkable hypercellularity because of myeloid hyperplasia and markedly increased megakaryocytes. Although some of the megakaryocytes morphologically demonstrate slight size variations, most of the megakaryocytes are unremarkable (×200).

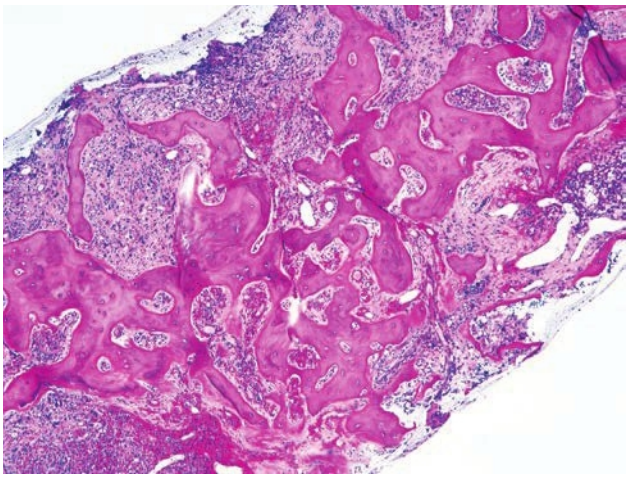


FIGURE 6–2 Extensive bone remodeling and osteosclerosis are occasional features encountered in bone marrow biopsies during the postpolycythemic myelofibrosis phase of PV (×40).

in men and >48% in women in the 2016 criteria) for diagnostic purposes. These cutoffs were found to discriminate best between mPV and *JAK2*-mutated ET.[44] This view is not universally held, however, and some experts still advocate use of direct RCM measurement for PV diagnosis[45]; however, RCM measurement is not available virtually anywhere in the United States, outside of a select few centers where this is still routinely performed. For patients suspected to have PV (based on elevated Hgb/Hct, presence of symptoms, or thrombotic/hemorrhagic complications), initial evaluation in most cases should include a BM biopsy with testing for the *JAK2* mutation (on either peripheral blood or BM)[46] and measurement of serum Epo. Because red cell proliferation is autonomous in PV, serum Epo is generally low but can be within the normal range. Classical morphologic features seen in BM biopsies in PV and post-PV MF are shown in Figs. 6–1 to 6–3.

Treatment

The main goal of therapy in PV is to prevent thrombotic events.[47] In general, this is achieved with the use of phlebotomy and low-dose aspirin in low-risk patients, and with cytoreductive therapy and low-dose aspirin in high-risk patients. The target Hct is <45%, established by the seminal Cytoreductive Therapy in Polycythemia Vera (CYTO-PV) study, discussed below.[48] Regular phlebotomy induces iron deficiency, which has not been shown to be detrimental in the absence of anemia. Patients with PV who become iron deficient as a result of phlebotomy use should not routinely receive iron supplementation. Although

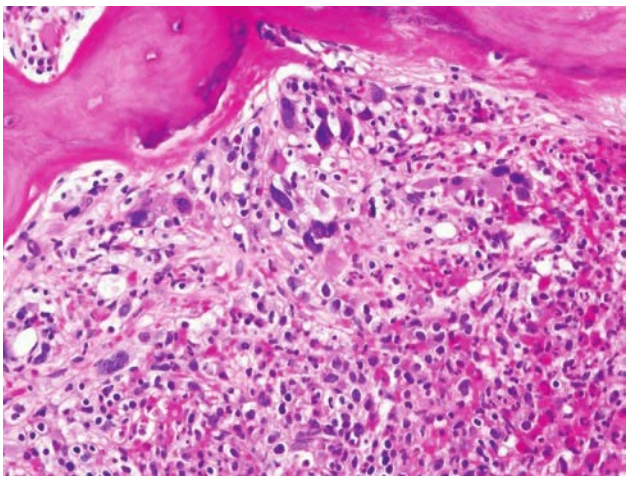


FIGURE 6–3 In contrast to the relatively normal megakaryocytes seen during the early stages of PV, megakaryocytes become markedly atypical during the postpolycythemic myelofibrosis phase. The atypical morphologic features include pronounced size variations, usually because of the presence of numerous small forms. Classically, megakaryocyte nuclei become hyperchromatic during this advanced stage of PV (×200).

the impact of therapeutic lowering of elevated WBC counts in PV is unclear, most clinicians try to control leukocytosis, given its known associations with inferior survival and risk of leukemic transformation, and possibly with thrombotic events.[15,30,31,33,40] Guidelines from the US National Comprehensive Cancer Network (NCCN) recognize the need for cytoreductive therapy in low-risk patients under certain circumstances—eg,

new thrombosis or disease-related major bleeding, frequent and/or persistent need for phlebotomy but with poor tolerance of phlebotomy, splenomegaly, symptomatic thrombocytosis, progressive leukocytosis, and troublesome disease-related symptoms such as pruritus, night sweats, and fatigue.[49] Hepcidin mimetics (NCT04057040) represent a novel class of agents that may have the potential to reduce the need for phlebotomy.[50]

Platelets from patients with PV have been shown to profoundly overproduce thromboxanes, and this can effectively be suppressed by low-dose aspirin.[51] In the ECLAP study, Landolfi et al randomized 518 PV patients of any age without a clear indication for, or contraindication to aspirin, to low-dose aspirin (100 mg daily) or placebo.[52] All patients continued to be treated with phlebotomy, cytoreductive therapy, and standard cardiovascular drugs; the median Hct was 46%. The use of aspirin resulted in a 60% reduction in the risk of nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis, and death from cardiovascular causes (P = .03). The incidence of major bleeding episodes was not significantly increased in the low-dose aspirin group; virtually all excess bleeding in the aspirin group was caused by an 83% increase in the rate of minor bleeding episodes. Largely based on this trial, all patients with PV should receive low-dose aspirin unless contraindicated.

The CYTO-PV randomized controlled trial (RCT) evaluated the benefit of maintaining stringent control of Hct (target <45%) versus less intense treatment (target 45%–50%) in 365 adults with *JAK2*-mutated PV treated with phlebotomy or HU or both.[48] Patients with tight control of Hct (<45%) had a significantly lower rate of major thrombosis and death from cardiovascular causes (2.7% vs 9.8% after a median follow-up of 31 months).

Although not based on prospective RCT data, HU is the most preferred first-line cytoreductive therapy for patients with PV; however, weekly subcutaneously administered pegylated IFN-α-2a, which has been associated with high rates of both hematologic and molecular responses in single-arm, noncomparative phase 2 trials.[53,54] is also a reasonable option. The Myeloproliferative Disorders Research Consortium (MPD-RC) conducted a global phase 3 RCT, the MPD-RC 112 study, comparing HU with pegylated IFN-α-2a in 168 patients with high-risk PV or ET.[55] No meaningful differences were apparent between the two treatment arms at 1 or 2 years of follow-up, with respect to rates of complete response (CR) by IWG-MRT/European LeukemiaNet (ELN) criteria[56] or BM histopathologic or molecular responses. However, the rate of grade 3/4 toxicity was higher in the IFN group. Interferon's lack of leukemogenicity and teratogenicity makes it attractive for treatment of young patients and during pregnancy, but discontinuation rates are high (range, 20%–25%) because of side effects such as depression and flulike symptoms.[57] A newer, longer-acting form of monopegylated IFN-α (PEG-proline-IFN-α-2b, also called ropeginterferon-α-2b), which allows for subcutaneous dosing every two weeks, has recently been approved in Europe for patients with PV without symptomatic splenomegaly. In the pivotal PROUD/CONTINUATION-PV phase 3 RCTs,[58] ropeginterferon-α-2b was compared 1:1 with HU in 257 patients with PV who had never received cytoreductive therapy or had received HU for less than 3 years without achievement of CR or development of resistance/intolerance to HU (Table 6–4).[59] The primary end point of PROUD-PV, a noninferiority study—complete hematologic response (CHR) with normal spleen size at 12 months—was met (21% for ropeginterferon-α-2b and 28% for HU). One hundred seventy-one patients were rolled over into the CONTINUATION-PV trial. Fifty-three percent of the patients in the ropeginterferon-α-2b group versus 38% in the HU/standard therapy group (P = .044) met the coprimary end point of CHR with improved disease burden at 36 months. Tolerability of ropeginterferon-α-2b was good, and both hematologic and molecular responses to it improved over time, showing superiority over HU after two and three years of treatment. The histone deacetylase inhibitor givinostat is also in clinical development for PV.[60]

The oral JAK1/2 inhibitor ruxolitinib was approved by the FDA for HU-resistant/intolerant PV in December 2014, based on the results of a randomized phase 3 clinical trial, RESPONSE, in which 222 patients were randomized 1:1 to receive ruxolitinib (starting dose 10 mg twice daily) or standard therapy.[61] Twenty-one percent of the patients in the ruxolitinib arm achieved the primary end point (Hct control without phlebotomy through week 32 and a ≥35% spleen volume reduction [SVR] from baseline at week 32) versus 1% in the standard therapy arm (P < .001). Sixty percent versus 20% of the patients achieved Hct control, 38% versus 1% saw ≥35% SVR, 24% versus 9% achieved CHR and 49% versus 5% of patients in the standard therapy arm had a ≥50% improvement in the MPN-Symptom Assessment Form total symptom score (TSS), a validated measure of MPN patient-reported symptoms.[62] Herpes zoster reactivation was more common in the ruxolitinib arm. Crossover was permitted after week 32, and all standard therapy patients had crossed over to receiving ruxolitinib by week 80. A similarly designed phase 3 trial, RESPONSE-2, conducted in HU-resistant/intolerant patients without splenomegaly, produced very similar results.[63] The benefits of ruxolitinib were sustained after 5 years of follow-up, and no new safety concerns emerged.[64] Thromboembolic events were numerically

Table 6–4 European Leukemia Net (ELN) Definition of Hydroxyurea Resistance/Intolerance in PV

1. Need for phlebotomy to keep hematocrit <45% after 3 months of at least 2 g/day of hydroxyurea, **OR**
2. Uncontrolled myeloproliferation, ie, platelet count >400 × 10^9/L **AND** white blood cell count >10 × 10^9/L after 3 months of at least 2 g/day of hydroxyurea, **OR**
3. Failure to reduce massive[a] splenomegaly by >50% as measured by palpation, **OR** failure to completely relieve symptoms related to splenomegaly, after 3 months of at least 2 g/day of hydroxyurea, **OR**
4. Absolute neutrophil count <1.0 × 10^9/L **OR** platelet count <100 × 10^9/L or hemoglobin <10 g/dL at the lowest dose of hydroxyurea required to achieve a complete or partial clinico- hematologic response[b], **OR**
5. Presence of leg ulcers or other unacceptable hydroxyurea- related non- hematologic toxicities, such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis, or fever at any dose of hydroxyurea

[a]Organ extending by more than 10 cm from the costal margin.
[b]Complete response was defined as: hematocrit <45% without phlebotomy, platelet count ≤400 × 10^9/L, white blood cell count ≤10 × 10^9/L, and no disease-related symptoms. Partial response was defined as: hematocrit <45% without phlebotomy, or response in three or more of the other criteria.
Reproduced with permission from Barosi G, Birgegard G, Finazzi G, et al: A unified definition of clinical resistance and intolerance to hydroxycarbamide in polycythaemia vera and primary myelofibrosis: results of a European LeukemiaNet (ELN) consensus process, *Br J Haematol* 2010 Mar;148(6):961-963.

lower in the ruxolitinib group than in the standard therapy group. A recent meta-analysis also found a numerically, but not statistically significant ($P = .098$), lower incidence of thrombotic events with ruxolitinib in patients with PV.[65]

Pegylated IFN-α-2a is also a therapeutic option after failure of HU in PV. In the single-arm, phase 2 MPD-RC 111 trial, the overall response rate (ORR) to pegylated IFN-α-2a at 12 months in 50 HU-resistant/intolerant patients with PV was 60% (22% CR + 38% partial response [PR]).[66] Retrospective studies have demonstrated that resistance/intolerance to HU (Table 6–4) has prognostic implications. In a Spanish registry study, resistance and intolerance to HU were found in 11% and 13% of patients with PV, and resistance to HU was associated with a higher risk of death and leukemic transformation.[67] In another such study, development of cytopenias at the lowest dose of HU needed to achieve CR or PR was an independent risk factor for transformation to acute leukemia, whereas the risk of progression to MF was higher in patients in whom cytopenia or massive splenomegaly developed.[68] Based on induction of murine double minute 2 (MDM2) by *JAK2*V617F,[69] MDM2 inhibition has been pursued as a therapeutic strategy for HU-resistant/intolerant PV. However, although clearly active,[70] the toxicity of these agents (eg, idasanutlin) has thwarted their clinical development for PV.

Treatment Conclusions

All patients with PV should receive low-dose aspirin unless contraindicated. Patients who are at high risk for thrombosis (age >60 years or a history of thrombosis) should receive cytoreductive therapy. The targeted Hct is <45% in all patients. We believe that when cytoreductive therapy is used, the goal should be to eliminate phlebotomy, although studies have arrived at opposite conclusions on whether persistent need for phlebotomies while receiving HU is associated with adverse outcomes.[71,72] Although HU is widely used as first-line cytoreductive therapy, data support the use of pegylated IFN-α-2a/ropeginterferon-α-2b up front as well. Both ruxolitinib and pegylated IFN-α-2a are reasonable options in the setting of HU resistance/intolerance.

ESSENTIAL THROMBOCYTHEMIA

Essential thrombocythemia (ET) is characterized by persistent thrombocytosis with a predisposition to thrombosis and bleeding. ET is not a cytogenetically or a morphologically defined disease entity and remains a diagnosis of exclusion, although the discovery of driver mutations in exon 9 of *CALR,* detected in the vast majority of *JAK2/MPL*-wild-type cases,[9,10] has substantially simplified the diagnosis. Generally, it is a disease of older adults; the median age at diagnosis is 55 to 60 years. ET is more common in women than in men. Survival in ET has been reported to be no different from to slightly worse (median, 19.8 years) than that of the age- and sex-matched general population in different studies.[16,73] The annual incidence of ET has been reported to be 0.21 to 2.27 per 100,000 population.[12] The US prevalence of ET has been estimated to be in the range of 38 to 57 individuals per 100,000.[13]

Reactive causes of thrombocytosis should be excluded. Most often, the underlying cause is apparent (postsplenectomy, acute infection, blood loss, iron deficiency). Other MPNs, such as PV or CML, can also present with thrombocytosis, as can MDS with isolated deletion 5q and the overlap syndrome, MDS/MPN-RS-T, and should be ruled out. The magnitude of elevation in the platelet count does not help distinguish between reactive and clonal causes of thrombocytosis. Reactive thrombocytosis, irrespective of the degree of

elevation of platelet counts, does not increase the risk of thromboembolic or bleeding complications. Such complications, if seen, are the consequences of underlying disease conditions (malignancy, iron deficiency from gastrointestinal bleeding) rather than of elevated platelets.

Pathophysiology

Approximately 50% of patients with ET harbor the *JAK2*V617F mutation, and 3% to 5% have a mutation in the thrombopoietin receptor (MPL) (W515L/K; tryptophan to leucine or lysine substitution at residue 515),[74] both of which lead to dysregulated JAK-STAT signaling. Most patients with ET are heterozygous for *JAK2*V617F, with allele burdens less than 50%, suggesting that lower *JAK2*V617F gene dosage may lead to the development of ET versus PV, in which the allele burden is generally higher.[75] The order of mutation acquisition has also been shown to influence disease phenotype, with *JAK2*-first mutation acquisition more likely to lead to a PV phenotype with a greater predisposition to thrombosis, as opposed to *TET2*-first mutation acquisition, which is associated with an ET phenotype.[76]

Recently, mutations in the gene encoding the endoplasmic reticulum chaperone protein calreticulin (CALR) have been found in nearly 70% of patients with ET negative for *JAK2* or *MPL* mutations (20%–30% of all patients with ET).[9,10] The *CALR* mutation may define a distinct subset of ET. In a series of 717 patients with ET, those with *CALR* mutations were younger and predominantly male and had a lower incidence of thrombosis, lower hemoglobin levels, lower leukocyte counts, and higher platelet counts than those with the *JAK2*V617F mutation.[77] Other studies have confirmed these observations and also noted that "triple-negative" ET patients (ie, those without detectable *JAK2*, *CALR*, or *MPL* mutations, ~10%–15%) share some of the same characteristics (ie, younger age, lower Hgb levels, lower leukocyte counts, and lower risk of thrombosis than *JAK2*-mutated patients).[78] Survival has been reported to be the longest for these "triple-negative" patients, and shortest for *MPL*-mutated patients.[78] There are data suggesting that the favorable impact of *CALR* mutations on thrombosis risk in ET might be confined to younger patients.[79]

There are two major types of *CALR* mutations: type 1 (52 base-pair deletions) and type 2 (5 base-pair insertions). Both result in an altered C-terminal of the mutant protein with loss of negative charge that impairs calcium binding, and in loss of the endoplasmic reticulum retention motif, culminating in JAK-STAT pathway activation. Several studies have shown that mutant CALR requires its altered C-terminal and needs to physically bind to the extracellular domain of MPL to exert its oncogenic effects.[80–85] Another function of mutant CALR shown to be essential for oncogenic transformation, termed its *rogue chaperone activity*, is its ability to stabilize and transport MPL and mutants thereof to the cell surface in states that would not normally pass quality control.[86] Types 1 and 2 *CALR* mutations occur at approximately equal frequencies in ET and do not appear to impact prognosis,[87] although one study has shown that type 1 *CALR* mutations may confer a higher risk of progression to post-ET MF.[88] *MPL* mutations have been associated with shorter myelofibrosis-free survival in ET.[87] Male sex may be associated exclusively with type 1 *CALR* mutations, and younger age with type 2; this study also found platelet counts to be significantly higher in type 2 than in type 1 *CALR*-mutated patients.[89]

Clinical Features

With the increasing use of automated blood counters and routine blood count screenings, more patients with ET are being diagnosed while they are asymptomatic. In an international, internet-based survey of 304 patients with ET, 72% reported fatigue, and about 40% of ET patients reported itching, night sweats, and bone pain.[22] Vasomotor manifestations such as dizziness, lightheadedness, acral paresthesia, livedo reticularis, and erythromelalgia were noted in 34% of patients in one study of 147 patients with ET.[90] Mild splenomegaly (<5 cm) was noted in up to 40% of patients, leukocytosis in 30% to 40%, and mild anemia in 10% to 20%. Thromboembolic and bleeding complications are the major cause of morbidity and mortality in ET. A series of 322 patients with ET from one institution reported a 26% incidence of major thrombosis and 11% incidence of major bleeding at diagnosis.[91] Hemorrhagic complications increase with extreme thrombocytosis (platelet count >1.5 million/μL) and with the use of antiplatelet therapy such as aspirin.

The most serious late complications of ET include transformation to AML and progression to post-ET MF. In a single-institution study of 605 patients with ET who were followed for a median of 7 years, the incidence of AML transformation was 3.3%.[92] Risk factors for transformation included anemia and platelet count $>1000 \times 10^9$/L. In a more contemporary large series from seven centers in Europe, the diagnosis of ET (per 2008 WHO criteria) was confirmed in 891 patients and revised to early/prefibrotic MF in 180 patients.[93] Among the patients with ET, the 10- and 15-year cumulative incidences of transformation to AML and progression to post-ET MF were 0.7% and 2.1%, and 0.8% and 9.3%, respectively. In another study of 292 patients with ET with a median follow-up of 17.3

Table 6–5 2016 WHO Criteria for Diagnosis of Essential Thrombocythemia

Major Criteria
1. Platelet count ≥450 × 10^9/L
2. Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei; no significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers
3. Not meeting WHO criteria for PV, PMF, *BCR-ABL1*$^+$ CML, MDS, or other myeloid neoplasm
4. Presence of *JAK2*, *CALR*, or *MPL* mutation
Minor Criterion
Presence of a clonal marker or absence of evidence for reactive thrombocytosis
Diagnosis of ET requires meeting all four major criteria or the first 3 major criteria and the minor criterion.

Reproduced with permission from Arber DA, Orazi A, Hasserjian R, et al: The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia, *Blood* 2016 May 19;127(20):2391-2405.

years, the cumulative incidence of AML was 3.8% and of progression to MF was 10.3%.[16] Overall, the risk of progression to post-ET MF has been reported in the literature to be 0.8% to 4.9% at 10 years and 4% to 11% at 15 years; the corresponding rates for post-ET AML are 0.7% to 3% at 10 years and 2.1% to 5.3% at 15 years.[34]

Diagnosis

The diagnostic criteria for ET did not change appreciably from the 2008 to the 2016 WHO classification, other than the addition of *CALR* mutations to the list of known driver mutations (Table 6–5).[11] An important change in the 2008 WHO classification was lowering the platelet count threshold for ET diagnosis from >600 × 10^9/L to >450 × 10^9/L.[94] BM biopsy is mandatory for diagnosis to rule out "masked" PV, PMF (especially pre-PMF), and MDS/MPN. A BM biopsy typically shows large but mature-appearing megakaryocytes with deeply lobulated or hyperlobulated nuclei (Fig. 6–4). The peripheral blood smear shows markedly increased platelets (Fig. 6–5). Reticulin staining should be done to rule out any underlying fibrosis; very rarely, a grade 1 increase in reticulin fibers is encountered.[11] The presence of megakaryocytic atypia in the BM biopsy suggests "prefibrotic" MF, which implies a higher risk of progression to overt MF and transformation to AML, and poorer OS.[93] Also, pre-PMF often exhibits decreased erythropoiesis and granulocytic proliferation, and some reticulin fibrosis (but not >grade 1).[11] CML should be ruled out by testing for the *BCR-ABL1* fusion gene. Beyond testing for *JAK2*, *MPL*, and *CALR* mutations, a myeloid mutation (targeted next generation sequencing) panel is recommended to establish the clonal nature of the disease, ruling out reactive thrombocytosis in "triple-negative" cases.

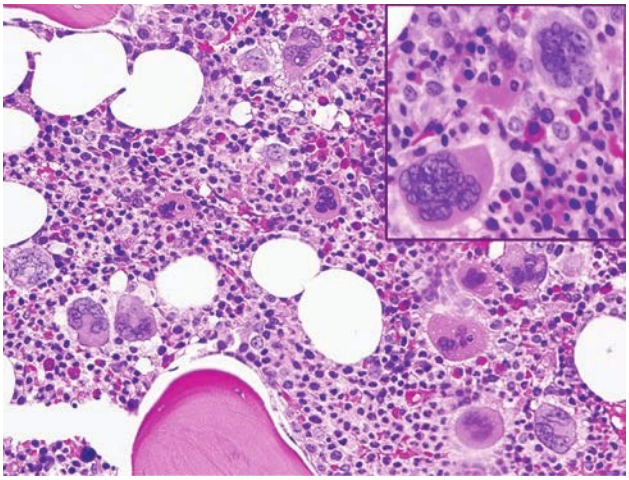


FIGURE 6–4 Essential thrombocythemia is characterized by increased bone marrow cellularity, myeloid hyperplasia, and notably increased megakaryocytes (×200). The megakaryocytes in ET tend to display larger than normal size, and they also contain large hyperlobulated nuclei (inset, ×400).

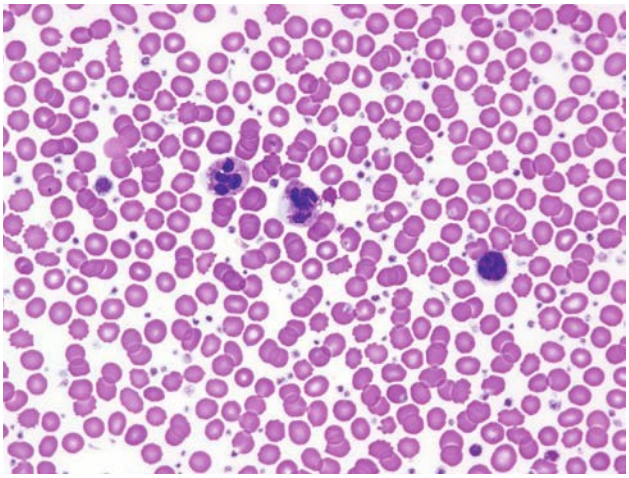


FIGURE 6–5 Peripheral blood smear from a patient with ET shows markedly increased platelets with scattered large forms (×400).

Thrombotic Risk Stratification and Survival Prediction in ET

As in PV, thrombosis and hemorrhage are the main complications of ET. Older age and a history of prior thrombosis have been shown to predict for future thrombotic events in most studies, whereas cardiovascular risk factors have been predictive in only some. As discussed previously, *CALR*-mutated and triple-negative patients with ET appear to be at lower risk of thrombosis compared with *JAK2*/*MPL*-mutated patients.[77,78] Platelet count does not correlate with risk of thrombosis in ET (Table 6–6). Some studies have found an inverse relationship between the platelet count and the thrombotic risk. This is thought to be the result of acquired von Willebrand disease (AVWD) with elevated platelet counts (eg, >1.5 million/μL), predisposing the patient to more bleeding and relative protection from thrombosis.

A study from the IWG-MRT on a cohort of 891 patients from seven centers in Europe diagnosed with WHO 2008–defined ET reported a 6% cumulative

Table 6–6 Risk Factors for Thrombosis in Patients with ET

		Risk Factors Studied					
Study	No. of Patients	Age >60 Years, Odds Ratio/ Hazard Ratio/ Significance Level	History of Thrombosis	Risk Factors for Cardiovascular Events (Smoking, Diabetes, Hypertension, Hyperlipidemia)	Platelet Count >1000 × 10^9/L	Leukocytosis	JAK-2 Status
Colombi (1991[a])	103	NS	$P < .001$	—	NS	—	—
Cortelazzo (1990[b])	100	10.3	13	NS	NS	—	—
Besses (1999[c])	148	3.3	3.0	4.7	NS	—	—
Bazzan (1999[d])	187	NS	—	NS	NS	—	—
Jantunen (2001[e])	132	NS	—	$P = .01$	NS	—	—
Chim (2005[f])	231	$P = .01$	NS	—	NS	—	—
Wolanskyj[91]	322	1.51	2.3 (arterial only)	NS	–	1.74 (WBC > 15,000)	NS
Carobbio (2007)[98]	439	2.3 (age and previous thrombosis evaluated together)	2.3	—	NS	2.3 (WBC >8700)	NS
Alvarez-**Larrán** (2007[g])	126 (<40 y)	NA	NS	Smoking	NS	—	NS
Radaelli (2007[h])	306	NS	7.6	$P < .05$	NS	—	—
Tefferi (2007[i])	605	NS	$P < .001$	NS	—	WBC (≥15,000) $P < .01$ for thrombosis at baseline (NS for thrombosis on follow-up)	NS

(*Continued*)

Table 6–6 Risk Factors for Thrombosis in Patients with ET (*Cont.*)

		Risk Factors Studied					
Study	No. of Patients	Age >60 Years, Odds Ratio/ Hazard Ratio/ Significance Level	History of Thrombosis	Risk Factors for Cardiovascular Events (Smoking, Diabetes, Hypertension, Hyperlipidemia)	Platelet Count >1000 × 10^9/L	Leukocytosis	JAK-2 Status
Passamonti (2008[j])	605	$P < .001$	$P = .03$	NS	NS	NS	—
Carobbio[97]	1063	1.7 (age and previous thrombosis evaluated together)	1.7	—	Patients with WBC <11,000 and platelet <1000: most likely to have JAK-2 mutation and highest risk of thrombosis		
Carobbio (ref. 94)	891	1.5	1.93	1.56	0.50	1.14	2.04

[a]Colombi M, et al. *Cancer*. 1991;67(11):2926-2930.
[b]Cortelazzo S, et al. *J Clin Oncol*. 1990;8(3):556-562.
[c]Besses C, et al. *Leukemia*. 1999;13(2):150-154.
[d]Bazzan M, et al. *Ann Hematol*. 1999;78(12):539-543.
[e]Jantunen R, et al. *Ann Hematol*. 2001;80(2):74-78.
[f]Chim CS, et al. *Arch Intern Med*. 2005;165(22):2651-2658.
[g]Alvarez-Larrán A, et al. *Leukemia*. 2007;21(6):1218-1223.
[h]Radaelli F, et al. *Hematol Oncol*. 2007;25(3):115-120.
[i]Tefferi A, et al. *Blood*. 2007;109(9):4105.
[j]Passamonti F, et al. *Haematologica*. 2008;93(11):1645-1651.
NS, nonsignificant; —, not studied.

incidence of major bleeding at a rate of 0.79 patients/year.[95] The cumulative incidence of thrombosis (fatal and nonfatal events) was 25% at a rate of 1.9% of patients/year.[93,96] The rate of nonfatal arterial events (1.2% of patients/year) was higher than that of venous events (0.6% patient/year).[96] Factors independently associated with bleeding included previous hemorrhage and aspirin therapy.[95] Factors independently associated with major thrombosis included age older than 60 years, cardiovascular risk factors (diabetes, hypertension, or smoking), previous thrombosis, and presence of the *JAK2V617F* mutation.[96] Leukocytosis (>11 × 10^9/L) was an additional independent risk factor for arterial thrombosis (though not when the analysis was restricted to *JAK2*-mutated cases), whereas male gender increased the risk of venous thrombosis. Extreme thrombocytosis (platelet count >1000 × 10^9/L) was independently associated with a reduced risk of arterial thrombosis.[96] This is thought to be caused by AVWD with elevated platelet counts, predisposing to more bleeding and relative protection from thrombosis, consistent with previous reports showing an inverse relationship between platelet count and thrombotic risk.[97] The link between leukocytosis, both at diagnosis and during follow-up, and thrombosis in ET has been confirmed in other studies.[98,99]

Using these risk factors, a prognostic model was proposed to predict risk of thrombosis in patients with ET (International Prognostic Score for Thrombosis in Essential Thrombocythemia [IPSET-thrombosis]).[100] The model assigned relative weights to the four risk factors, and the patients could be stratified into three risk categories, with an annual risk of thrombosis ranging from 1.03% of patients/year for the low-risk group to 3.56% of patients/year for the high-risk group (Table 6–7). *CALR* mutational status has been shown not to modify the IPSET-thrombosis score.[101]

In a more recent "practice-relevant" revision of the IPSET-thrombosis model, patients with ET were subdivided into four groups—very low, low, intermediate, and high—based on thrombotic risk, using age, thrombosis history, and *JAK2* mutation status as the

Table 6–7 International Prognostic Score for Essential Thrombocythemia (IPSET) and IPSET-Thrombosis[100,103]

Risk Factor	IPSET	IPSET-Thrombosis (IPSET-t)
Age >60 years[a]	2	1
Previous thrombosis	1	2
WBC count ≥11 × 10^9/L[†]	1	
Cardiovascular risk factors		1
*JAK2*V617F positive		2
Prognostic Score (Median Survival or Rate of Thrombosis)		
Low	0 points (not reached)	<2 points (1.03% patients/y)
Intermediate	1–2 points (24.5 y)	2 points (2.35% patients/y)
High	3–4 points (13.8 y)	>2 points (3.56% patients/y)

[a]≥60 years for IPSET, >60 years for IPSET-t.
[†]≥11 × 10^9/L for IPSET, >11 × 10^9/L for IPSET-t.

Table 6–8 The revised IPSET-t and Treatment Recommendations for Essential Thrombocythemia[102]

Risk Category	Description	Recommended Intervention
Very low	Age ≤60 years, *JAK2* WT, no h/o thrombosis	Observation, low dose aspirin[a] if CV risk factors
Low	Age ≤60 years, *JAK2* V617F+, no h/o thrombosis	Low-dose aspirin[a]; consider twice daily if CV risk factors
Intermediate	Age >60 years, *JAK2* WT, no h/o thrombosis	Cytoreductive therapy and low dose aspirin[a], possibly twice daily aspirin[a] without cytoreductive therapy
High	Age >60 years AND *JAK2* V617F+, or h/o thrombosis	Cytoreductive therapy and low-dose aspirin[a]

[a]Use aspirin with caution in patients with extreme thrombocytosis; always rule out acquired von Willebrand disease first. WT, wild type; CV, cardiovascular.

variables (Table 6–8).[102] Consensus guidelines from the NCCN recommend the use of this model to risk stratify patients with ET for disease management decisions.[49]

Data from the same cohort of patients were used to develop a prognostic score to predict OS of ET at diagnosis (IPSET).[103] The final prognostic score included age 60 years or older (2 points), leukocyte count 11 × 10^9/L or greater (1 point), and prior thrombosis (1 point) as independent risk factors for survival (see Table 6–7). The model stratified patients into three risk categories, with median survival not reached in the low-risk group to 24.5 years in the intermediate-risk group to 13.8 years for the high-risk group. Although the *JAK2* V617F mutation was associated with increased thrombosis risk,[93] it was not predictive of survival, which was consistent with findings from other studies.[16] In another study, *JAK2* V617F was identified as an independent predictor of pregnancy complications[104]; however, subsequent studies failed to confirm this observation.[105,106] Although cytogenetic abnormalities are uncommon in ET (<10% at diagnosis) and have not been correlated with survival or transformation risk,[107] targeted deep sequencing has identified some adverse mutations/sequence variants, *viz*. *SH2B3*, *SF3B1*, *U2AF1*, *TP53*, *IDH2*, and *EZH2*.[39] The recently published MIPSS-ET model integrates clinical and molecular information into a three-tiered (low, intermediate, and high) prognostic model for ET that allocates points, based on hazard ratios, to age older than 60 years, male sex, *SF3B1*/*SRSF2* mutations, and leukocytosis >11 × 10^9/L.[40]

Treatment

The goal of therapy in ET is to prevent the major cause of morbidity and mortality: thromboembolic events. Because the majority of patients have a normal life expectancy, aggressive treatments that could cause potentially dangerous side effects should be avoided. Cardiovascular risk factors should be aggressively managed in all patients. Smoking was an important risk factor for thrombosis in many studies; all patients should be counseled regarding smoking cessation. The two major classes of therapies used for the treatment of ET are antiplatelet drugs and cytoreductive drugs (Table 6–8).

Antiplatelet Therapy

Antiplatelet therapy with aspirin is useful in treating the microvascular symptoms of ET, such as erythromelalgia. The role of antiplatelet therapy in reducing thrombotic episodes in ET is less clear because no placebo-controlled, randomized trial is available. In a retrospective study, Van Genderen et al showed decreased thrombosis risk and improvements in microvascular symptoms with aspirin monotherapy.[108] Extrapolating from the ECLAP study results in PV,[52] the general consensus is to use low-dose aspirin (75–100 mg daily) in patients with ET unless contraindicated by bleeding history. Caution should be exercised in using aspirin in patients with a very high platelet count (>1500 × 10^9/L) because of the increased risk of bleeding from AVWD.[109] In the UK Medical Research Council Primary Thrombocythemia 1 (MRC PT-1) trial comparing HU and anagrelide in ET, all patients received antiplatelet therapy unless it was contraindicated.[110] An increased risk of bleeding was noted in the anagrelide arm compared with the HU arm, possibly because of the synergistic antiplatelet effect of aspirin with anagrelide. It has been suggested that low-dose aspirin given twice a day may be effective in patients whose symptoms are not controlled with once-daily dosing.[111] Several studies have shown that once-daily aspirin incompletely suppresses platelet thromboxane biosynthesis, possibly a result of accelerated renewal of platelet cyclooxygenase in ET,[112] and that twice-daily dosing more effectively inhibits platelet aggregation.[113–115]

Cytoreductive Therapy

Hydroxyurea, anagrelide, and IFNs are the main cytoreductive agents currently used in patients with ET. Hydroxyurea is a nonspecific, cytotoxic, and myelosuppressive drug that works through inhibition of ribonucleotide reductase. Anagrelide has a selective effect on the megakaryocyte lineage. Two randomized studies in ET have established HU as the frontline cytoreductive therapy of choice. In an Italian study by Cortelazzo et al, 114 patients with high-risk ET (age >60 years, history of thrombosis, or both) were randomized to receive either placebo or HU, with a goal platelet count of <600 × 10^9/L.[116] After a median follow-up of 27 months, 3.6% of patients in the HU group had thrombotic episodes compared with 24% in the placebo group (P = .003). This study established the antithrombotic effect of HU in ET. Harrison et al reported the results of the UK MRC PT-1 study of 809 high-risk patients with ET who were randomly grouped to receive HU plus aspirin or anagrelide plus aspirin.[110] The goal platelet count was <400 × 10^9/L. After a median follow-up of 39 months, anagrelide therapy was associated with higher rates of arterial thrombosis (P = .004) and serious hemorrhage (P = .008), but a lower rate of venous thromboembolism (P = .006) compared with the HU arm. Serious hemorrhage with anagrelide was likely the result of a synergistic antiplatelet effect of aspirin. The risk of developing post-ET MF was significantly higher in the anagrelide arm (5-year risk, 7% vs 2% in the HU arm, P = .01), and significantly more patients in the anagrelide arm withdrew from the study because of side effects (22% vs 11%, P < .001). The risk of developing MDS/AML was similar in the two arms. Largely based on this trial, HU has been widely adopted as the first-line treatment of choice in high-risk ET. However, the more recently reported ANAHYDRET study showed noninferiority of a controlled release preparation of anagrelide to HU in 259 patients with WHO-defined ET; aspirin was not allowed in either arm of this trial.[117] The utility of adding HU to aspirin in young patients (age 40–59 years) with ET without high-risk features (thrombosis, embolism, hemorrhage, hypertension, or diabetes requiring therapy) or extreme thrombocytosis (platelet count ≥1500 × 10^9/L) was assessed in a randomized trial (N = 382).[118] After a median follow-up of 73 months, there was no significant difference between the arms in the likelihood of patients reaching the primary end point (arterial or venous thrombosis, serious hemorrhage, or death from vascular causes, P = 1.0). There were also no differences in OS, the composite end point of disease evolution to MF, AML, or MDS; adverse event (AE) profile; or patient-reported quality of life (QOL). A recent pooled analysis of 1500 cases of MPN-associated thrombosis showed that although HU reduced the rate of recurrent arterial thrombotic events, this could not be conclusively shown with respect to recurrent venous thrombotic events, in particular, recurrent splanchnic vein thrombosis.[119]

The experience with IFN in ET generally mirrors that in PV. Response rates, both hematologic and molecular, are high,[54] but patients with nondriver mutations outside the JAK-STAT pathway have a lower likelihood of achieving complete molecular response.[120] Although pegylated IFN-α-2a is better tolerated and allows for weekly dosing, discontinuation rates because of AEs remain substantial.[57] As discussed in the section on PV, the MPD-RC 112 trial showed no meaningful differences between HU and pegylated IFN-α-2a after one or two years of treatment in patients with previously untreated high-risk PV or ET.[55] Interferon's lack of leukemogenicity and teratogenicity make it attractive for use in very young patients with ET in need of cytoreductive therapy,[47,49] and it is the cytoreductive drug of choice in pregnant patients.[121] Ropeginterferon-α-2b will be compared with anagrelide in patients with ET who are resistant to or intolerant of HU (NCT04285086). Pegylated IFN-α-2a has been studied in this setting and led to a 69.2% ORR (43.1% CR

Table 6–9 Consensus Criteria for Hydroxyurea Resistance or Intolerance in Essential Thrombocythemia

Platelet count >600,000/μL after 3 months of at least 2 g/day of HU (2.5 g/day in patients with a body weight >80 kg)
Platelet count >400,000/μL and WBC <2500/μL at any dose of HU
Platelet count >400,000/μL and Hgb <10 g/dL at any dose of HU
Presence of leg ulcers or other unacceptable mucocutaneous manifestations at any dose of HU
HU-related fever

Reproduced with permission from Barosi G, Besses C, Birgegard G, et al: A unified definition of clinical resistance/intolerance to hydroxyurea in essential thrombocythemia: results of a consensus process by an international working group, *Leukemia* 2007 Feb;21(2):277-280.

+ 26.2% PR) in 65 patients with ET; CR rates were higher in patients with *CALR* mutations.[66]

Ruxolitinib was compared with best available therapy (BAT) in 110 patients with HU-resistant/intolerant ET in the MAJIC-ET trial.[122] At one year, there was no significant difference in CR rates, and at two years, rates of thrombosis, bleeding, and disease evolution to MF or AML were not significantly different; however, some disease-related symptoms were significantly improved in the ruxolitinib arm. Other studies have suggested efficacy of ruxolitinib in providing sustained count control and symptom benefits in patients with HU-resistant/intolerant ET[123]. Table 6–9 lists consensus criteria for HU resistance/intolerance in ET.[124] The RUXO-BEAT study compares ruxolitinib with BAT in high-risk PV or ET (NCT02577926). Bomedemstat, an oral inhibitor of lysine demethylase-1, will also be studied in patients with ET in whom at least standard therapy has failed (NCT04254978).

Special Issues

Management of Extreme Thrombocytosis (Platelet Count >1.5 Million/μL)

Aspirin should be avoided because of the risk of bleeding secondary to AVWD. The use of cytoreductive agents is suggested, especially when bleeding is present, to lower platelet counts and decrease the risk of bleeding. Many experts regard extreme thrombocytosis as a high-risk category and treat all such patients with cytoreductive therapy; others reserve it for patients with bleeding complications or symptoms.[111]

Management of Essential Thrombocythemia in Pregnancy

Essential thrombocythemia is the most common of the Ph^- MPNs encountered in pregnancy. In a prospective study from the UK, pregnancies in 58 women with underlying MPN, 47 (81%) with ET, were identified.[125] The incidence of miscarriage was 1.7% and that of maternal complications was 9%; there were no maternal deaths or thrombotic events. Eighty-five percent delivered at term. There were no neonatal deaths; 22% of neonates were below the 10th decile for growth. Pregnant women with MPNs should be cared for in a multidisciplinary setting by both an obstetrician experienced in managing high-risk pregnancies and a hematologist.[121] In general, low-dose aspirin is recommended throughout pregnancy unless contraindicated (eg, by AVWD). Whether low-molecular-weight-heparin provides additional benefit is controversial,[126] but some experts recommend it for women with prior thrombosis or poor pregnancy outcome, and those with at least one other risk factor for thrombosis (besides pregnancy), with appropriate interruption around delivery.[121] When cytoreductive therapy is indicated, eg, by prior thrombosis or hemorrhage, or platelets >1500 × 10^9/L, IFN-α is preferred. Low-molecular-weight heparin should generally be offered postpartum for six weeks.

PRIMARY MYELOFIBROSIS

Primary myelofibrosis is a clonal disorder of a multipotent hematopoietic stem/progenitor cell of unknown etiology; it is characterized by myeloid cell proliferation, megakaryocytic atypia, BM fibrosis, a leukoerythroblastic peripheral blood picture, anemia, occasional extramedullary hematopoiesis (EMH), splenomegaly, and poor survival.[127] Primary myelofibrosis was previously known as CIMF, myelofibrosis with myeloid metaplasia, or agnogenic myeloid metaplasia. Myelofibrosis can occur either de novo (PMF) or as a late complication of PV or ET (post-PV/ET MF). In either case, it manifests as a stem/progenitor cell–derived clonal myeloproliferation accompanied by intense marrow stromal reaction, including collagen fibrosis, osteosclerosis, and angiogenesis. The US prevalence of MF has been estimated to be 4 to 6 individuals per 100,000 population.[13] The annual incidence of MF ranges from 0.1 to 1 per 100,000.[12,128]

Pathophysiology

Fibrogenesis and angiogenesis have long been thought to develop consequent to the release of growth-promoting factors (such as vascular endothelial growth factor, platelet-derived growth factor [PDGF], basic fibroblast growth factor, and transforming growth factor β) from proliferating atypical megakaryocytes in the BM.[129] More recently, however, fibrocytes, the fibrosis-driving cells in the BM of persons with PMF, have been shown to be clonal (neoplastic) and derived from blood monocytes.[130,131] The *JAK2* V617F mutation is found in 50% to 60% of patients with PMF. Persistent JAK-STAT signaling, resulting in the overproduction of proinflammatory cytokines, has been observed in all patients with PMF, regardless of driver mutation status.[132,133] Proinflammatory cytokines have been associated with many of the symptoms of MF, as well as splenomegaly, transfusion dependence, thrombocytopenia, and shortened survival.[134] Mutations in the thrombopoietin receptor (MPL) are found in 5% to 10% of patients, and *CALR* mutations are found in an additional 25%.[9,10] Approximately 10% of patients are "triple negative" (discussed previously in this chapter). Rare inactivating mutations in negative regulators of JAK-STAT signaling (eg, *LNK*, *SOCS*, and *CBL*) also contribute to the dysregulated JAK-STAT signaling in PMF.[135]

As in ET, disease phenotype appears to differ by driver mutation. In a study of 617 patients with PMF, those with *CALR* mutations had a lower risk of developing anemia, thrombocytopenia, and leukocytosis.[136] In another series of 428 patients with PMF, *CALR* mutations were associated with younger age, lower leukocyte count, and higher platelet count, whereas *MPL* W515K/L mutations were associated with younger age and lower leukocyte count when compared with *JAK2* V617F mutations.[16] A number of other mutations have also been found in PMF, albeit at much lower frequencies than *JAK2* and *CALR* mutations (eg, mutations in *ASXL1*, *EZH2*, *SRSF2*, *CBL*, *IDH1/IDH2*, *TP53*, *TET2*, and *DNMT3A*).[135] These "nondriver" mutations can be extremely helpful in establishing the clonal nature of the disease in triple-negative cases.

Clinical Features

PMF is a heterogeneous disorder with variable age of onset, presenting features, phenotypic manifestations, and prognosis. The incidence of PMF increases with age. In a series of 1054 patients, the median age at diagnosis was 64 years; 17% of patients were younger than 50 years and 5% were younger than 40 years.[137] Clinical presentation can range from no or minimal symptoms, where disease is discovered during a workup for leukocytosis or splenomegaly, to severe symptoms and poor QOL. Severe fatigue is the most common presenting symptom. Constitutional symptoms (fatigue, weight loss, pruritus, low-grade fever, night sweats) are a prominent feature of PMF and can be debilitating. In an internet-based survey of 456 patients with MF, 84% reported fatigue, 50% itching, 56% night sweats, and 47% bone pain.[22] Myeloproliferation is one of the major features of the disease and can lead to sequestration of immature cells and production of blood cells in sites other than the BM, a phenomenon known as extramedullary hematopoiesis (EMH). This commonly manifests as marked hepatosplenomegaly, with associated pain, early satiety, portal hypertension, anemia, and thrombocytopenia. Splenomegaly is present in 80% of the patients and may extend into the pelvis. Hepatomegaly is seen in 40% to 70% of patients. EMH might cause symptoms in various other organs, leading to respiratory distress, pulmonary hypertension, ascites, pericardial tamponade, cord compression, and paralysis. Teardrop red cells and a leukoerythroblastic picture (presence of immature myeloid cells including blasts in the peripheral blood) are characteristic of MF. Anemia is present in about one third of patients at diagnosis and eventually develops in all patients, many of whom require transfusion.[138] Some patients may present with leukocytosis and thrombocytosis; however, leukopenia and thrombocytopenia develops in later stages of the disease in most patients. Among the most feared complications of PMF is transformation to AML, with an actuarial probability of 20.6% in the first 100 months from diagnosis in one study.[139] The outcome after transformation is poor, with a median survival of 6 to 8 months, even with modern, targeted approaches.[140,141] Transformation to AML is the most common cause of death in MF, followed by MF progression without acute transformation, thrombosis, and cardiovascular complications, infection, bleeding, and portal hypertension.

As discussed previously, prefibrotic PMF is now a separate entity from overt PMF in the 2016 WHO classification.[11] The vast majority of patients now considered to have pre-PMF would previously have been categorized as having ET. Compared with ET, pre-PMF is characterized by significantly worse survival and higher rates of progression to overt MF (12.3% at 10 years and 16.9% at 15 years) and transformation to AML (5.8% at 10 years and 11.7% at 15 years).[93] Thrombotic risk is similar, and the IPSET-thrombosis model for ET has been found to accurately risk stratify patients with pre-PMF.[142] Bleeding risk is higher in pre-PMF than in ET. Compared with patients with overt PMF, patients with pre-PMF have lower rates of cytopenias, lower blast counts, fewer symptoms, and are less likely to exhibit large splenomegaly or unfavorable karyotypes.[143] The distribution of driver mutations is similar, but patients with overt PMF are enriched for "high molecular risk (HMR)" nondriver mutations (discussed below) and are more likely to be in higher

Table 6–10 2016 WHO Criteria for Diagnosis of Prefibrotic and Overt Primary Myelofibrosis (PMF)

Major Criteria
1. Megakaryocyte proliferation and atypia: a. without reticulin fibrosis >grade 1, accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often decreased erythropoiesis (pre-PMF); b. accompanied by either reticulin and/or collagen fibrosis grades 2 or 3 (overt PMF)
2. Not meeting WHO criteria for PV, ET, *BCR-ABL1*$^+$ CML, MDS, or other myeloid neoplasms
3. Presence of *JAK2*, *CALR*, or *MPL* mutation or in the absence of these mutations, presence of another clonal marker[a], or absence of (minor, in the case of pre-PMF) reactive bone marrow reticulin fibrosis[b]
Minor Criteria: Presence of At Least One of the Following, Confirmed on Two Consecutive Determinations
1. Leukocytosis ≥11 × 10^9/L
2. Serum lactate dehydrogenase level above upper limit of normal
3. Anemia not attributed to a comorbid condition
4. Palpable splenomegaly
5. Leukoerythroblastosis (this criterion is only applicable to overt PMF and is absent from the minor criteria for pre-PMF)
Diagnosis of PMF, whether overt or prefibrotic, requires meeting all three major criteria and at least one minor criterion.

[a]In the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations (eg, *ASXL1*, *EZH2*, *TET2*, *IDH1/2*, *SRSF2*, *SF3B1*) are of help in determining the clonal nature of the disease.
[b]BM fibrosis secondary to infection, autoimmune disorder, or other chronic inflammatory conditions, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.
Reproduced with permission from Arber DA, Orazi A, Hasserjian R, et al: The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia, *Blood* 2016 May 19;127(20):2391-2405.

International Prognostic Scoring System (IPSS) risk categories. Median survival was 7.2 years for overt PMF and 17.6 years for pre-PMF in one large study.[143]

Diagnosis

The 2016 WHO criteria for diagnosis of both overt and prefibrotic PMF are listed in Table 6–10. Marrow fibrosis by itself is not specific for a diagnosis of PMF. Various degrees of fibrosis are observed in other MPNs, and MDS with fibrosis must be excluded. Morphologic features of the BM during the prefibrotic (cellular) phase of PMF are shown in Fig. 6–6, and those during the fibrotic phase are depicted in Figs. 6–7 to 6–9. Classical morphologic features consistent with PMF and seen in the peripheral blood smear are displayed in Fig. 6–10. BM histology, especially megakaryocyte morphology, is a critical diagnostic criterion for PMF. All patients suspected of having PMF should undergo BM biopsy with reticulin and collagen staining and molecular testing, first for *JAK2* V617F and then for *CALR* and *MPL* mutations. Myeloid mutation panels can support the diagnosis by uncovering mutations in nondriver genes in triple-negative cases. Diagnostic criteria for post-PV and post-ET MF appear in Table 6–11.

Prognosis

Survival in PMF is much shorter than in ET or PV; median OS was reported to be 6.5 years in a cohort of 368 patients diagnosed in four European countries between 1996 and 2007.[144] Median OS was 5.9 years in another cohort of 267 patients with PMF seen at the Mayo Clinic.[16] Over the years, many studies have

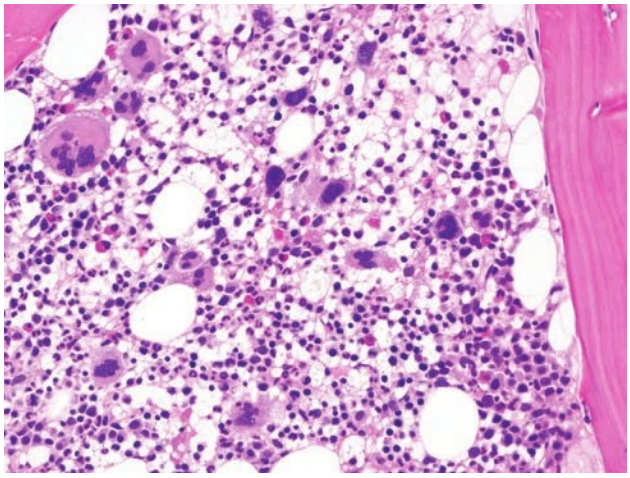


FIGURE 6–6 It is difficult to distinguish the prefibrotic phase of PMF from other types of chronic myeloproliferative neoplasms based on morphologic criteria alone. However, careful microscopic examination of the bone marrow biopsy usually reveals scattered atypical megakaryocytes with morphologic criteria classical for PMF in the fibrotic phase. As shown, some of the megakaryocytes in this bone marrow biopsy are remarkably variable in size and shape and characteristically contain markedly hyperchromatic nuclei (×200).

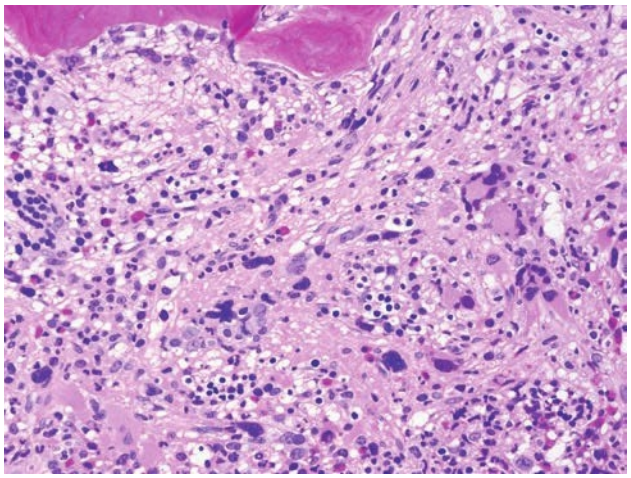


FIGURE 6–7 During the fibrotic phase of PMF, bone marrow hematopoietic cellular elements tend to decrease in number with interstitial infiltration of the bone marrow by fibroblasts, which leads to a streaming effect. Characteristically, the megakaryocytes demonstrate variability in size and shape, and megakaryocytes containing hyperchromatic and hyperlobulated nuclei are frequently encountered during the fibrotic phase of PMF (×200).

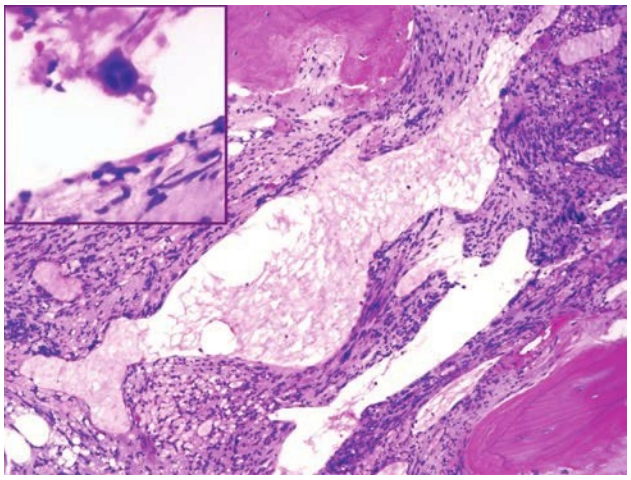


FIGURE 6–8 During the fibrotic phase, another common feature of the bone marrow is marked expansion of bone marrow sinusoids, which are usually rudimentary under normal conditions (×100). Hematopoietic cellular elements can be detected within the bone marrow sinuses; a megakaryocyte is shown, comprising what is known as intrasinusoidal hematopoiesis (inset, ×400).

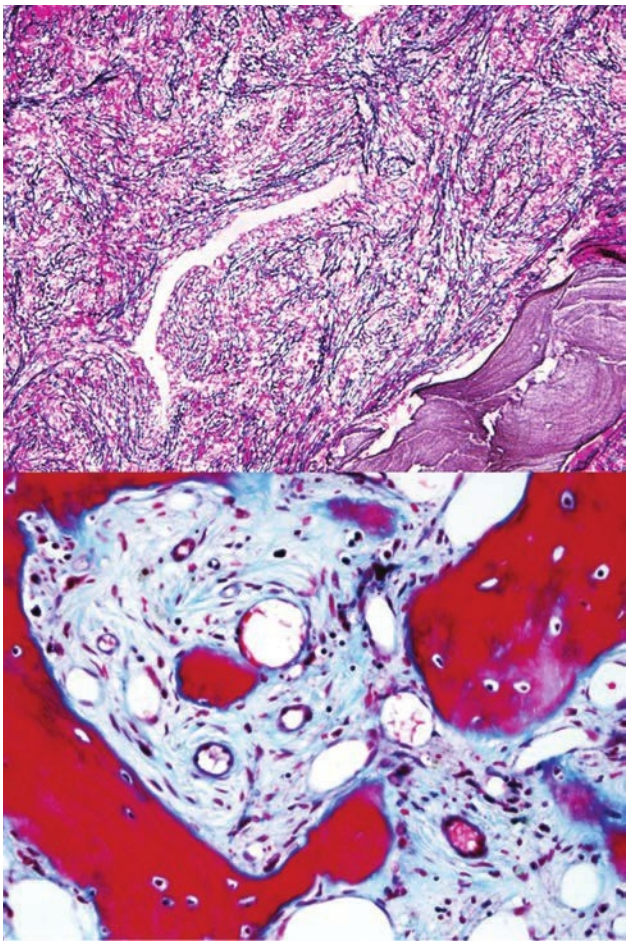


FIGURE 6–9 During the fibrotic phase of PMF, the bone marrow is characterized by increased interstitial reticulin fibrosis (upper panel, ×100), which might be associated with the abnormal presence of collagen fibers that are detected by trichrome staining (lower panel, ×200).

identified a number of clinical variables as adversely affecting survival.[145] These efforts culminated in the development of the IPSS in 2009, which uses five readily available pieces of information at the time of diagnosis—age, Hgb, WBC count, circulating blasts, and constitutional symptoms—to separate patients into four prognostic categories: low, intermediate-1, intermediate-2, and high risk.[137] The Dynamic IPSS (DIPSS), published in 2010, refined the IPSS by assigning two points, rather than one, to anemia (Hgb <10 g/dL), based on a higher hazard ratio for death, and was found to prognosticate patients accurately at any point in their disease course, not just at diagnosis.[146] The DIPSS was also shown to predict leukemic transformation.[147] Cytogenetic abnormalities associated with an unfavorable prognosis in PMF include complex karyotype, and a single or two of the following abnormalities: +8, i(17q), -7/7q-, -5/5q-, 12p-, inv(3), and 11q23 rearrangement.[148] A "very-high-risk" karyotype (single/multiple abnormalities of -7, i(17q), inv(3)/3q21,12p-/12p11.2,11q-/11q23, or other autosomal trisomies not including +8/+9 [eg, +21, +19]) has also been recently recognized.[149] The DIPSS-plus model adds a point each for thrombocytopenia (platelets <100,000/μL), RBC transfusion need, and unfavorable karyotype to the DIPSS score and can also be used at any time point in the patient's disease course.[150] These models are

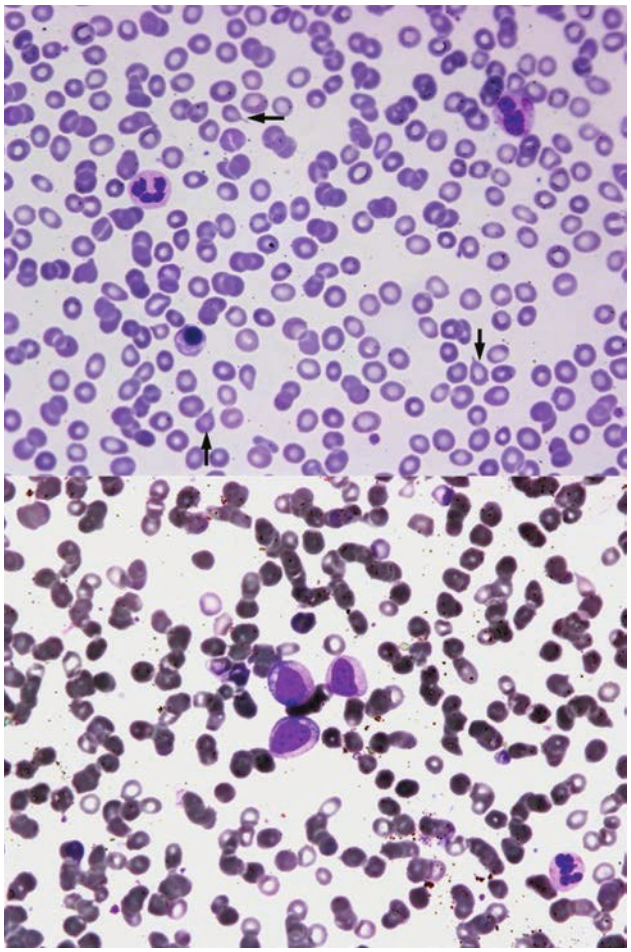


FIGURE 6–10 Careful examination of peripheral blood smears from patients with PMF usually reveals teardrop red blood cells (*arrows*, upper panel; ×400). In addition, nucleated red blood cells (upper panel) and left-shifted granulopoiesis (lower panel; ×400) are seen, two morphologic criteria collectively described as leukoerythroblastosis.

summarized in Table 6–12. Of note, all these models were developed for overt PMF, although the IPSS has been shown to effectively risk stratify patients with pre-PMF.[143] Growing recognition that these models do not work well for patients with post-PV/ET MF[151–153] led to the development of the MYSEC-PM, discussed further below.

Recent studies have explored the prognostic relevance of various mutations. In a study of 617 patients with PMF, *CALR* mutations were associated with longer survival (median, 17.7 years).[136] Patients with triple-negative PMF had a higher incidence of transformation to AML and a shorter survival (median, 3.2 years). Another study of 253 patients with PMF reported similar findings.[154] Patients with *CALR* mutations had the longest survival (median, 8.2 years), whereas patients without any of these mutations (triple negative) had the shortest survival (median, 2.5 years). Triple-negative patients also displayed inferior LFS. However, unlike in ET, the favorable prognostic impact of *CALR* mutations in PMF appears to be restricted to the much more common type 1/type 1–like mutations.[155–157] In 2013, in a seminal paper, Vannucchi and colleagues identified several nondriver mutations as being associated with worse OS and LFS in a cohort of 879 patients with PMF—these were termed HMR (high molecular risk) mutations and included *ASXL1*, *SRSF2*, *IDH1*, *IDH2*, and *EZH2*, although only *ASXL1* mutation status provided additional prognostic information beyond the IPSS or DIPSS-plus.[135] This group went on to show that the presence of two or more HMR mutations further reduced survival (median OS, 2.6 years for ≥2 mutations, 7 years for one, and 12.3 years for none).[158] Much more recently, the *U2AF1* Q157 mutation has been added to the list of prognostically unfavorable mutations in PMF.[159] This wealth of

Table 6–11 Diagnostic Criteria for Post-Polycythemia Vera/Essential Thrombocythemia Myelofibrosis[102]

Required Criteria
1. Documentation of a previous diagnosis of PV or ET as defined by the WHO criteria
2. Bone marrow fibrosis grade 2–3 (on a 0–3 scale) or grade 3–4 (on a 0–4 scale)
Additional Criteria (2 Required)
1. A leucoerythroblastic blood picture
2. Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly
3. Development of ≥1 of 3 constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5 °C)
4. Anemia or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis (for post-PV MF); Anemia and a ≥2 g/dL decrease from baseline Hgb level (for post-ET MF)
5. Increased serum LDH (for post-ET MF only)

Table 6–12 The IPSS, DIPSS, and DIPSS-plus Prognostic Models for Primary Myelofibrosis[137,146,150]

Factors	IPSS	DIPSS	DIPSS-plus
Age >65 years	1	1	Calculate DIPSS first[a]
Constitutional symptoms	1	1	Calculate DIPSS first[a]
Hemoglobin <10 g/dL	1	2	Calculate DIPSS first[a]
Leukocytes >25 × 10^9/L	1	1	Calculate DIPSS first[a]
Circulating blasts ≥1%	1	1	Calculate DIPSS first[a]
Platelet count <100 × 10^9/L			1
RBC transfusion need			1
Unfavorable karyotype			1
Risk stratification (Median Survival)			
Low	0 points (11.25 y)	0 points (not reached)	0 points (15.4 y)
Intermediate-1	1 point (7.9 y)	1–2 points (14.2 y)	1 point (6.5 y)
Intermediate-2	2 points (4 y)	3–4 points (4 y)	2–3 points (2.9 y)
High	3–5 points (2.25 y)	5–6 points (1.5 y)	4–6 points (1.3 y)

[a]To arrive at the DIPSS-plus score, calculate the DIPSS score first. Assign 0 points for DIPSS low risk, 1 point for DIPSS intermediate-1 risk, 2 points for DIPSS intermediate-2 risk, and 3 points for DIPSS high risk. Then add 1 point each for RBC transfusion need, platelets <100,000/μL, and unfavorable karyotype.
RBC, red blood cell.

genetic information that has become available in the last few years has since been integrated into a number of newer prognostic models for patients with PMF.[160] These include the mutation-enhanced IPSS and mutation-enhanced IPSS-plus for transplantation-age (≤70 years) patients with PMF (MIPSS70/MIPSS70-plus).[161] Compared with the MIPSS70, the MIPSS70-plus adds karyotypic information (unfavorable vs favorable), but omits BM fibrosis grade, leukocytosis and thrombocytopenia as prognostic variables, and classifies patients into four prognostic categories (the MIPSS70 model has 3 prognostic categories: low, intermediate, and high). There is also a version 2.0 of the MIPSS70-plus, which incorporates *U2AF1* Q157 status, very-high-risk karyotype, and sex- and severity-adjusted Hgb thresholds into the MIPSS70-plus to further enhance its power to discriminate between prognostic categories, of which there are five in this model.[162] Both the MIPSS70 and the MIPSS70-plus version 2.0 scores can readily be calculated in the clinic at http://mipss70score.it. Finally, the genetically inspired prognostic scoring system, distinguished by its reliance on genomic information alone for prognostication, is not widely used.[163]

Although managed similarly and characterized by the same general clinical features and complications, the underlying biology of post-PV and post-ET MF differs fundamentally from that of PMF. Passamonti and colleagues studied 685 molecularly annotated patients with post-PV/ET MF to develop a prognostic model, the MYSEC-PM, specifically for this population.[36] Median OS for the entire cohort was 9.3 years (8.1 years for post-PV MF and 14.5 years for post-ET MF). The model, which places a heavy emphasis on patient age, also allocates points for anemia (Hgb <11 g/dL), thrombocytopenia (platelets <150 × 10^9/L), circulating blasts (≥3%), driver mutation status (*CALR* wild type), and constitutional symptoms to assign patients to one of four prognostic categories: low, intermediate-1, intermediate-2, and high. The score can be calculated at www.mysec-pm.eu. The superiority of the MYSEC-PM over the IPSS for prognostication in patients with post-PV/ET MF has been independently validated.[164] Among patients with post-ET MF, the MYSEC study documented superior survival for *CALR*-mutated patients compared with *JAK2*-mutated patients, with no differences observed between type 1/-like and type 2/-like *CALR* mutations in terms of clinical presentation or outcome (in contrast to PMF); thrombosis incidence did not differ by driver mutation status, unlike in ET.[165]

Treatment

Before the approval by the FDA of the JAK1/2 inhibitor ruxolitinib in 2011, treatment of MF was largely unsatisfactory. Cytoreductive drugs such as HU or cladribine were used to control hyperproliferation, although their effects are transient and rarely result in complete spleen regression. Oral alkylating agents have also been used, but often induce severe myelosuppression and are associated with an increased risk of transformation to AML. Corticosteroids, erythroid-stimulating agents (ESAs), immunomodulatory drugs (IMiDs), and androgens have proven helpful in the treatment of anemia. Patients with low endogenous

serum Epo (<125 U/L) can benefit from ESAs; response rates range from 23% to 60% and median duration of response is about one year.[166] Oral danazol (200 mg 2 or 3 times daily) can be useful for both anemia (30% ORR) and thrombocytopenia.[167] Prostate cancer should be ruled out before starting danazol, and liver enzymes should be monitored in patients taking it. IMiDs (low-dose thalidomide and lenalidomide) have anticytokine and antiangiogenic effects and have been shown to reduce splenomegaly and improve anemia (in 20%–30% of patients).[166] They are usually used with tapering doses of prednisone for three months. Pomalidomide showed significant promise in a phase 2 study,[168] but failed to improve rates of transfusion independence in a phase 3 study.[169] Low-dose thalidomide (50 mg/d) may be particularly useful to treat thrombocytopenia.[170–172] Interferon-α has been used with some success, but significant toxicity prevents its use in many patients. It may slow disease progression in patients with early MF, as well as reverse BM fibrosis in some patients.[173] If used, IFN-α should be prescribed early in the disease because patients with HMR mutations tend not to respond well.[174] Splenectomy is used only rarely in the JAK inhibitor era. When performed, it should be performed in carefully selected patients, because perioperative morbidity and mortality can be substantial.[175] Splenic irradiation is effective for palliating splenomegaly, but its benefits are transient and it can result in prolonged and profound cytopenias and make subsequent splenectomy more difficult.[176]

JAK Inhibitors

Two pivotal phase 3 randomized trials provided evidence for the regulatory approval of the oral JAK1/2 inhibitor ruxolitinib. The COMFORT-I trial randomly assigned patients to receive ruxolitinib (n = 155) or placebo (n = 154),[177] whereas the COMFORT-II trial compared ruxolitinib (n = 146) with BAT (n = 73).[178] Patients in both trials had to have baseline platelets ≥100 × 10^9/L and IPSS intermediate-2/high-risk disease. Significantly more patients in the ruxolitinib arms had 35% or higher SVR (roughly approximating ≥50% reduction in spleen size by palpation) from baseline at week 24 (COMFORT-I) or week 48 (COMFORT-II). Both studies showed significant improvements in MF-related symptoms and QOL in patients treated with ruxolitinib. Thrombocytopenia and anemia were the most common toxicities associated with ruxolitinib therapy. These were most pronounced in the first 3 to 6 months of treatment and were managed with dose reductions or transfusions. Headaches, dizziness, and bruising are the most common nonhematologic adverse effects of ruxolitinib.

Long-term follow-up analyses have demonstrated that the effects of ruxolitinib are durable.[179,180] Response rates improved over time, although the median duration of spleen response was about 3 years. No new toxicity concerns emerged. Importantly, ruxolitinib improved survival, reducing the risk of death by 30% in a pooled analysis of 5-year data from both COMFORT trials (median OS, 5.3 vs 3.8 years).[181] Spleen responses to ruxolitinib are dose-dependent and correlate with survival.[182,183] Furthermore, anemia caused by ruxolitinib does not carry the adverse prognosis of disease-associated anemia, and ruxolitinib overcomes the negative prognostic impact of the latter.[184,185] For these reasons, we attempt to optimize ruxolitinib dosing whenever possible and manage the anemia with transfusions, ESAs, danazol, IMiDs, etc. However, although the ruxolitinib prescribing information suggests initial dosing based on the platelet count, an alternative dosing strategy of 10 mg twice daily for the first 12 weeks before escalating in anemic patients is also reasonable.[186,187] Although the recommended starting dose for patients with 50–99 × 10^9/L platelets is 5 mg twice daily, studies support using the more effective 10 mg twice daily dose in this population.[188,189] Patients taking ruxolitinib should be vaccinated against shingles and be monitored regularly for weight gain and hyperlipidemia. Although the US approval of ruxolitinib is restricted to patients with intermediate- and high-risk disease, NCCN guidelines support its use in symptomatic low-risk patients when required.[190] There is no guidance for or published experience with the use of ruxolitinib in patients with platelets <50 × 10^9/L.

The JAK2 inhibitor fedratinib was approved by the FDA for patients with intermediate-2/high-risk MF in August 2019. In the placebo-controlled JAKARTA trial, fedratinib produced rates of 35% or greater SVR and 50% or higher TSS improvement at week 24, which were significantly superior to those observed with placebo and similar to those seen with ruxolitinib in the COMFORT trials.[191] Apart from anemia and thrombocytopenia (expected from inhibition of JAK2), fedratinib was also associated with a relatively high incidence of gastrointestinal side effects, likely because of its inhibition of fms-like tyrosine kinase 3 (FLT3). JAKARTA enrolled patients with baseline platelets ≥50 × 10^9/L, and while the numbers were small, there were no significant differences in response rates between the ≥50–99 × 10^9/L and ≥100 × 10^9/L platelet groups.[192] Fedratinib dosing is not based on platelet count. Development of fedratinib had been halted owing to concerns over Wernicke encephalopathy but was recently resumed given that this complication is very rare and of uncertain relationship to fedratinib[193]; however, thiamine levels must be checked before fedratinib initiation, repleted if low, and monitored during therapy. In the setting of ruxolitinib failure, fedratinib yielded a 35% or higher SVR rate of 30% and a 50% or higher TSS reduction rate of 27% at 24 weeks in a

relatively small trial (JAKARTA-2),[194] and is being studied further in the FREEDOM trials (NCT03755518, NCT03952039).

Allogeneic Stem Cell Transplantation

Allogeneic stem cell transplant (alloSCT) is potentially curative in MF; however, few patients undergo alloSCT because of older age or severe comorbidities. Reduced-intensity conditioning regimens are an option in older patients and those with comorbidities.[195] In general, patients in a risk category with a predicted median OS of fewer than 5 years should be considered for alloSCT.[47] Indeed, the primary goal of prognostication in MF is to inform selection of patients for alloSCT. This typically includes patients younger than 70 years with intermediate-2 or high-risk disease by the IPSS, DIPSS, or DIPSS-plus.[196] AlloSCT should also be considered in patients younger than 65 years who have intermediate-1–risk disease but have refractory, transfusion-dependent anemia, more than 2% circulating blasts, adverse cytogenetics (as defined in the DIPSS-plus model), are triple negative for driver mutations, or have *ASXL1* mutations. Our practice is to transplant patients at best response to ruxolitinib. Consensus recommendations are to initiate ruxolitinib at least two months before transplant and optimize the dose for best spleen response.[196] Ruxolitinib should then be tapered over 5 to 7 days to avoid a "flare" and stopped the day before conditioning. The recently published myelofibrosis transplant scoring system incorporates a number of clinical and genomic pretransplant variables (age, performance status, platelet count, leukocyte count, donor type, driver mutation, and *ASXL1* status) to predict outcomes after alloSCT.[197]

Combination and Novel Therapies

Momelotinib, a JAK1/2 inhibitor that can improve anemia, and pacritinib, a JAK2/FLT3 inhibitor that is relatively nonmyelosuppressive, are active agents that are reentering phase 3 pivotal studies with new end points and eligibility criteria (NCT04173494, NCT03165734) after previous phase 3 trials showed mixed results.[198–201] Regulatory approval of these agents would fulfill important unmet needs in the JAK inhibitor space. The activin receptor ligand trap luspatercept has shown promise for the treatment of anemia, both as a single agent and in combination with ruxolitinib.[202] Imetelstat, a telomerase inhibitor, has demonstrated an intriguing apparent OS benefit in the "ruxolitinib failure" setting.[203] A phase 3 trial of this agent and one of the antifibrotic drug PRM-151[204] are planned. Many other novel agents are being studied in the ruxolitinib failure and/or suboptimal response settings.[205] Encouraging results have been reported with some laboratory-based synergistic combinations, eg, those with the BH3-mimetic navitoclax[206] and the bromodomain inhibitor CPI-0610[207]; these combinations are moving into phase 3 trials in the JAK inhibitor–naïve setting.

Treatment Conclusions

Patients with MF should first be assigned to a risk category using one of the standard prognostic models. For patients with low-risk disease, a watch-and-wait approach is acceptable, although ruxolitinib may be needed for symptom control. Patients in the intermediate- and high-risk groups should be treated based on their clinical needs, eg, anemia, splenomegaly, symptoms, EMH, and increased blasts. For younger patients in the intermediate-2 and high-risk categories and select intermediate-1 risk patients, alloSCT should be offered. Patients who are not eligible for alloSCT and are intolerant of, have a suboptimal response, or lose their response to JAK inhibitors should be offered enrollment in clinical trials. Ruxolitinib and fedratinib have been effective in reducing splenomegaly, in improving symptoms and QOL, and, in the case of ruxolitinib, prolonging survival in patients with MF. JAK inhibitors have not been shown to eradicate the mutant clone, and patients lose their response to therapy over time. Results from ongoing trials of new targeted agents and rational combinations are eagerly awaited.

CHRONIC EOSINOPHILIC DISORDERS: HYPEREOSINOPHILIC SYNDROME/CHRONIC EOSINOPHILIC LEUKEMIA

Chronic eosinophilic disorders (further referred to as hypereosinophilic syndromes/chronic eosinophilic leukemia [HES/CEL]) are a heterogeneous group of rare disorders characterized by chronic eosinophil overproduction (an absolute eosinophil count [AEC] in peripheral blood >1.5 × 10^9/L) and eosinophilic tissue infiltration with possible end-organ damage. Although the largest portion of these disorders represent primary BM diseases classified as myeloid/lymphoid neoplasms with eosinophilia (MLN-Eo), clinical presentation is mostly driven by the presence of eosinophils irrespective of the underlying cause. HES/CEL can be clinically subdivided into six variants: 1. myeloproliferative, 2. lymphoproliferative, 3. overlap, 4. associated, 5. familial, and 6. Idiopathic.[208] The first 2 categories represent primary MLN-Eo diagnoses. The classification, as revised by the 2016 WHO criteria, is shown in Table 6–1. Hypereosinophilia >1.5

$\times 10^9$/L for more than 6 months, absence of obvious reactive and clonal causes, and evidence of end-organ damage define HES. Idiopathic hypereosinophilia is the preferred diagnosis when end-organ damage is absent. Patients found to have clonal disease (ie, a cytogenetic or molecular abnormality proving the existence of a malignant clone), or peripheral blood blasts 2% or higher, or BM blasts 5% or higher (but both <20%) have chronic eosinophilic leukemia, not otherwise specified (CEL, NOS).[11] Per WHO 2016, the major category of MLN-Eo represents myeloid/lymphoid neoplasm with eosinophilia and rearrangement of *PDGFRα*, *PDGFRβ*, *FGFR1*, and provisional entity of *PCM1-JAK2* (Table 6–1 and Tables 6–13 to 6–18). The identification of the clonal marker, fused *FIP1L1* gene to the *PDGFRα* gene located on 4q12 chromosome in 2003 by Cools et al,[209] led to recognition of other causes of primary eosinophilic disorders driven by constitutively active TKs: genes encoding *PDGFRβ* (chromosome 5q31–q33; >30 gene fusion partners [Table 6–14]),[210,211] fibroblast growth factor receptor 1 (*FGFR1*, chromosome 8p11; ~15 gene fusion partners[212] (Table 6–16); and recently, provisionally added Janus kinase 2 gene, *JAK2* (chromosome 9p24; mostly *PCM1-JAK2* fusion).[11] Some patients, including those with the above classified HES/CEL, may exhibit expansion of cytokine-producing, immunophenotypically aberrant T cells, leading to clonal as well as reactive hypereosinophilia (abnormal overstimulation of eosinophilopoietic growth factors), and might be classified as a lymphoproliferative variant.

HES/CEL are more common in men than women, and patients are usually younger (20–50 years old). The clinical presentation varies; patients might have minimal nonspecific symptoms (such as fatigue, myalgias, low-grade fever), "allergic" symptoms (urticaria, pruritus, angioedema, erythematous papules, cough with pulmonary infiltrates), or serious organ involvement (acute heart failure, mural thrombi, cardiomyopathy, polyneuropathies, optic neuritis).[213] Despite the fact that the skin, lungs, and gastrointestinal tract are the most commonly affected organs, congestive heart failure represents a prototypical illustration of eosinophil-mediated tissue injury.[214]

Diagnosis

The initial step in diagnosis of HES/CEL is to rule out secondary, or reactive, causes of eosinophilia such as infections (especially parasitic), atopy, drug reactions, connective tissue disorders, or vasculitis. Assessment of organ involvement should always be performed as

Table 6–13 Diagnostic Criteria for Chronic Eosinophilic Leukemia, NOS

• Eosinophilia (eosinophil count ≥1.5 × 10^9/L)
• WHO criteria for *BCR-ABL1*–positive chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, primary myelofibrosis, chromic neutrophilic leukemia, chronic myelomonocytic leukemia, and *BCR-ABL1*–negative atypical chronic myeloid leukemia are not met
• No rearrangement of *PDGFRα, PDGFRβ*, or *FGFR1*, and no *PCM1-JAK2, ETV6-JAK2*, or *BCR-JAK2* fusion
• Blast cells constitute <20% of the cells in the peripheral blood and bone marrow, and inv(16)(p13.1q22), t(16;16)(p13.1;q22), t(8;21)(q22;q22.1), and other diagnostic features of acute myeloid leukemia are absent
• There is a clonal cytogenetic or molecular genetic abnormality or blast cells account for ≥2% of cells in the peripheral blood or ≥5% in the bone marrow

Table 6–14 Diagnostic Criteria for Myeloid/Lymphoid Neoplasms with Eosinophilia Associated with *FIP1L1-PDGFRα* or a Variant Fusion Gene

A myeloid or lymphoid neoplasm, usually with prominent eosinophilia **AND**
The presence of *FIP1L1-PDGFRα* fusion gene or a variant fusion gene with rearrangement of *PDGFRα* or an activating mutation of *PDGFRα*

Table 6–15 Diagnostic Criteria for Myeloid/Lymphoid Neoplasms Associated with *ETV6-PDGFRβ* or Other Rearrangement of *PDGFRβ*

A myeloid or lymphoid neoplasm, often with prominent eosinophilia and sometimes with neutrophilia or monocytosis **AND**
The presence of t(5;12)(q32;p13.2) or a variant translocation or demonstration of *ETV6-PDGFRβ* fusion gene or other rearrangement of *PDGFRβ*

Table 6–16 Variant Translocation-Associated Myeloid/Lymphoid Neoplasms with *PDGFRβ* Rearrangement

Translocation	Fusion Gene	Hematologic Diagnosis
t(1;3;5)(p36;p22.2;q32)	*WDR48-PDGFRβ*	CEL
der(1)t(1;5)(p34;q32), der(1)t(1;5)(p34;q15), der(11)ins(11;5)(p13;q15q32)	*CAPRIN1-PDGFRβ*	CEL
t(1;5)(q21.3;q32)	*TPM3-PDGFRβ*	
t(1;5)(q21.2;q32)	*PDE4DIP-PDGFRβ*	MDS/MPN with eosinophilia
t(2;5)(p16.2;q32)	*SPTBN1-PDGFRβ*	
t(4;5;5)(q21.2;q31;q32)	*PRKG2-PDGFRβ*	Chronic basophilic leukemia
t(3;5)(p22.2;q32)	*GOLGA4-PDGFRβ*	CEL or aCML with eosinophilia
Cryptic interstitial deletion of 5q	*TNIP1-PDGFRβ*	CEL with thrombocytosis
t(5;7)(q32;q11.2)	*HIP1-PDGFRβ*	CMML with eosinophilia
t(5;7)(q32;p14.1)	*HECW1-PDGFRβ*	JMML
t(5;9)(q32;p24.3)	*KANK1-PDGFRβ*	Essential thrombocythemia without eosinophilia
t(5;10)(q32;q21.2)	*CCDC6-PDGFRβ*	aCML with eosinophilia or MPN with eosinophilia
Uninformative	*SART3-PDGFRβ*	MPN with eosinophilia and myelofibrosis
t(5;12)(q32;q24.1)	*GIT2-PDGFRβ*	CEL
t(5;12)(q32;p13.3)	*ERC1-PDGFRβ*	AML without eosinophilia
t(5;12)(q32;q13.1)	*BIN2-PDGFRβ*	aCML with eosinophilia
t(5;14)(q32;q22.1)	*NIN-PDGFRβ*	Ph-negative CML (13% eosinophils)
t(5;14)(q32;q32.1)	*CCDC88C-PDGFRβ*	CMML with eosinophilia
t(5;15)(q32;q15.3)	*TP53BP1-PDGFRβ*	Ph-negative CML with prominent eosinophilia
t(5;16)(q32;p13.1)	*NDE1-PDGFRβ*	CMML
t(5;17)(q32;p13.2)	*RABEP1-PDGFRβ*	CMML
t(5;17)(q32;p11.2)	*SPECC1-PDGFRβ*	JMML
t(5;17)(q32;q11.2)	*MYO18A-PDGFRβ*	MPN with eosinophilia
t(5;17)(q32;q21.3)	*COL1A1-PDGFRβ*	MDS or MPN with eosinophilia
t(5;20)(q32;p11.2)	*DTD1-PDGFRβ*	CEL

Table 6–17 Diagnostic Criteria for Myeloid/Lymphoid Neoplasms with *FGFR1* Rearrangement

A myeloproliferative or myelodysplastic/myeloproliferative neoplasm with prominent eosinophilia and sometimes with neutrophilia or monocytosis **OR**
Acute myeloid leukemia, T- or B-lymphoblastic leukemia/lymphoma or mixed-phenotype acute leukemia (usually associated with peripheral blood or bone marrow eosinophilia) **AND**
The presence of t(8;13)(p11.2;q12) or a variant translocation leading to *FGFR1* rearrangement, demonstrated in myeloid cells, lymphoblasts, or both

guided by clinical presentation, and should include various laboratory and imaging tests such as chest radiograph, pulmonary function tests, electrocardiogram, echocardiogram, computed tomography of the chest/abdomen/pelvis, and measurement of serum troponin levels, vitamin B12, or tryptase. When secondary causes are excluded, patients must undergo evaluation of primary marrow disorders, including examination of peripheral blood smear, BM, cytogenetic and molecular analysis for *FIP1L1-PDGFRα* (by using polymerase chain reaction or fluorescence in situ hybridization analysis aimed at detecting a deletion/excision of the CHIC2 locus at chromosome 4q12), because treatment modalities for patients with this

Table 6–18 Cytogenetics (Chromosomal Rearrangements) and Molecular Genetics (Fusion Genes) Reported in Myeloid/Lymphoid Neoplasms with *FGFR1* Rearrangement

Cytogenetics	Molecular Genetics
t(8;13)(p11.2;q12.1)	*ZMYM2-FDFR1*
t(8;9)(p11.2;q33.2)	*CNTRL-FGFR1*
t(6;8)(q27;p11.2)	*FDFR1OP-FGFR1*
t(8;22)(p11.2;q11.2)	*BCR-FGFR1*
t(7;8)(q33;p11.2)	*TRIM24-FGFR1*
t(8;17)(p11.2;q11.2)	*MYO18A-FGFR1*
t(8;19)(p11.2;q13.3)	*HERV-FGFR1*
ins(12;8)(p11.2;p11.2;p22)	*FGFR1OP2-FGFR1*
t(1;8)(q31.1;p11.2)	*TPR-FGFR1*
t(2;8)(q13;p11.2)	*RANBP2-FGFR1*
t(2;8)(q37.3;p11.22)	*LRRFIP1-FGFR1*
t(7;8)(q22.1;p11.2)	*CUX-FGFR1*
t(8;12)(p11.2;q15)	*CPSF6-FGFR1*

mutation are different. Figures 6–11 and 6–12 illustrate the morphologic findings in HES/CEL. The frequency of the *FIP1L1-PDGFRα* rearrangement in patients with hypereosinophilia has been reported between 3% and 88%,[209,215] with the largest series (741 and 376 patients, respectively) showing more realistic percentages of 3%[216] and 11%.[216] Absence of *FIP1L1-PDGFRα* fusion should prompt evaluation for other clonal disorders, including rearrangements of *PDGFRβ* (5q31–q33), *FGFR1* (8p11), and fusion of *PMC1-JAK2*. Additional workup with genetic molecular sequencing, cytogenetic analysis, T-cell immunophenotyping, and T-cell receptor gene rearrangement might reveal other clonal–not otherwise classified abnormalities, further deciphering HES/CEL diagnoses.

A diagnostic and therapeutic algorithm of a patient with suspected primary eosinophilia is summarized in Fig. 6–13.

Treatment

Clinical presentation and its acuity direct initial treatment in patients with HES/CEL. For asymptomatic patients with no organ damage and normal troponin levels, no active therapy is recommended, and these patients should be followed closely. There is no official

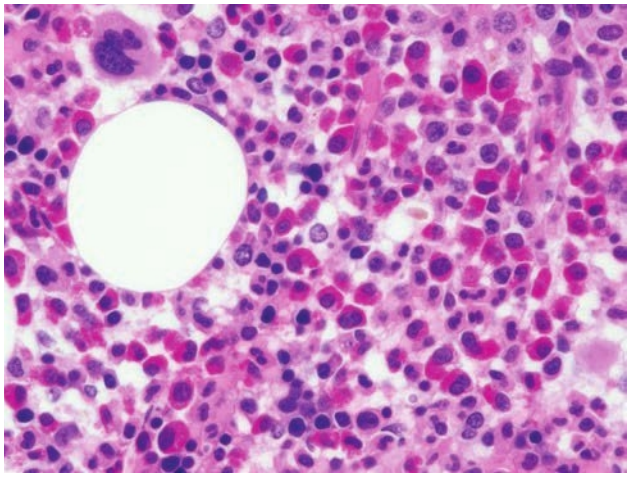


FIGURE 6–11 In CEL/HES, the bone marrow typically shows increased cellularity with striking interstitial infiltration by eosinophils (×400).

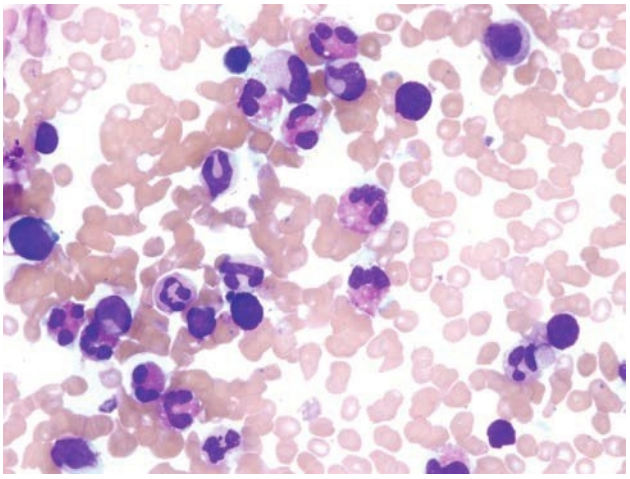


FIGURE 6–12 Markedly increased, morphologically unremarkable eosinophils are typically detected in the bone marrow aspirate smears from patients with CEL/HES (×400).

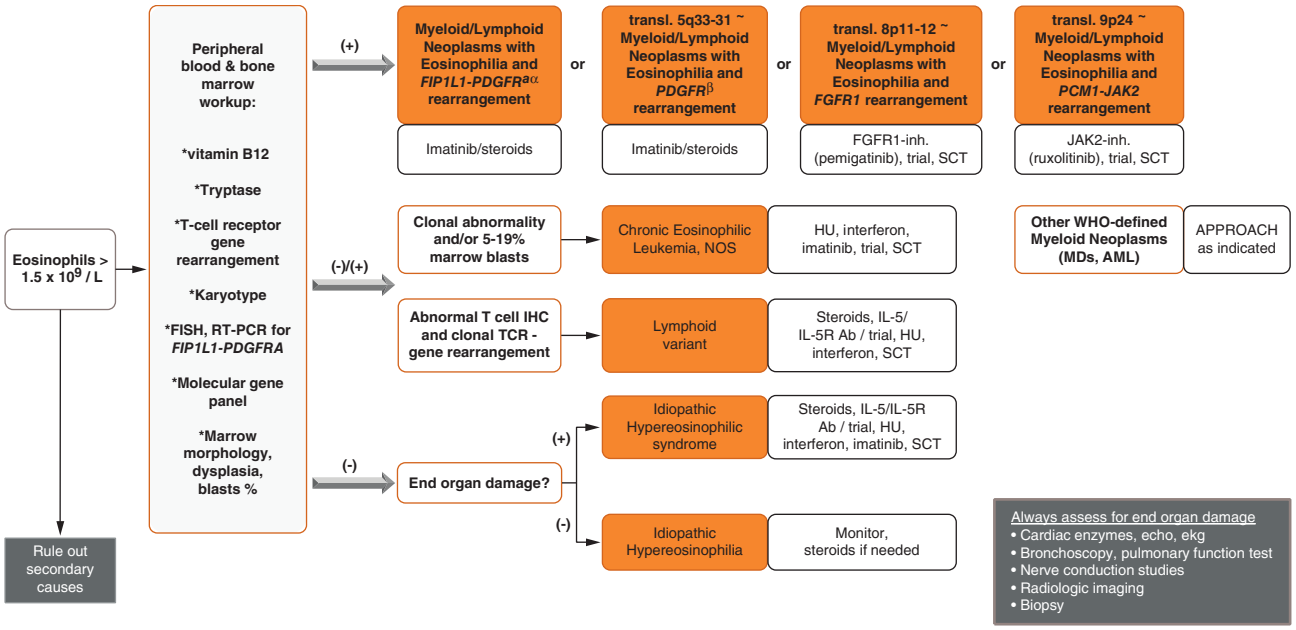


FIGURE 6–13 **Diagnostic and treatment algorithm of eosinophilic disorders based on the 2016 WHO classification. Ab, antibody; *FGFR1*, fibroblasts–growth factor receptor 1; HU, hydroxyurea; IL, interleukin; inh, inhibitor; *PDGFRα*, platelet-derived growth factor receptor alpha; *PDGFRβ*, platelet-derived growth factor beta; SCT, stem cell transplant; transl, translocation.**

consensus to recommend therapy solely based on the degree of hypereosinophilia, but AEC 1.5–2 × 10^9/L is generally accepted as a treatment threshold. The exceptions are patients with imatinib-sensitive *PDFGRA/B* rearrangement, who should be treated even in the absence of organ dysfunction to decrease the risk of end-organ damage. For the remaining patients with symptomatic disease or evidence of end-organ damage, therapy for HES generally entails the use of corticosteroids, IFN-α, or cytoreductive agents such as HU, vincristine, or cyclosporine. Glucocorticosteroids (usually prednisone at starting dose of 1 mg/kg/day) are the first line for the treatment of most forms of HES/CEL, and also remain the initial therapy of choice for patients who show life-threatening manifestations. ORR to first-line prednisone is about 70% to 80%,[214] but relapses often occur with cessation of therapy. In patients with possible exposure to *Strongyloides stercoralis,* empiric ivermectin therapy (200 μg/kg orally × 2 days) should be given concomitantly with steroids to prevent potentially fatal steroid-induced hyperinfection syndrome and disseminated disease.[217] Second-line options after steroids include IFN-α, HU, cyclosporin, or low-dose methotrexate. Other agents, such as vincristine, cyclophosphamide, cladribine, or cytarabine, are mostly useful for acute reductions when the total eosinophil count is very high (≥50 × 10^9/L).[214,218–222]

Patients with known imatinib-sensitive mutations, including *FIP1L1-PDGFRα* and *PDGFRβ* involvement (chromosomal translocations of 5q31–q33), should receive imatinib mesylate as a first therapy at a starting dose of 100 mg daily with the possibility to increase to 400 mg daily. Imatinib is also approved as therapy for patients with HES/CEL, whose *FIP1L1-PDGFRα* status is negative or unknown, at a recommended dose of 400 mg daily. The response to imatinib in *FIP1L1-PDGFRα*–negative patients is limited, and it might represent a second-line treatment for refractory patients, unless they have typical clinical presentation (male gender, splenomegaly, elevated tryptase, and typical marrow features) where frontline imatinib shall be considered. Imatinib mesylate, a highly potent tyrosine kinase inhibitor against ABL, PDGFR, and KIT protein kinases, could induce complete hematologic and complete molecular remission in as much as 99% and 95% of patients with *FIP1L1-PDGFRα* and HES, respectively.[211,223,224] Long-term follow-up studies (median duration of imatinib therapy of 6.6 years) showed that these responses are durable in the majority of patients,[225–227] but maintenance therapy is required; otherwise, relapses occur. Of note, in patients with eosinophil-mediated heart damage or even elevated troponin, it is recommended to co-initiate glucocorticoids for the first 10 days of imatinib therapy to avoid sudden heart deterioration.

Patients with *FGFR1* rearrangement usually have a very aggressive disease course with progression to acute leukemia within one to two years.[228] Until recently, high-dose chemotherapy followed by alloSCT represented the only therapeutic option, and SCT still represents the only curative tool. As of this writing,

the oral, small-molecule inhibitor of *FGFR1-3,* pemigatinib (INCB054828), showed excellent efficacy in patients with *FGFR1*-rearranged myeloid/lymphoid neoplasms in interim analysis of the currently ongoing phase 2 FIGHT-203 study (NCT03011372). Among 10 evaluable patients with *FGFR1*-rearranged myeloid/lymphoid neoplasms in whom at least one previous therapy failed, 8 (80%) achieved a major cytogenetic response (including 6 patients with complete cytogenetic response) after therapy with pemigatinib for a median of 6.9 cycles.[229,230]

For patients with HES/CEL refractory to conventional therapies, the use of monoclonal antibody therapy should be considered. So far, antibodies that have been explored include those against interleukin-5 and its receptors, mepolizumab and benralizumab; and the antibody targeting CD52 antigen expressed by eosinophils, alemtuzumab. Initial safety and efficacy of mepolizumab, a humanized antibody against interleukin-5, were shown in a randomized, double-blind, placebo-controlled phase 2 trial in 85 *PDGFRα*-negative patients with HES without life-threatening complications.[231] The primary end point (reduction of the prednisone dose to ≤10 mg/day for ≥8 consecutive weeks) was achieved in 84% of the patients receiving mepolizumab (750 mg monthly intravenously) compared with 43% of the patients in the placebo group ($P < .001$). Long-term safety and efficacy of mepolizumab were confirmed in a long-term extension study in which 78 patients received mepolizumab for a median of 251 weeks (range, 4–302): 69% were still receiving mepolizumab at the end of the study, and 62% of the patients were prednisone-free without other HES treatments for 12 weeks or more.[232] A registrational, placebo controlled, phase 3 study of mepolizumab (300 mg subcutaneously monthly) to prevent flares of HES (NCT02836496) has been recently published.[233] Eligible patients with uncontrolled HES (2 or more flares of symptoms or increased eosinophils in the previous 12 months) were randomized 1:1 to mepolizumab (n = 54) vs placebo (n = 54) for 32 weeks. The primary outcome, reduction of HES flares, was significantly lower with mepolizumab: the proportion of patients experiencing 1 or more flares was 28% with mepolizumab vs 56% with placebo, $P = 0.002$). Rate of adverse events was comparable in both arms (89% vs 87% with mepolizumab vs placebo, respectively), with the most common adverse events on mepolizumab being upper respiratory track infections and extremities pain.[233] Based on these findings, FDA has approved mepolizumab for the therapy of primary HES in patients older than 12 years who had HES for 6 months or older in September 2020. It is possible that efficacy of mepolizumab in patients with steroid-refractory HES/CEL will be lower than when it is used as a steroid-sparing agent. In a trial evaluating compassionate use of mepolizumab at multiple centers, CR was 43% versus 83% in steroid-refractory versus -sensitive disease.[234] Mepolizumab is currently available on a compassionate-use basis for patients with life-threatening HES/CEL in whom other therapies failed.

Monoclonal antibody against interleukin-5 receptor, benralizumab, which is currently approved for adults with severe eosinophilic asthma, has been evaluated in a double-blind, placebo-controlled, randomized phase 2 study in 20 patients with *PDFRA*-negative HES.[235] The primary end point was a reduction of 50% or higher AEC by week 12, and it was met in 9 of 10 patients who received benralizumab vs 3 of 10 patients receiving placebo ($P = .02$). Clinical and hematologic responses with benralizumab were sustained for 48 weeks in 14 of 19 patients (74%) during the open-label phase, with a median duration of 84 weeks. Adverse events, mostly headache and elevated lactate dehydrogenase, did not limit therapy. Patients with lymphoid variant HES and those with *JAK2* mutation lacked any response to benralizumab.

Alemtuzumab is another monoclonal antibody that is used off label in patients with HES/CEL. Among 11 patients with HES/CEL (9 previously treated) prescribed alemtuzumab,[236] 10 achieved CHR (reduction of the AEC and the percentage of eosinophils in peripheral blood to normal values) and 9 had complete symptoms resolution after a median of two weeks. The median duration of CHR was short-lived (3 months), and 7 of the 10 patients with CHR experienced relapse. In a long-term follow-up study of 12 patients (9 from original report),[237] 10 achieved CHR and elimination of disease symptoms after a median of one week; this was sustained for a median duration of 66 weeks. Five patients with CHR receiving maintenance alemtuzumab for a median duration of 20 weeks (range, 1–266) had a significantly longer time to disease progression than those who were not given maintenance therapy ($P = .01$). Eleven patients eventually experienced relapse (only one was on maintenance therapy). Five of six patients achieved a second CHR for a median duration of 123 weeks after re-challenge with alemtuzumab. Alemtuzumab side effects, mostly prolonged myelosuppression and the necessity for maintenance therapy, limit its use in clinical practice.

Another agent explored in patients with *PDGFRα*-negative HES (n = 10) was a small-molecule, orally bioavailable aminobenzothiazole, dexpramipexole (150 mg orally twice daily), as a glucocorticoid-sparing agent.[238] The two primary end points were: the proportion of 50 or more patients with a decrease in the minimum effective glucocorticoid dose (MED) to maintain AEC lower than 1000/μL and control symptoms, and the MED after 12 weeks of treatment as a percentage of the MED at the start of therapy. Of 10 patients, four

Table 6–19 Diagnostic Criteria for Chronic Neutrophilic Leukemia

1. Peripheral blood white blood cell count ≥25 × 10^9/L – Segmented neutrophils plus banded neutrophils constitute ≥80% of the white blood cells – Neutrophil precursors (promyelocytes, myelocytes, metamyelocytes) constitute <10% of the white blood cells – Myeloblasts rarely observed – Monocyte count <1 × 10^9/L – No dysgranulopoiesis
2. Hypercellular bone marrow – Neutrophil granulocytes increased in percentage and number – Neutrophil maturation appears normal – Myeloblasts constitute <5% of the nucleated cells
3. Not meeting WHO criteria for *BCR-ABL1*–positive chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, or primary myelofibrosis
4. No rearrangement of *PDGFRα*, *PDGFRβ*, or *FGFR1*, and no *PCM1-JAK2* fusion
5. *CSF3R*^{T618I} or another activating *CSF3R* mutation **OR** Persistent neutrophilia (≥3 months), splenomegaly, and no identifiable cause of reactive neutrophilia including absence of a plasma cell neoplasm or, if a plasma cell neoplasm is present, demonstration of clonality of myeloid cells by cytogenetic or molecular studies

achieved 50% or higher reduction in MED, and the median ratio of MEDs at 12 versus 0 weeks was 66% (significantly reduced, $P = .03$). All adverse events were self-limited and did not lead to therapy discontinuation. In responders, BM biopsy samples showed selective absence of mature eosinophils. Dexpramipexole appears to be a promising steroid-sparing agent in patients with HES, and evaluation of its efficacy in a phase 3 clinical trial is planned.

CHRONIC NEUTROPHILIC LEUKEMIA

Chronic neutrophilic leukemia (CNL) is an extremely rare neoplasm and was first included as a distinct entity in the 2001 WHO classification system. Diagnostic criteria in 2016 reflected recent changes in the genomic landscape of CNL, endorsing strong association of the colony-stimulating factor 3 receptor (*CSF3R*) mutation with CNL (Table 6–19). The presence of activating *CSF3R* mutation (most frequently T618I) now comprises one of the five diagnostic criteria of CNL. The disease is characterized by the chronic overproduction of mature neutrophils (>80% segmented neutrophils and bands out of WBCs ≥25 × 10^9/L) and an increased number of granulocytes in the BM.

In 2013, the discovery of disease-defining oncogenic mutations in the *CSF3R* revolutionized our understanding of the pathogenesis of CNL and provided a biomarker for diagnosis as well as a potential therapeutic target.[239] Deep sequencing of coding regions of 1862 genes in patients with CNL (n = 9) and atypical CML (aCML) (n = 20) identified mutations in the *CSF3R* gene in 8 of 9 patients with CNL. Two mutational variants were identified: most were point mutations on the membrane proximal region (T618I or T615A); others were nonsense mutations leading to a premature truncation of the cytoplasmic tail of *CSF3R*. The proportion of patients with CNL/aCML harboring only membrane proximal region mutation versus compounding mutations of both was 75% and 25%, respectively. Under normal conditions, *CSF3R*, which is activated by binding its ligand granulocyte colony-stimulating factor, promotes the differentiation of granulocyte progenitor cells into neutrophils. Mutations in the membrane proximal region lead to constitutive activation of the JAK-STAT pathway, whereas truncation mutations result in ligand hypersensitivity and activation of the downstream SRC kinase pathway. Other pathways involved in neutrophilic differentiation, proliferation, and survival include nonreceptor tyrosine kinase SYK, Ras/Raf/MAP kinases, and PI3K/Akt.[240] This study revealed two major dysregulated signaling pathways in CNL and represents a proof of concept for the use of targeted therapies: JAK inhibitor ruxolitinib for membrane proximal region mutations (via JAK-STAT pathway), and tyrosine kinase inhibitor dasatinib for truncating mutations (via SRC pathway).

Studies in mice support the leukemogenic role of *CSF3R* mutations in CNL; deletion of CSFR3 in mice leads to neutropenia, and mice transplanted with *CSF3R*^{T618I}-positive hematopoietic cells develop a CNL-like phenotype, with mature granulocytosis, marrow hypercellularity, and infiltration of the spleen and liver with mature granulocytes.[241]

In another study, the coding region of *CSF3R* was sequenced in patients with clinically suspected CNL (n = 35) or aCML (n = 19), as well as 170 cases of CMML and PMF.[242] The diagnoses were reevaluated using

WHO criteria. Twelve cases of CNL were confirmed, 5 were associated with a monoclonal gammopathy-associated CNL, and 9 were confirmed as aCML. Of the 13 patients found to have the *CSF3R* mutation, 12 had WHO-defined CNL, and one had unconfirmed CNL. All mutations were found in the membrane proximal region, with T618I being the most common (10 patients). None of the cases of monoclonal gammopathy–associated CNL had *CSF3R* mutations, suggesting that patients with evidence of a plasma cell dyscrasia should not be classified as having CNL.

Clinical Features

The median age at diagnosis is around 66 years. The clinical presentation of CNL is heterogeneous, but the majority of patients are asymptomatic at diagnosis, or have nonspecific constitutional symptoms, such as fatigue, palpable splenomegaly, weight loss, easy bruising, bone pain, and night sweats. The median survival in CNL is about 24 months.[242,243] Intracranial hemorrhage is the most common cause of death, followed by leukemic transformation,[243] eventually occurring in a substantial proportion of the patients. There are no prognostic scores to predict survival of patients with CNL, but presence of *ASXL1* or *SETBP1* mutations as well as thrombocytopenia may be associated with shorter survival or blast phase.[242,244]

Diagnosis

Most patients are asymptomatic at presentation and are diagnosed after finding leukocytosis on routine blood testing. Most patients have mild anemia, and platelet counts are usually normal or slightly low. Diagnosis requires exclusion of a number of potential causes of neutrophilia, such as infections and occult malignancy, as well as other myeloid neoplasms (Table 6–19). Until the discovery of *CSF3R* mutation, the absence of *BCR-ABL1* and rearrangement of *PDGFRα*, *PDGFRβ*, and *FGFR1* were key diagnostic criteria. The presence of mostly mature neutrophils, and the notable absence of circulating blasts, monocytes, basophilia, and eosinophilia are important features of CNL that distinguish it from other myeloproliferative disorders (especially from CML). BM is hypercellular (>90% cellularity) as a result of granulocytic hyperplasia, with no dysplastic features. Unlike other MPNs, megakaryocytic hyperplasia or clusters of large atypical megakaryocytes are not seen. Most patients have normal cytogenetics.

Treatment

There is no standard treatment for CNL. HU has historically been the most frequently used agent and could control leukocytosis and splenomegaly in about 75% of the patients, with a median duration of about 12 months.[243] Second-line agents evaluated in these patients include IFN-α, cladribine, or thalidomide, with limited success in decreasing leukocytosis, but they do not possess any ability to modify the natural disease course.[243] Splenic radiation and splenectomy have been used, but splenectomy has been associated with further increases in neutrophil counts.[243] Induction chemotherapy followed by SCT has been used to treat patients in the blast phase, offering possible long-term remission in selected cases.[243,245] After *CSF3R*-mutated cells were shown to be sensitive to the JAK1/2 inhibitor ruxolitinib, this agent was evaluated in a few patients with CNL and some were encouraging, although transient responses, including hematologic, symptomatic, and molecular were observed.[246–248] The role of ruxolitinib in patients with CNL is currently under evaluation in a phase 2 study (NCT02092324). Preliminary results in 21 patients with CNL reported clinical response (defined as at least 50% improvement in counts and spleen size) in 65% of patients. Median time on study was 15.3 months with 86% of patients receiving > 6 cycles.[249]

MAST CELL DISEASE/SYSTEMIC MASTOCYTOSIS

Mast cell disease is a heterogeneous group of disorders characterized by clonal expansion of mast cells (MCs) and their excessive accumulation in various organs such as the skin, BM, gastrointestinal tract, lymph nodes, liver, and spleen. Its clinical course can vary from minimal symptoms to diffuse systemic involvement. In the revised 2016 WHO classification, mastocytosis was removed as one of the subtypes of MPN and listed as a separate major disease entity,[11] further divided into: cutaneous mastocytosis, systemic mastocytosis (SM) with subvariants of indolent SM (ISM), smoldering SM (SSM), aggressive SM (ASM), SM with an associated hematologic neoplasm (SM-AHN), and MC leukemia (MCL) (Table 6–20 through Table 6–22). SM requires the presence of one major (multifocal, dense infiltrates of ≥15 MC) and one minor or at least three minor (presence of atypical MCs/presence of KIT^{D618V} mutation/aberrant expression of CD25 with or without CD2 on MC or persistently elevated tryptase >20 μg/mL) diagnostic criteria (Table 6–22). The presence or absence of B and C findings defines SM subtype: (1) indolent SM with no B/C findings, (2) smoldering SM with B findings (higher disease burden but no organ damage), and (3) aggressive SM with C findings (organ damage by MC infiltration) as shown in Table 6–23. MCL is defined by the presence of ≥20% neoplastic MC

Table 6–20 Classification of Mastocytosis Variants

The complete diagnosis of these variants requires information regarding B (burden of disease) and C (cyto-reduction-requiring) (Table 6–21), all of which may not be available at the time of initial tissue diagnosis.
Cutaneous Mastocytosis
Urticaria pigmentosa/maculopapular cutaneous mastocytosis Diffuse cutaneous mastocytosis Mastocytoma of skin
Systemic Mastocytosis
Indolent systemic mastocytosis[a] (including the bone marrow mastocytosis subtype) Smoldering systemic mastocytosis[a] Systemic mastocytosis with an associated hematologic neoplasm[a] Aggressive systemic mastocytosis[a] Mast cell leukemia
Mast Cell Sarcoma

[a]This variant is equivalent to the previously described entity "systemic mastocytosis with an associated clonal hematologic non–mast cell lineage disease," and the terms can be used synonymously.

Table 6–21 Diagnostic Criteria for Cutaneous and Systemic Mastocytosis

Cutaneous Mastocytosis
Skin lesions, demonstrating the typical findings of urticaria pigmentosa/maculopapular cutaneous mastocytosis, diffuse cutaneous mastocytosis, or solitary mastocytoma, and typical histologic infiltrates of mast cells in a multifocal or diffuse pattern in an adequate skin biopsy[a] In addition, features/criteria sufficient to establish the diagnosis of systemic mastocytosis must be absent. There are three variants of cutaneous mastocytosis (see Table 6–20).
Systemic Mastocytosis
The diagnosis of systemic mastocytosis can be made when the major criterion and at least 1 minor criterion are present, or when ≥3 minor criteria are present.
Major Criterion
Multifocal dense infiltrates of mast cells (≥ 15 mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organ(s).
Minor Criteria
In biopsy sections of bone marrow or other extracutaneous organs: • >25% of the mast cells in the infiltrate are spindle shaped or have atypical morphology **OR** • >25% of all mast cells in bone marrow aspirate smears are immature or atypical • Detection of an activating point mutation at codon 816 of *KIT* in the bone marrow, blood, or another extracutaneous organ • Mast cells in bone marrow, blood, or another extracutaneous organ express CD25, with or without CD2, in addition to normal mast cell markers[b] • Serum total tryptase is persistently >20 ng/mL, unless there is an associated myeloid neoplasm, in which case this parameter is not valid

[a]This criterion applies to both the dense focal and the diffuse mast cell infiltrates in the biopsy.
[b]CD25 is the more sensitive marker, by both flow cytometry and immunohistochemistry.

in the BM, and mostly presents as an acute leukemia with C findings/organ damage. Interestingly, the aleukemic variant with fewer than 10% circulating MCs is more common. Advanced SM (AdvSM) is a combined term for ASM, SM-AHN, and MCL and indicates subtypes with frequent organ damage and reduced OS.

Clinical Features

Symptoms of mastocytosis reflect MC mediators release or MC organ infiltration. Vasoactive mediators (histamine, leukotrienes, prostaglandins) released from MCs can lead to itching, flushing, lightheadedness, syncope, palpitations, diarrhea, heartburn, fatigue, and headache and can be exacerbated by infections,

Table 6–22 Diagnostic Criteria for the Variants of Systemic Mastocytosis

Indolent Systemic Mastocytosis
Meets the general criteria for systemic mastocytosis No C findings[a] No evidence of an associated hematologic neoplasm Low mast cell burden Skin lesions are almost invariably present
Bone Marrow Mastocytosis
As above (indolent systemic mastocytosis), but with bone marrow involvement and no skin lesions
Smoldering Systemic Mastocytosis
Meets the general criteria for systemic mastocytosis ≥2 B findings; no C findings[a] No evidence of an associated hematologic neoplasm High mast cell burden Does not meet the criteria for mast cell leukemia
Systemic Mastocytosis With an Associated Hematologic Neoplasm
Meets the general criteria for systemic mastocytosis Meets the criteria for an associated hematologic neoplasm (ie, a myelodysplastic syndrome, myeloproliferative neoplasm, acute myeloid leukemia, lymphoma, or another hematologic neoplasm classified as a distinct entity in the WHO classification)
Aggressive Systemic Mastocytosis
Meets the general criteria for systemic mastocytosis ≥1 C finding[a] Does not meet the criteria for mast cell leukemia Skin lesions are usually absent
Mast Cell Leukemia
Meets the general criteria for systemic mastocytosis Bone marrow biopsy shows diffuse infiltration (usually dense) by atypical, immature mast cells Bone marrow aspirate smears show ≥20% mast cells In classic cases, mast cells account for ≥10% of the peripheral blood white blood cells, but the aleukemic variant (in which mast cells account for <10%) is more common Skin lesions are usually absent

[a]B and C findings indicate organ involvement without and with organ dysfunction, respectively; these findings are listed in Table 6–23.

Table 6–23 B (Burden of Disease) and C (Cytoreduction-Requiring) Findings in Symmetric Mastocytosis, Which Indicate Organ Involvement Without and With Organ Dysfunction, Respectively

B findings
• High mast cell burden (shown on bone marrow biopsy): >30% infiltration of cellularity by mast cells (focal, dense, aggregates) and serum total tryptase >200 ng/mL • Signs of dysplasia or myeloproliferation in non–mast cell lineage(s), but criteria are not met for definitive diagnosis of an associated hematologic neoplasm, with normal or only slightly abnormal blood counts • Hepatomegaly without impairment of liver function, palpable splenomegaly without hypersplenism, and/or lymphadenopathy or palpation or imaging
C findings
• Bone marrow dysfunction caused by neoplastic mast cell infiltration, manifested by cytopenia: absolute neutrophil count $<1.0 \times 10^9$/L, hemoglobin level <10 g/dL, and/or platelet count $<100 \times 10^9$/L • Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension • Skeletal involvement, with large osteolytic lesions with or without pathologic fractures (pathologic fractures caused by osteoporosis do not qualify as a C finding) • Palpable splenomegaly with hypersplenism • Malabsorption with weight loss caused by gastrointestinal mast cell infiltrates

alcohol, exercise, and medications. Common sites of organ infiltration include the skin and gastrointestinal tract. Urticaria pigmentosa is the most common skin manifestation, characterized by reddish-brown macules and papules. Scratching of affected skin characteristically leads to development of urticaria and erythema (Darier sign). Gastrointestinal involvement can present as chronic diarrhea, steatorrhea, malabsorption, nausea, vomiting, and ascites. Cardiovascular symptoms include dizziness, palpitations, and anaphylaxis with hypotension and syncopal events. Anemia is the most common hematologic abnormality caused by BM infiltration, and peripheral eosinophilia is seen in around 20% of the patients. Bone and muscle pain and bone fractures can also occur.

Diagnosis

Diagnosis relies primarily on the identification of neoplastic MCs in various organs (see Table 6–11). Bone marrow examination is imperative for diagnosis of SM, because most patients would have underlying BM involvement. Figures 6–14 and 6–15 illustrate a case of SM detected in the BM. Neoplastic MCs are characteristically spindle shaped and present in multifocal aggregates (≥15 MCs in aggregates) and, unlike normal MCs, neoplastic MCs express the surface marker CD25, with or without CD2. Serum tryptase and urinary histamine are generally increased. One of the most reliable indicators of progressive SM is a steadily increasing serum level of tryptase. Using a sensitive polymerase chain reaction–based assay, a point mutation, resulting in the substitution of valine for aspartate at codon 816 (D816V) in the TK domain of the KIT receptor (*KIT*^{D816V} mutation), is noted in more than 90% of patients with SM.[250] KIT is a TK receptor encoded by the *c-KIT* gene located on chromosome 4q12 in humans, and *KIT*^{D816V} is located in exon 17. Binding of stem cell factor to KIT leads to receptor dimerization and phosphorylation of the downstream signaling molecules,[251] playing an important role in normal hematopoiesis. Furitsu et al first showed that KIT was constitutively activated and expressed in the absence of stem cell factor in a MC cell line derived from a patient with MC leukemia.[252]

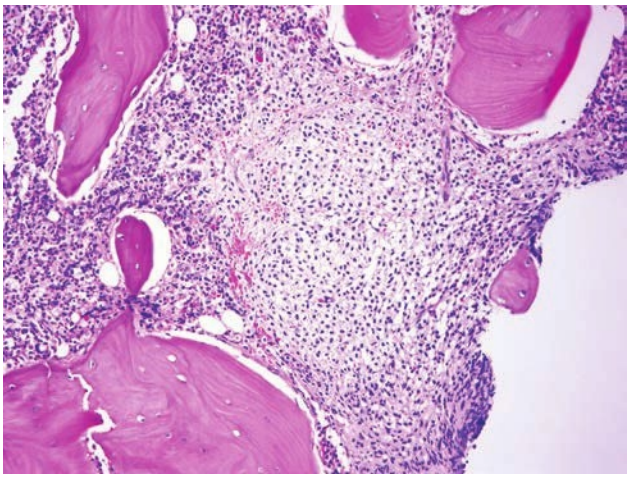


FIGURE 6–14 Bone marrow biopsy from a patient with SM demonstrates total focal replacement of the normal cellular elements by mast cells (×100). Immunohistochemical staining performed on this specimen demonstrated that the neoplastic mast cells aberrantly expressed CD2 and CD25.

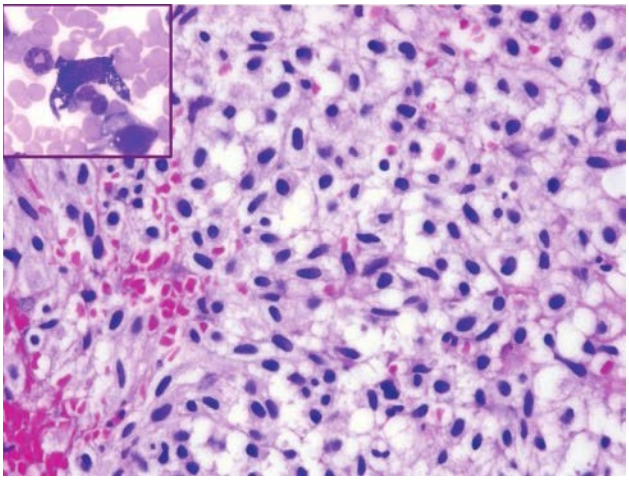


FIGURE 6–15 In SM, in the bone marrow biopsy, mast cells tend to have abundant, colorless cytoplasm and contain elongated-to-oval nuclei (×400). In the bone marrow aspirate smear, the mast cells increase in number and size and attain a spindle shape (inset; original magnification ×400).

Molecular analysis not only led to the discovery of *KIT*^{D816V} as a major oncogenic driver of MC differentiation, proliferation, and survival, but also enhanced our prognostic abilities for this disease. A few prognostic scores were developed and identified the negative prognostic impact of increased age (>60 years), markers of advanced disease (eg, anemia, thrombocytopenia, leukocytosis, high tryptase levels, splenomegaly, BM blasts >5%), poor risk karyotype (eg, monosomy 7 or complex), and additional molecular mutations, especially the presence and number of non-*KIT* mutations: *SRSF2/ASXL1/RUNX1* (S/A/R), or *EZH2, CBL, DNMT3A*.[253–261] The mutation-adjusted risk score for AdvSM (MARS) (N = 383) identified three risk groups with distinct OS (not reached, median 3.9, and 1.9 years, respectively) based on the presence of age older than 60 years, hemoglobin lower than 10 g/dL, platelets <100 × 10^9/L, and one or two S/A/R mutations.[254] The International Prognostic Scoring System for Mastocytosis (IPSM) (N = 1639) stratified patients with AdvSM as well as ISM into subgroups with different

outcomes based on the following risk factors: (1) ISM: age 60 years or older, alkaline phosphatase 100 U/L or more; and (2) AdvSM: age 60 years or older, tryptase level 125 ng/mL or higher, leukocyte count ≥16 × 10^9/L, hemoglobin 11 g/dL or lower, platelets ≤100 × 10^9/L, and absence of skin involvement.[253]

Although ISM has no impact on life expectancy, patients with AdvSM have significantly shortened OS, estimated at about 4 years for ASM, 2 years for SM-AHD, and less than 6 months for patients with MCL.[262,263]

Excellent guidance for diagnosis, symptom management, prognostic evaluation, and therapy of SM is provided in the recent NCCN guidelines for systemic mastocytosis.[264]

Treatment

Treatment of the most common form of noncutaneous SM, ISM, is focused exclusively on symptom relief, whereas reduction of MC burden and prevention of organ damage are the goals in treating AdvSM. All patients should avoid factors that can trigger MC degranulation, such as emotional stress, cold exposure, alcohol use, strenuous exercise, and the use of nonsteroidal antiinflammatory drugs. Symptomatic treatments include the use of oral antihistamines and MC stabilizers. Both sedating and nonsedating H1 antihistamines can be used to alleviate pruritus and itching. Cetirizine has been shown to be equivalent to hydroxyzine in relieving pruritus in patients with chronic urticaria, with the advantage that it does not cause sedation and thus is usually initiated first.[265] Higher doses of sedating antihistamines could be used for patients with severe symptoms. Because both H1 and H2 receptors are present in the skin (85% cutaneous histamine receptors are H1 and 15% are H2), the addition of an H2 blocker should be considered for patients who do not respond to H1 antihistamines alone.[265] Cromolyn sodium is beneficial in patients with gastrointestinal symptoms (eg, diarrhea, vomiting, abdominal pain).[266] Short courses of prednisone can be considered for patients with severe symptoms, especially malabsorption and ascites. Aspirin can cause MC degranulation but may help with flushing. Therefore, patients should be given H1 and H2 antihistamine therapy before starting aspirin therapy.[266] Patients with a history of anaphylaxis or cardiovascular collapse should carry an epinephrine pen. Omalizumab (a humanized murine monoclonal antibody that inhibits immunoglobulin E binding to MCs and basophils) is effective in patients with SM and syncopal episodes and skin manifestations.[267] Patients with osteoporosis might be treated with bisphosphonates or the anti-RANKL monoclonal antibody, denosumab.

Cytoreductive therapies (IFN-α and cladribine) are used for severe disease symptoms and in the case of organ damage. IFN-α plays an especially important role in pregnant patients or in patients with slowly progressive disease. In a multicenter trial in 20 patients with SM, IFN-α-2b led to a partial or minor response in 13 patients.[268] The combination of IFN-α-2b with prednisone has also been studied. Cladribine was the most frequently evaluated chemotherapeutic agent in AdvSM, especially in patients requiring rapid debulking of disease, and can induce overall RR in as much as 72% of patients.[269,270] Stem cell transplantation should be considered in patients with AdvSM and acute MCL at remission.[271]

Mutation in *KIT*^{D816V} is an attractive target because of its high frequency in patients with SM. It confers primary resistance against the tyrosine kinase inhibitor imatinib, which is approved by the FDA for patients with AdvSM without the *KIT*^{D816V} mutation or unknown *KIT* mutation status (at 400 mg daily) and for AdvSM associated with eosinophilia (starting dose 100 mg daily with dose escalation to 400 mg daily as needed). An important subgroup of patients with SM and imatinib responsiveness is the subset with the *FIP1L1-PDGFRα* mutation. In a study by Pardanani et al, 56% of the patients with SM and eosinophilia had the *FIP1L1-PDGFRα* fusion oncogene,[272] and all responded to imatinib (100 mg daily).

Midostaurin, an oral multikinase inhibitor including *KIT*,^{D816V} was approved by the FDA in April 2017 for patients with AdvSM irrespective of *KIT* mutational status. In an open-label study of 116 patients with AdvSM (≥1 measurable C finding), 100 mg of midostaurin orally twice daily resulted in an overall RR of 60% (45% with a major response, eg, complete resolution of ≥1 C finding).[273] Responses were similar across all subtypes (75% for ASM, 58% SM-AHD, 50% for MCL), regardless of *KIT* mutation or number of previous therapies. Symptoms and QOL were significantly improved with midostaurin. The median OS and PFS were the longest in patients with ASM (not reached and 29 months, respectively) than in patients with SM-AHN (21 and 11 months, respectively) and MCL (9 and 11 months, respectively). Additionally, 40% (8/20) and 100% (4/4) patients achieved RBCs and platelets transfusion independence. Therapy with midostaurin was associated with a high incidence of adverse events. The most common AEs included nausea (79% all grades), vomiting (66%), and diarrhea (54%); grade ≥3 AEs occurred in fewer than 10% of patients, but prophylactic antiemetics were recommended before each dose. Grade ≥3 anemia, thrombocytopenia, and neutropenia (new or worsening) occurred in 41%, 29%, and 24% of patients, respectively, and were more common in patients with preexisting cytopenias. Long-term follow-up (median

duration of 10 years) confirmed a similar spectrum of side effects without a new unexpected toxicity, and durable activity with the ORR of 69% (50% major response), 50% or higher reduction in MC burden and serum tryptase in 68% and 46% of the patients, respectively. OS for ASM, SM-SHN, and MCL patients was not reached, 40 months, and 18.5 months, respectively.[274] The negative impact of *ASXL1/SRSF2/RUNX1* mutations and the lack of 25% or more reduction in the KIT^{D816V} allele burden during therapy with midostaurin was shown on ORR, treatment duration, and OS.[275]

Another effective agent in SM is the highly selective TKI inhibitor, avapritinib (BLU-285), with an approximately tenfold higher potency for KIT^{D816V} inhibition than midostaurin, which has just received FDA approval in June 2021 for aggressive SM with platelets > 50×10e9/L at a dose of 200 mg daily. The approval was based on results from phase 1 (EXPLORER, NCT02561988) and phase 2 (PATHFINDER, NCT03580655) trails showing an objective response rate of 57% in all 53 evaluable patients in both trials with a median duration of response of 38.3 months (95% CI, 19-NE).[276,278] A phase 1 clinical trial of avapritinib in AdvSM with at least 1 C finding (EXPLORER trial) began in 2016. Preliminary data were reported on 52 patients treated in the initial escalation phase (32 patients), exploring 7 doses ranging from 30 mg to 400 mg once daily, and in the expansion phase (20 patients) on 300 mg daily. Six patients (12%) did not carry *KIT* mutation. Overall RR was noticed in 83% of patients, including 50% or higher BM MC reduction in 33% (undetectable BM MCs in 58%), reduction of serum tryptase to less than 20 µg/L in 66%, and complete resolution of splenomegaly in 47% of the patients. Decrease in 50% or more of BM KIT^{D861V} allele burden was noticed in 88% of the patients. Treatment-related grade 3 or 4 AEs were noticed in 28 (54%) patients. The most common AEs, most of which were mild, were periorbital edema (62%), fatigue (31%), and nausea (33%). Concerning AEs included ascites (10%), pleural effusion (10%), and cognitive impairment, eg, confusion and short-term memory effects (19%). Grade ≥3 anemia and thrombocytopenia occurred in 15% and 17% of the patients, respectively.[277] Updated results on 80 patients (48 evaluable for response) showed 77% overall RR; with 50% or higher BM MC reduction, 50% or higher reduction of serum tryptase, and 35% or higher reduction in spleen size by imaging were seen in 93%, 99%, and 80% of patients, respectively. Median time to initial response was two cycles, and responses deepened over time. Median OS was not reached for any subtype of AdvSM. Nonhematologic AEs were observed at similar rates over a long time, with grade ≥3 anemia and thrombocytopenia at 29% and 26%, respectively. Importantly, these responses were noticed in patients regardless of previous exposure to midostaurin (ORR of 60% and 85% with and without previous midostaurin, respectively).[278] Phase 2 study PATHFINDER enrolled 62 patients with advSM at the 200 mg daily dose. 81% of patients had SM-AHN, 13% had MCL and 6% had ASM. Interim results in 32 evaluable patients showed overall response of 75% with a median time to response of 2 months. Median OS was not reached at the time of the analysis. The most common adverse events included peripheral (50%) and periorbital (35%) edema and thrombocytopenia (32%). Treatment discontinuation due to treatment related AE was in 5% of patients.

Avapritinib is also being evaluated in symptomatic patients with ISM and SSM in a randomized, placebo-controlled registration trial, PIONEER, and part 1, the dose-finding phase (25 mg, 50 mg, and 100 mg daily), has already completed enrollment. Preliminary data were reported on 39 patients (10 patients in each avapritinib dose cohort and 9 patients in the placebo cohort). Across all avapritinib dose cohorts, mean percent reductions in serum tryptase occurred rapidly during cycle 1, with 48%, 67%, and 62% reduction on 25 mg, 50 mg, and 100 mg of avapritinib per day at 12 weeks. The placebo cohort showed no change in serum tryptase at 12 weeks (0.39%). All tested dose levels of avapritinib were well tolerated, with 5 patients (16.7%) having grade 3 AEs (including one cognitive effect on 100 mg). The recommended phase 2 dose for the next phase was 25 mg daily.[279] Updated data showed a statistically significant mean decline in symptoms (30% vs 3%), improved QOL, and reduction of MC burden, serum tryptase level, and *KIT* D816V allele burden at 16 weeks in patients treated with avapritinib versus those who received placebo.[280]

Masitinib, an inhibitor of pathways involved in MC pathogenesis (eg, KIT, FLN, and LYN), was evaluated in patients with indolent or smoldering SM in a phase 3 randomized, placebo-controlled trial (N = 135, 1:1 randomization). The response rate measured by improvement of symptoms (pruritus, flushes, depression, asthenia) was 18.7% taking masitinib versus 7.4% taking placebo. Most AEs were mild and included diarrhea, rash, or asthenia.[281] Masitinib has not yet been tested clinically in patients with AdvSM.

MD ANDERSON PRACTICE TIPS

- **Polycythemia Vera:** Risk stratify patients by age and thrombosis history. The goal is to keep the hematocrit (Hct) under 45% at all times. Monitor leukocyte counts and symptoms and watch for signs of resistance to or intolerance of hydroxyurea (HU). Aspirin is generally recommended. Interferons (IFNs) are a reasonable alternative to HU for first-line therapy, particularly in very young patients. Ruxolitinib is the cytoreductive drug of choice after failure of HU.
- **Essential Thrombocythemia:** Risk stratify patients by the revised IPSET model and consider observation for "very-low-risk" patients. Low-, intermediate-, and high-risk patients should receive aspirin unless it is contraindicated by acquired von Willebrand disease or extreme thrombocytosis (>1.5 million platelets/μL). Some patients may benefit from twice-daily administration of aspirin. Hydroxyurea is generally the drug of choice when cytoreductive therapy is indicated; IFNs are acceptable as well and may be preferred in very young patients.
- **Myelofibrosis:** Pre-PMF is managed similarly to ET but carries an inferior prognosis. A number of models exist for risk stratification of overt PMF; one that incorporates both clinical and genomic risk factors, eg, MIPSS70/MIPSS70 plus v2.0 is recommended for use in transplantation-age patients. Use the MYSEC-PM for patients with post-V/ET MF. In general, consider allogeneic stem cell transplantation in patients whose predicted life expectancy is less than 5 years. Ruxolitinib is the mainstay of therapy and confers a survival benefit in patients with intermediate-2/high-risk disease. Fedratinib is a reasonable choice after failure of ruxolitinib. Patients with anemia as their main or only disease manifestation may not need JAK inhibition and could be better served by anemia-directed therapies.
- **Chronic Eosinophilic Disorders/Hypereosinophilic Syndromes:** Rule out secondary causes and evaluate for organ damage. Pay particular attention to possible heart involvement and use steroids up to 1 mg/kg with any life-threatening manifestation. Consider using empiric therapy for *Strongyloides*, especially when using steroids. Evaluate for clonality and identify *PDGRA/B* rearrangements because these are sensitive to imatinib. Responses are high, but lifelong maintenance may be necessary. For all other patients, use steroids as first-line treatment but try to find a steroid-sparing agent for a long-term benefit. Consider clinical trials with novel agents for patients with *FGFR1* rearrangement and utilize stem cell transplantation.
- **Chronic Neutrophilic Leukemia:** Rule out secondary causes and confirm the presence of *CSF3R* mutation. There are no prognostic models for survival, but patients with advanced clinical features and multiple molecular abnormalities have inferior outcomes. Disease often progresses to acute leukemia. Use cytoreduction to control counts, such as HU or IFN. Consider clinical trials (ruxolitinib) when possible. Chemotherapy and stem cell transplantation is reserved for aggressive course and blast phase.
- **Systemic Mastocytosis:** It is important to distinguish between cutaneous mastocytosis and systemic mastocytosis (SM) by performing a BM evaluation. Test for KIT^{D816V} mutation and measure tryptase. Once SM is confirmed, patients need to be evaluated for the presence of B and C findings, indicating indolent versus aggressive SM. Treat symptoms and advise patients to avoid triggers. Aggressive SM has limited life expectancy, and patients experience various organ involvements. Monitor for the presence of advanced features/molecular mutations that suggest inferior outcome. Use of kinase inhibitors, midostaurin, or avapritinib in clinical trials, is recommended. Chemotherapy, such as a cladribine-based regimen, has a role in aggressive mast cell leukemia and refractory disease. Stem cell transplantation shall be considered in all patients with aggressive disease.

ACKNOWLEDGEMENT

The authors thank Helen Chifotides, PhD, for excellent scientific editing of the chapter.

REFERENCES

1. Dameshek W. Some speculations on the myeloproliferative syndromes. *Blood*. 1951;6(4):372-375.
2. Baxter EJ, Scott LM, Campbell PJ, et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. *Lancet*. 2005;365(9464):1054-1061.
3. James C, Ugo V, Le Couedic JP, et al. A unique clonal *JAK2* mutation leading to constitutive signalling causes polycythaemia vera. *Nature*. 2005;434(7037):1144-1148.
4. Kralovics R, Passamonti F, Buser AS, et al. A gain-of-function mutation of *JAK2* in myeloproliferative disorders. *N Engl J Med*. 2005;352(17):1779-1790.
5. Levine RL, Wadleigh M, Cools J, et al. Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. *Cancer Cell*. 2005;7(4):387-397.
6. Nagata H, Worobec AS, Oh CK, et al. Identification of a point mutation in the catalytic domain of the protooncogene c-KIT in peripheral blood mononuclear cells of patients who have mastocytosis with an associated hematologic disorder. *Proc Natl Acad Sci U S A*. 1995;92(23):10560-10564.
7. Pikman Y, Lee BH, Mercher T, et al. *MPL*W515L is a novel somatic activating mutation in myelofibrosis with myeloid metaplasia. *PLoS Med*. 2006;3(7):e270.
8. Pardanani AD, Levine RL, Lasho T, et al. *MPL*515 mutations in myeloproliferative and other myeloid disorders: a study of 1182 patients. *Blood*. 2006;108(10): 3472-3476.
9. Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic mutations of calreticulin in myeloproliferative neoplasms. *N Engl J Med*. 2013;369(25):2379-2390.
10. Nangalia J, Massie CE, Baxter EJ, et al. Somatic *CALR* mutations in myeloproliferative neoplasms with Nonmutated *JAK2*. *N Engl J Med*. 2013;369(25):2391-2405.
11. Arber DA, Orazi A, Hasserjian R, et al. The 2016 Revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391-2405.
12. Titmarsh GJ, Duncombe AS, McMullin AF, et al. How common are myeloproliferative neoplasms? A systematic review and meta-analysis. *Am J Hematol*. 2014;89(6):581-587.
13. Mehta J, Wang H, Iqbal SU, Mesa R. Epidemiology of Myeloproliferative Neoplasms in the United States. *Leuk Lymphoma*. 2014;55(3):595-600.
14. Finazzi G, Caruso V, Marchioli R, et al. Acute leukemia in polycythemia vera: an analysis of 1,638 patients enrolled in a prospective observational study. *Blood*. 2005;105(7):2664-2670.
15. Tefferi A, Rumi E, Finazzi G, et al. Survival and prognosis among 1545 patients with contemporary polycythemia vera: an international study. *Leukemia*. 2013;27(9):1874-1881.
16. Tefferi A, Guglielmelli P, Larson DR, et al. Long-term survival and blast transformation in molecularly annotated essential thrombocythemia, polycythemia vera, and myelofibrosis. *Blood*. 2014;124(16):2507-2513.
17. Mullally A, Lane SW, Ball B, et al. Physiological *JAK2*V617F expression causes a lethal myeloproliferative neoplasm with differential effects on hematopoietic stem and progenitor cells. *Cancer Cell*. 2010;17(6):584-596.
18. Scott LM, Tong W, Levine RL, et al. *JAK2* exon 12 mutations in polycythemia vera and idiopathic erythrocytosis. *N Engl J Med*. 2007;356(5):459-468.
19. Patel AB, Franzini A, Leroy E, et al. *JAK2* ex13indel drives oncogenic transformation and is associated with chronic eosinophilic leukemia and polycythemia vera. *Blood*. 2019;139(26):2388-2398.
20. Lasho TL, Pardanani A, Tefferi A, et al. *LNK* mutations in JAK2 mutation-negative erythrocytosis. *N Engl J Med*. 2010;363(12):1189-1190.
21. Vannucchi AM. How I treat polycythemia vera. *Blood*. 2014;124(22):3212-3220.
22. Mesa RA, Niblack J, Wadleigh M, et al. The burden of fatigue and quality of life in Myeloproliferative Disorders (MPDs): an international internet-based survey of 1179 MPD patients. *Cell*. 2007;109(1):68-76.
23. Wasserman LR. The treatment of polycythemia vera. *Semin Hematol*. 1976;13(1):57-78.
24. Gruppo Italiano Studio Policitemia. Polycythemia vera: the natural history of 1,213 patients followed for 20 years. *Ann Intern Med*. 1995;123(9):656-664.
25. Barbui T, Carobbio A, Rumi E, et al. In contemporary patients with polycythemia vera, rates of thrombosis and risk factors delineate a new clinical epidemiology. *Blood*. 2014;124(19):3021-3023.
26. Marchioli R, Finazzi G, Landolfi R, et al. Vascular and neoplastic risk in a large cohort of patients with polycythemia vera. *J Clin Oncol*. 2005;23(10):2224-2232.
27. Berk PD, Goldberg JD, Donovan PB, et al. Therapeutic recommendations in polycythemia vera based on polycythemia vera study group protocols. *Semin Hematol*. 1986;23(2):132-143.
28. De Stefano V, Teofili L, Leone G, et al. Spontaneous erythroid colony formation as the clue to an underlying myeloproliferative disorder in patients with Budd-Chiari syndrome or portal vein thrombosis. *Semin Thromb Hemost*. 1997;23(5):411-418.
29. Kiladjian JJ, Cervantes F, Leebeek FW, et al. The impact of *JAK2* and *MPL* mutations on diagnosis and prognosis of splanchnic vein thrombosis: a report on 241 cases. *Blood*. 2008;111(10):4922-4929.
30. Landolfi R, Di Gennaro L, Barbui T, et al. Leukocytosis as a major thrombotic risk factor in patients with polycythemia vera. *Blood*. 2007;109(6):2446-2452.
31. Barbui T, Masciulli A, Rosa M, et al. White blood cell counts and thrombosis in polycythemia vera: a subanalysis of the CYTO-PV study. *Blood*. 2015;126(4):560-561.
32. Passamonti F, Rumi E, Pietra D, et al. A prospective study of 338 patients with polycythemia vera: the impact of JAK2 (V617F) allele burden and leukocytosis on fibrotic or leukemic disease transformation and vascular complications. *Leukemia*. 2010;24(9):1574-1579.
33. Ronner L, Podoltsev N, Gotlib J, et al. Persistent leukocytosis in polycythemia vera is associated with disease evolution but not thrombosis. *Blood*. 2020;135(19):1969-1703.
34. Cerquozzi S, Tefferi A. Blast transformation and fibrotic progression in polycythemia vera and essential thrombocythemia: a literature review of incidence and risk factors. *Blood Cancer J*. 2015;5(11):e366.
35. Barosi G, Mesa RA, Thiele J, et al. Proposed criteria for the diagnosis of post-polycythemia vera and post-essential thrombocythemia myelofibrosis: a consensus statement from the International Working Group for Myelofibrosis Research and Treatment. *Leukemia*. 2008;22(2):437-438.
36. Passamonti F, Giorgino T, Mora B, et al. A clinical-molecular prognostic model to predict survival in patients with post polycythemia vera and post essential thrombocythemia myelofibrosis. *Leukemia*. 2017;31(12):2726-2731.
37. Kiladjian J-J, Chevret S, Dosquet C, et al. Treatment of polycythemia vera with hydroxyurea and pipobroman: Final results of a randomized trial initiated in 1980. *J Clin Oncol*. 2011;29(29):3907-3913.
38. Björkholm M, Derolf AR, Hultcrantz M, et al. Treatment-related risk factors for transformation to acute myeloid leukemia and myelodysplastic syndromes in myeloproliferative neoplasms. *J Clin Oncol*. 2011;29(17):2410-2415.
39. Tefferi A, Lasho TL, Guglielmelli P, et al. Targeted deep sequencing in polycythemia vera and essential thrombocythemia. *Blood*. 2016;1(1):21-30.

40. Tefferi A, Guglielmelli P, Lasho TL, et al. Mutation-enhanced international prognostic systems for essential thrombocythemia and polycythemia vera. *Br J Haematol.* 2020;189(2):291-302.
41. Barbui T, Thiele J, Gisslinger H, et al. Masked Polycythemia Vera (mPV): results of an international study. *Am J Hematol.* 2014;19(1):52-54.
42. Barbui T, Thiele J, Carobbio A, et al. Masked polycythemia vera diagnosed according to WHO and BCSH classification. *Am J Hematol*. 2014;89(2):199-202.
43. Lussana F, Carobbio A, Randi ML, et al. A lower intensity of treatment may underlie the increased risk of thrombosis in young patients with masked polycythaemia vera. *Br J Haematol*. 2014;167(4):541-546.
44. Barbui T, Thiele J, Carobbio A, et al. Discriminating between essential thrombocythemia and masked polycythemia vera in *JAK2* mutated patients. *Am J Hematol*. 2014;89(6):588-590.
45. Spivak JL, Silver RT. The revised World Health Organization diagnostic criteria for polycythemia vera, essential thrombocytosis, and primary myelofibrosis: an alternative proposal. *Blood*. 2008;112(2):231-239.
46. Takahashi K, Patel KP, Kantarjian H, et al. *JAK2* p.V617F detection and allele burden measurement in peripheral blood and bone marrow aspirates in patients with myeloproliferative neoplasms. *Blood*. 2013;122(23):3784-3786.
47. Barbui T, Tefferi A, Vannucchi AM, et al. Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management recommendations from European LeukemiaNet. *Leukemia*. 2018;32(5):1057-1069.
48. Marchioli R, Finazzi G, Specchia G, et al. Cardiovascular events and intensity of treatment in polycythemia vera. *N Engl J Med*. 2013;368(1):22-33.
49. Mesa RA, Jamieson C, Bhatia R, et al. NCCN Guidelines Insights: Myeloproliferative Neoplasms, Version 2.2018. *J Nat Compr Canc Netw*. 2017;15(10):1193-1207.
50. Ginzburg YZ, Feola M, Zimran E, et al. Dysregulated iron metabolism in polycythemia vera: etiology and consequences. *Leukemia*. 2018;32:2105-2116.
51. Landolfi R, Ciabattoni G, Patrignani P, et al. Increased thromboxane biosynthesis in patients with polycythemia vera: evidence for aspirin-suppressible platelet activation *in vivo*. *Blood*. 1992;80(8):1965-1971.
52. Landolfi R, Marchioli R, Kutti J, et al. Efficacy and safety of low-dose aspirin in polycythemia vera. *N Engl J Med*. 2004; 350(2):114-124.
53. Kiladjian JJ, Cassinat B, Chevret S, et al. Pegylated interferon-alfa-2a induces complete hematologic and molecular responses with low toxicity in polycythemia vera. *Blood*. 2008;112(8):3065-3072.
54. Quintas-Cardama A, Kantarjian H, Manshouri T, et al. Pegylated interferon alfa-2a yields high rates of hematologic and molecular response in patients with advanced essential thrombocythemia and polycythemia vera. *J Clin Oncol*. 2009;27(32):5418-5424.
55. Mascarenhas J, Kosiorek HE, Prchal JT, et al. Results of the Myeloproliferative Neoplasms—Research Consortium (MPN-RC) 112 randomized trial of pegylated interferon alfa-2a (PEG) versus hydroxyurea (HU) therapy for the treatment of high risk polycythemia vera (PV) and high risk essential thrombocythemia (ET). *Blood*. 2018;132(suppl 1):abstract 577.
56. Barosi G, Mesa R, Finazzi G, et al. Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project. *Blood*. 2013;121(23):4778-4781.
57. Masarova L, Patel KP, Newberry KJ, et al. Pegylated interferon alfa-2a in patients with essential thrombocythaemia or polycythaemia vera: a *post-hoc*, median 83 month follow-up of an open-label, phase 2 trial. *Lancet Haematol*. 2017;4(4):e165-e175.
58. Gisslinger H, Klade C, Georgiev P, et al. Ropeginterferon alfa-2b versus standard therapy for polycythaemia vera (PROUD-PV and CONTINUATION-PV): a randomised, non-inferiority, phase 3 trial and its extension study. *Lancet Haematol.* 2020;7(3):e196-e208.
59. Barosi G, Birgegard G, Finazzi G, et al. A unified definition of clinical resistance and intolerance to hydroxycarbamide in polycythaemia vera and primary myelofibrosis: results of a European LeukemiaNet (ELN) consensus process. *Br J Haematol*. 2010;148(6):961-963.
60. Rambaldi A, Iurlo A, Vannucchi AM, et al. Safety and efficacy of the maximum tolerated dose of givinostat in polycythemia vera: a two-part phase Ib/II study. *Leukemia*. 2020;34(8):2234-2237.
61. Vannucchi AM, Kiladjian JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. *N Engl J Med*. 2015;372(5):426-435.
62. Scherber R, Dueck AC, Johansson P, et al. The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF): international prospective validation and reliability trial in 402 patients. *Blood*. 2011;118(2):401-408.
63. Passamonti F, Griesshammer M, Palandri F, et al. Ruxolitinib for the treatment of inadequately controlled polycythaemia vera without splenomegaly (RESPONSE-2): a randomised, open-label, phase 3b study. *Lancet Oncol*. 2017;18(1):88-99.
64. Kiladjian J-J, Zachee P, Hino M, et al. Long-term efficacy and safety of ruxolitinib versus best available therapy in polycythemia vera (RESPONSE): 5-year follow up of a phase 3 study. *Lancet Haematol.* 2020;7(3):e226-e237.
65. Masciulli A, Ferrari A, Carobbio A, et al. Ruxolitinib for the prevention of thrombosis in polycythemia vera: a systematic review and meta-analysis. *Blood Adv.* 2020;4(2):380-386.
66. Yacoub A, Mascarenhas J, Kosiorek H, et al. Pegylated interferon alfa-2a for polycythemia vera or essential thrombocythemia resistant or intolerant to hydroxyurea. *Blood*. 2019;134(18):1498-1509.
67. Alvarez-Larrán A, Pereira A, Cervantes F, et al. Assessment and prognostic value of the European LeukemiaNet criteria for clinicohematologic response, resistance, and intolerance to hydroxyurea in polycythemia vera. *Blood*. 2012;119(6):1363-1369.
68. Alvarez-Larrán A, Kerguelen A, Hernández-Boluda JC, et al. Frequency and prognostic value of resistance/intolerance to hydroxycarbamide in 890 patients with polycythaemia vera. *Br J Haematol*. 2016;172(5):786-793.
69. Nakatake M, Monte-Mor B, Debili M, et al. JAK2(V617F) negatively regulates p53 stabilization by enhancing MDM2 via La expression in myeloproliferative neoplasms. *Oncogene*. 2012;31(10):1323-1333.
70. Mascarenhas J, Lu M, Kosiorek H, et al. Oral idasanutlin in patients with polycythemia vera. *Blood.* 2019;134(6):525-533.
71. Alvarez-Larrán A, Perez-Encinas M, Ferrer-Marin F, et al. Risk of thrombosis according to need of phlebotomies in patients with polycythemia vera treated with hydroxyurea. *Haematologica*. 2017;102(1):103-109.
72. Barbui T, Carobbio A, Ghirardi A, et al. No correlation of intensity of phlebotomy regimen with risk of thrombosis in polycythemia vera: evidence from European collaboration on low-dose aspirin in polycythemia vera and cytoreductive therapy in polycythemia vera clinical trials. *Haematologica.* 2017;102(6):e219-e221.
73. Passamonti F, Rumi E, Pungolino E, et al. Life expectancy and prognostic factors for survival in patients with polycythemia vera and essential thrombocythemia. *Am J Med.* 2004;117(10):755-761.
74. Beer PA, Campbell PJ, Scott LM, et al. *MPL* mutations in myeloproliferative disorders: analysis of the PT-1 cohort. *Blood*. 2008;112(1):141-149.

75. Kittur J, Knudson RA, Lasho TL, et al. Clinical correlates of *JAK2*V617F allele burden in essential thrombocythemia. *Cancer*. 2007;109(11):2279-2284.
76. Ortmann CA, Kent DG, Nangalia J, et al. Effect of mutation order on myeloproliferative neoplasms. *N Engl J Med*. 2015;372(7):601-612.
77. Rumi E, Pietra D, Ferretti V, et al. *JAK2* or *CALR* mutation status defines subtypes of essential thrombocythemia with substantially different clinical course and outcomes. *Blood*. 2014;123(10):1544-1551.
78. Tefferi A, Wassie EA, Lasho TL, et al. Calreticulin mutations and long-term survival in essential thrombocythemia. *Leukemia*. 2014;28(12):2300-2303.
79. Gangat N, Wassie EA, Lasho TL, et al. Mutations and thrombosis in essential thrombocythemia: prognostic interaction with age and thrombosis history. *Eur J Haematol*. 2015;94(1):31-36.
80. Elf S, Abdelfattah NS, Chen E, et al. Mutant calreticulin requires both its mutant C-terminus and the thrombopoietin receptor for oncogenic transformation. *Cancer Discov*. 2016;6(4):368-381.
81. Elf S, Abdelfattah NS, Baral AJ, et al. Defining the requirements for the pathogenic interaction between mutant calreticulin and MPL in MPN. *Blood*. 2018;131(7):782-786.
82. Marty C, Pecquet C, Nivarthi H, et al. Calreticulin mutants in mice induce an MPL-dependent thrombocytosis with frequent progression to myelofibrosis. *Blood*. 2016;127(10):1317-1324.
83. Chachoua I, Pecquet C, El-Khoury M, et al. Thrombopoietin receptor activation by myeloproliferative neoplasm associated calreticulin mutants. *Blood*. 2016;127(10):1325-1335.
84. Nivarthi H, Cleary C, Kubesova B, et al. Thrombopoietin receptor is required for the oncogenic function of CALR mutants. *Leukemia*. 2016;30(8):1759-1763.
85. Araki M, Yang Y, Masubuchi N, et al. Activation of the thrombopoietin receptor by mutant calreticulin in *CALR*-mutant myeloproliferative neoplasms. *Blood*. 2016;127(10):1307-1316.
86. Pecquet C, Chachoua I, Roy A, et al. Calreticulin mutants as oncogenic rogue chaperones for TpoR and traffic-defective pathogenic TpoR mutants. *Blood*. 2019;133(25):2669-2681.
87. Elala YC, Lasho TL, Gangat N, et al. Calreticulin variant stratified driver mutational status and prognosis in essential thrombocythemia. *Am J Hematol*. 2016;91(5):503-506.
88. Pietra D, Rumi E, Ferretti VV, et al. Differential clinical effects of different mutation subtypes in *CALR*-mutant myeloproliferative neoplasms. *Leukemia*. 2016;30(2):431-438.
89. Tefferi A, Wassie EA, Gugielmelli P, et al. Type 1 versus type 2 calreticulin mutations in essential thrombocythemia: a collaborative study of 1027 patients. *Am J Hematol*. 2014;89(8):E121-124.
90. Fenaux P, Simon M, Caulier MT, et al. Clinical course of essential thrombocythemia in 147 cases. *Cancer*. 1990;66(3):549-556.
91. Wolanskyj AP, Schwager SM, McClure RF, et al. Essential thrombocythemia beyond the first decade: life expectancy, long-term complication rates, and prognostic factors. *Mayo Clin Proc*. 2006;81(2):159-166.
92. Gangat N, Wolanskyj AP, McClure RF, et al. Risk stratification for survival and leukemic transformation in essential thrombocythemia: a single institutional study of 605 patients. *Leukemia*. 2007;21(2):270-276.
93. Barbui T, Thiele J, Passamonti F, et al. Survival and disease progression in essential thrombocythemia are significantly influenced by accurate morphologic diagnosis: an international study. *J Clin Oncol*. 2011;29(23):3179-3184.
94. Vardiman JW, Thiele J, Arber DA, et al. The 2008 Revision of the World Health Organization (WHO) Classification of Myeloid Neoplasms and Acute Leukemia: rationale and important changes. *Blood*. 2009;114(5):937-951.
95. Finazzi G, Carobbio A, Thiele J, et al. Incidence and risk factors for bleeding in 1104 patients with essential thrombocythemia or prefibrotic myelofibrosis diagnosed according to the 2008 WHO criteria. *Leukemia*. 2012;26(4):716-719.
96. Carobbio A, Thiele J, Passamonti F, et al. Risk factors for arterial and venous thrombosis in WHO-defined essential thrombocythemia: an international study of 891 patients. *Blood*. 2011;117(22):5857-5859.
97. Carobbio A, Finazzi G, Antonioli E, et al. Thrombocytosis and leukocytosis interaction in vascular complications of essential thrombocythemia. *Blood*. 2008;112(8):3135-3137.
98. Carobbio A, Finazzi G, Guerini V, et al. Leukocytosis is a risk factor for thrombosis in essential thrombocythemia: interaction with treatment, standard risk factors, and *JAK2* mutation status. *Blood*. 2007;109(6):2310-2313.
99. Campbell PJ, MacLean C, Beer PA, et al. Correlation of blood counts with vascular complications in essential thrombocythemia: analysis of the prospective PT1 cohort. *Blood*. 2012;120(7):1409-1411.
100. Barbui T, Finazzi G, Carobbio A, et al. Development and validation of an International Prognostic Score of thrombosis in World Health Organization-essential thrombocythemia (IPSET-thrombosis). *Blood*. 2012;120(26):5128-5133; quiz 5252.
101. Finazzi G, Carobbio A, Guglielmelli P, et al. Calreticulin mutation does not modify the IPSET score for predicting the risk of thrombosis among 1150 patients with essential thrombocythemia. *Blood*. 2014;124(16):2611-2612.
102. Barbui T, Vannucchi AM, Buxhofer-Ausch V, et al. Practice-relevant revision of IPSET-thrombosis based on 1019 patients with WHO-defined essential thrombocythemia. *Blood Cancer J*. 2015;5(11):e369.
103. Passamonti F, Thiele J, Girodon F, et al. A prognostic model to predict survival in 867 World Health Organization-defined essential thrombocythemia at diagnosis: a study by the International Working Group on Myelofibrosis Research and Treatment. *Blood*. 2012;120(6):1197-1201.
104. Passamonti F, Randi ML, Rumi E, et al. Increased risk of pregnancy complications in patients with essential thrombocythemia carrying the *JAK2* (617V>F) mutation. *Blood*. 2007;110(2):485-489.
105. Gangat N, Wolanskyi AP, Schwager S, et al. Predictors of pregnancy outcome in essential thrombocythemia: a single institution study of 63 pregnancies. *Eur J Haematol*. 2009;82(5):350-353.
106. Rumi E, Bertozzi I, Casetti IC, et al. Impact of mutational status on pregnancy outcome in patients with essential thrombocytemia. *Haematologica*. 2015;100(11):e443-445.
107. Gangat N, Tefferi A, Thanarajasingam G, et al. Cytogenetic abnormalities in essential thrombocythemia: prevalence and prognostic significance. *Eur J Haematol*. 2009;83(1):17-21.
108. van Genderen PJ, Mulder PG, Waleboer M, et al. Prevention and treatment of thrombotic complications in essential thrombocythaemia: efficacy and safety of aspirin. *Br J Haematol*. 1997;97(1):179-184.
109. Budde U, Scharf RE, Franke P, et al. Elevated platelet count as a cause of abnormal von Willebrand factor multimer distribution in plasma. *Blood*. 1993;82(6):1749-1757.
110. Harrison CN, Campbell PJ, Buck G, et al. Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. *N Engl J Med*. 2005;353(1):33-45.
111. Tefferi A, Pardanani A. Essential thrombocythemia. *N Engl J Med*. 2019;381(22):2135-2144.
112. Pascale S, Petrucci G, Dragani A, et al. Aspirin-insensitive thromboxane biosynthesis in essential thrombocythemia is explained by accelerated renewal of the drug target. *Blood*. 2012;119(15):3595-3603.
113. Dillinger J-D, Sideris G, Henry P, et al. Twice daily aspirin to improve biological aspirin efficacy in patients with essential thrombocythemia. *Thromb Res*. 2012;129(1):91-94.
114. Larsen ML, Pedersen OH, Hvas A-M, et al. Once- versus twice-daily aspirin treatment in patients with essential thrombocytosis. *Platelets*. 2019;30(3):322-328.

115. Rocca B, Tosetto A, Betti S, et al. A randomized double-blind trial of 3 aspirin regimens to optimize antiplatelet therapy in essential thrombocythemia. *Blood*. 2020;136(2):171-182.
116. Cortelazzo S, Finazzi G, Ruggeri M, et al. Hydroxyurea for patients with essential thrombocythemia and a high risk of thrombosis. *N Engl J Med*. 1995;332(17):1132-1136.
117. Gisslinger H, Gotic M, Holowiecki J, et al. Anagrelide compared with hydroxyurea in WHO-classified essential thrombocythemia: the ANAHYDRET study, a randomized controlled trial. *Blood*. 2013;121(10):1720-1728.
118. Godfrey AL, Campbell PJ, MacLean C, et al. Hydroxycarbamide plus aspirin versus aspirin alone in patients with essential thrombocythemia age 40 to 59 years without high-risk features. *J Clin Oncol*. 2018;36(34):3361-3369.
119. De Stefano V, Rossi E, Carobbio A, et al. Hydroxyurea prevents arterial and late venous thrombotic recurrences in patients with myeloproliferative neoplasms but fails in the splanchnic venous district. Pooled analysis of 1500 cases. *Blood Cancer J*. 2018;8(11):112.
120. Quintás-Cardama A, Abdel-Wahab O, Manshouri T, et al. Molecular analysis of patients with polycythemia vera or essential thrombocythemia receiving pegylated interferon alpha-2a. *Blood*. 2013;122(6):893-901.
121. Robinson SE, Harrison CN. How we manage Philadelphia-negative myeloproliferative neoplasms in pregnancy. *Br J Haematol*. 2020;189(4):625-634.
122. Harrison CN, Mead AJ, Panchal A, et al. Ruxolitinib vs best available therapy for ET intolerant or resistant to hydroxycarbamide. *Blood*. 2017;130(17):1889-1897.
123. Verstovsek S, Passamonti F, Rambaldi A, et al. Ruxolitinib for essential thrombocythemia refractory to or intolerant of hydroxyurea: long-term phase 2 study results. *Blood*. 2017;130(15):1768-1771.
124. Barosi G, Besses C, Birgegard G, et al. A unified definition of clinical resistance/intolerance to hydroxyurea in essential thrombocythemia: results of a consensus process by an International Working Group. *Leukemia*. 2007;21(2):277-280.
125. Alimam S, Bewley S, Chappell LC, et al. Pregnancy outcomes in myeloproliferative neoplasms: UK Prospective Cohort Study. *Br J Haematol*. 2016;175(1):31-36.
126. Maze D, Kazi S, Gupta V, et al. Pregnancy outcomes in patients with myeloproliferative neoplasms: a systematic review and meta-analysis. *Blood*. 2018;132(suppl 1): abstract 3046.
127. Tefferi A. Myelofibrosis with myeloid metaplasia. *N Engl J Med*. 2000;342(17):1255-1265.
128. Moulard O, Mehta J, Fryzek J, et al. Epidemiology of myelofibrosis, essential thrombocythemia, and polycythemia vera in the European Union. *Eur J Haematol*. 2014;92(4):289-297.
129. Spivak JL. Myeloproliferative neoplasms. *N Engl J Med*. 2017;376(22):2168-2181.
130. Verstovsek S, Manshouri T, Pilling D, et al. Role of neoplastic monocyte-derived fibrocytes in primary myelofibrosis. *J Exp Med*. 2016;213(9):1723-1740.
131. Maekawa T, Osawa Y, Izumi T, et al. Myeloproliferative leukemia protein activation directly induces fibrocyte differentiation to cause myelofibrosis. *Leukemia*. 2017;31(12):2709-2716.
132. Anand S, Stedham F, Gudgin E, et al. Increased basal intracellular signaling patterns do not correlate with JAK2 genotype in human myeloproliferative neoplasms. *Blood*. 2011;118(6):1610-1621.
133. Rampal R, Al-Shahrour F, Abdel-Wahab O, et al. Integrated genomic analysis illustrates the central role of JAK-STAT pathway activation in myeloproliferative neoplasm pathogenesis. *Blood*. 2014;123(22):e123-e133.
134. Tefferi A, Vaidya R, Caramazza D, et al. Circulating interleukin (IL)-8, IL-2R, IL-12, and IL-15 levels are independently prognostic in primary myelofibrosis: a comprehensive cytokine profiling study. *J Clin Oncol*. 2011;29(10):1356-1363.
135. Vannucchi AM, Lasho TL, Guglielmelli P, et al. Mutations and prognosis in primary myelofibrosis. *Leukemia*. 2013;27(9):1861-1869.
136. Rumi E, Pietra D, Pascutto C, et al. Clinical effect of driver mutations of *JAK2*, *CALR*, or *MPL* in primary myelofibrosis. *Blood*. 2014;124(7):1062-1069.
137. Cervantes F, Dupriez B, Pereira A, et al. New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. *Blood*. 2009;113(13):2895-2901.
138. Birgegard G. Does anything work for anaemia for myelofibrosis? *Best Pract Res Clin Haematol*. 2014;27(2):175-185.
139. Cervantes F, Tassies D, Salgado C, Rovira M, Pereira A, Rozman C. Acute transformation in non-leukemic chronic myeloproliferative disorders: actuarial probability and main characteristics in a series of 218 patients. *Acta Haematol*. 1991;85(3):124-127.
140. Rampal RK, Mascarenhas JO, Kosiorek H, et al. Safety and efficacy of combined ruxolitinib and decitabine in accelerated and blast-phase myeloproliferative neoplasms. *Blood Adv*. 2018;2(24):3572-3580.
141. Bose P, Verstovsek S, Cortes JE, et al. A phase 1/2 study of ruxolitinib and decitabine in patients with post-myeloproliferative neoplasm acute myeloid leukemia. *Leukemia*. 2020;34(9):2489-2492.
142. Guglielmelli P, Carobbio A, Rumi E, et al. Validation of the IPSET score for thrombosis in patients with prefibrotic myelofibrosis. *Blood Cancer J*. 2020;10(2):21.
143. Guglielmelli P, Pacilli A, Rotunno G, et al. Presentation and outcome of patients with 2016 WHO diagnosis of prefibrotic and overt primary myelofibrosis. *Blood*. 2017;129(24):3227-3236.
144. Cervantes F, Dupriez B, Passamonti F, et al. Improving survival trends in primary myelofibrosis: an international study. *J Clin Oncol*. 2012;30(24):2981-2987.
145. Bose P, Verstovsek S. The evolution and clinical relevance of prognostic classification systems in myelofibrosis. *Cancer*. 2016;122(5):681-92.
146. Passamonti F, Cervantes F, Vannucchi AM, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). *Blood*. 2010;115(9):1703-1708.
147. Passamonti F, Cervantes F, Vannucchi AM, et al. Dynamic International Prognostic Scoring System (DIPSS) predicts progression to acute myeloid leukemia in primary myelofibrosis. *Blood*. 2010;116(15):2857-2858.
148. Caramazza D, Begna KH, Gangat N, et al. Refined cytogenetic-risk categorization for overall and leukemia-free survival in primary myelofibrosis: a single center study of 433 patients. *Leukemia*. 2011;25(1):82-88.
149. Tefferi A, Nicolosi M, Mudireddy M, et al. Revised cytogenetic risk stratification in primary myelofibrosis: analysis based on 1002 informative patients. *Leukemia*. 2018;32(5):1189-1199.
150. Gangat N, Caramazza D, Vaidya R, et al. DIPSS plus: a refined Dynamic International Prognostic Scoring System for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count, and transfusion status. *J Clinical Oncol*. 2011;29(4):392-397.
151. Hernández-Boluda J-C, Pereira A, Gómez M, et al. The International Prognostic Scoring System does not accurately discriminate different risk categories in patients with post-essential thrombocythemia and post-polycythemia vera myelofibrosis. *Haematologica*. 2014;99(4):e55-e57.
152. Masarova L, Bose P, Daver N, et al. Patients with post-essential thrombocythemia and post-polycythemia vera differ from patients with primary myelofibrosis. *Leuk Res*. 2017;59:110-116.
153. Gowin K, Coakley M, Kosiorek H, et al. Discrepancies of applying primary myelofibrosis prognostic scores for patients

with post polycythemia vera/essential thrombocytosis myelofibrosis. *Haematologica*. 2016;101(10):e405-e406.
154. Tefferi A, Lasho TL, Finke CM, et al. *CALR* vs *JAK2* vs *MPL*-mutated or triple-negative myelofibrosis: clinical, cytogenetic and molecular comparisons. *Leukemia*. 2014;28(7):1472-1477.
155. Tefferi A, Lasho TL, Finke C, et al. Type 1 vs type 2 calreticulin mutations in primary myelofibrosis: differences in phenotype and prognostic impact. *Leukemia*. 2014;28(7):1568-1570.
156. Tefferi A, Lasho TL, Tischer A, et al. The prognostic advantage of calreticulin mutations in myelofibrosis might be confined to type 1 or type 1-like CALR variants. *Blood*. 2014;124(15):2465-2466.
157. Tefferi A, Nicolosi M, Mudireddy M, Szuber N, Finke CM, Lasho TL, et al. Driver mutations and prognosis in primary myelofibrosis: Mayo-Careggi MPN alliance of 1,095 patients. *Am J Hematol*. 2018;93:348-355.
158. Guglielmelli P, Lasho TL, Rotunno G, et al. The number of prognostically detrimental mutations and prognosis in primary myelofibrosis: an international study of 797 patients. *Leukemia*. 2018;28(9):1804-1810.
159. Tefferi A, Finke CM, Lasho TL, Hanson CA, Rhett PK, Gangat N, Pardanani A. *U2AF1* mutation types in primary myelofibrosis: phenotypic and prognostic distinctions. *Leukemia.* 2018;32:2274–2278.
160. Bose P, Verstovsek S. Mutational profiling in myelofibrosis; implications for management. *Int J Hematol.* 2020;111:192-199.
161. Guglielmelli P, Lasho TL, Rotunno G, et al. MIPSS70: Mutation-Enhanced International Prognostic Score System for transplantation-age patients with primary myelofibrosis. *J Clin Oncol.* 2018;36(4):310-318.
162. Tefferi A, Guglielmelli P, Lasho TL, et al. MIPSS70+ Version 2.0: Mutation and Karyotype-Enhanced International Prognostic Scoring System for Primary Myelofibrosis. *J Clin Oncol.* 2018:36(17):1769-1770.
163. Tefferi A, Guglielmelli P, Nicolosi M, et al. GIPSS: Genetically Inspired Prognostic Scoring System for primary myelofibrosis. *Leukemia*. 2018;32(7):1631-1642.
164. Hernández-Boluda J-C, Pereira A, Correa J-G, et al. Performance of the Myelofibrosis Secondary to PV and ET-Prognostic Model (MYSEC-PM) in a series of 262 patients from the Spanish Registry of Myelofibrosis. *Leukemia.* 2018;32(2):553-555.
165. Passamonti F, Mora B, Giorgino T, et al. Driver mutations' effect in secondary myelofibrosis: an international multicenter study based on 781 patients. *Leukemia.* 2017;31(4):970-973.
166. Cervantes F. How I treat myelofibrosis. *Blood*. 2014;124(17):2635-2642.
167. Cervantes F, Isola IM, Alvarez-Larrán, et al. Danazol therapy for the anemia of myelofibrosis: assessment of efficacy with current criteria of response and long-term results. *Ann Hematol*. 2015;94(11):1791-1796.
168. Tefferi A, Verstovsek S, Barosi G, et al. Pomalidomide is active in the treatment of anemia associated with myelofibrosis. *J Clin Oncol*. 2009;27(27):4563-4569.
169. Tefferi A, Al-Ali HK, Barosi G, et al. A randomized study of pomalidomide vs placebo in persons with myeloproliferative neoplasm-associated myelofibrosis and RBC-transfusion dependence. *Leukemia*. 2017;31(4):896-902.
170. Mesa RA, Steensma DP, Pardanani A, et al. A phase 2 trial of combination low-dose thalidomide and prednisone for the treatment of myelofibrosis with myeloid metaplasia. *Blood*. 2003;101(7):2534-2541.
171. Weinkove R, Reilly JT, Frances M, et al. Low-dose Thalidomide in myelofibrosis. *Haematologica*. 2008;93(7):1100-1101.
172. Marchetti M, Barosi G, Balestri F, et al. Low-dose Thalidomide ameliorates cytopenias and splenomegaly in myelofibrosis with myeloid metaplasia: a phase II trial. *J Clin Oncol.* 2004;22(3):424-431.
173. Silver RT, Vandris K, Goldman JJ. Recombinant interferon-alpha may retard progression of early primary myelofibrosis: a preliminary report. *Blood*. 2011;117(24):6669-6672.
174. Silver RT, Barel AC, Lascu E, et al. The effect of initial molecular profile on response to recombinant interferon-α (rIFNα) treatment in early myelofibrosis. *Cancer*. 2017;123(14):2680-2687.
175. Mesa RA, Nagorney DS, Schwager S, Allfred J, Tefferi A. Palliative goals, patient selection, and perioperative platelet management: outcomes and lessons from 3 decades of splenectomy for myelofibrosis with myeloid metaplasia at the Mayo Clinic. *Cancer.* 2006;107(2):361-370.
176. Mesa RA. How I treat symptomatic splenomegaly in patients with myelofibrosis. *Blood*. 2009;113(22):5394-5400.
177. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med*. 2012;366(9):799-807.
178. Harrison C, Kiladjian JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med*. 2012;366(9):787-798.
179. Verstovsek S, Mesa RA, Gotlib J, et al. Long-term treatment with ruxolitinib for patients with myelofibrosis: 5-year update from the randomized, double-blind, placebo-controlled, phase 3 COMFORT-I trial. *J Hematol Oncol*. 2017;10(1):55.
180. Harrison CN, Vannucchi AM, Kiladjian J-J, et al. Long-term findings from COMFORT-II, a phase 3 study of ruxolitinib vs best available therapy for myelofibrosis. *Leukemia*. 2016;30(8):1701-1707.
181. Verstovsek S, Gotlib J, Mesa RA, et al. Long-term survival in patients treated with ruxolitinib for myelofibrosis: COMFORT-I and -II pooled analyses. *J Hematol Oncol.* 2017;10(1):156.
182. Verstovsek S, Kantarjian HM, Estrov Z, et al. Long term outcomes of 107 patients with myelofibrosis receiving JAK1/JAK2 inhibitor ruxolitinib: survival advantage in comparison to matched historical controls. *Blood*. 2012;120(6):1202-1209.
183. Vannucchi AM, Kantarjian HM, Kiladjian JJ, et al. A pooled analysis of overall survival in COMFORT-I and COMFORT-II, 2 randomized phase 3 trials of ruxolitinib for the treatment of myelofibrosis. *Haematologica.* 2015;100(9):1139-1145.
184. Gupta V, Harrison C, Hexner EO, et al. The impact of anemia on overall survival in patients with myelofibrosis treated with ruxolitinib in the COMFORT studies. *Haematologica*. 2016;101(12):e482-e484.
185. Al-Ali HK, Stalbovskaya V, Gopalakrishna P, Perez-Ronco J, Foltz L. Impact of ruxolitinib treatment on the hemoglobin dynamics and the negative prognosis of anemia in patients with myelofibrosis. *Leuk Lymphoma*. 2016;57(10):2464-2467.
186. Talpaz M, Erickson-Viitanen S, Hou K, Hamburg S, Baer MR. Evaluation of an alternative ruxolitinib dosing regimen in patients with myelofibrosis: an open-label phase 2 study. *J Hematol Oncol*. 2018;11(1):101.
187. Cervantes F, Gisslinger H, Radinoff A, et al. Safety and efficacy of ruxolitinib in patients with myelofibrosis (MF) and anemia (Hb <10 g/dl): results at week 24 of the REALISE trial. Abstract presented at: 24th Congress of European Hematology Association (EHA24), June 15, 2019; Amsterdam, The Netherlands. Abstract #PS1465.
188. Talpaz M, Paquette R, Afrin L, et al. Interim analysis of safety and efficacy of ruxolitinib in patients with myelofibrosis and low platelet counts. *J Hematol Oncol*. 2013;6(1):81.
189. Vannucchi AM, Boekhorst PAWT, Harrison CN, et al. EXPAND, a dose-finding study of Ruxolitinib in patients with myelofibrosis and low platelet counts: 48-week follow-up analysis. *Haematologica*. 2019;104(5):947-954.
190. Mesa R, Jamieson C, Bhatia R, et al. Myeloproliferative Neoplasms, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2016;14(12):1572-1611.

191. Pardanani A, Harrison C, Cortes JE, et al. Safety and efficacy of Fedratinib in patients with primary or secondary myelofibrosis: a randomized clinical trial. *JAMA Oncol*. 2015;1(5):643-651.
192. Harrison CN, Schaap N, Vannucchi AM, et al. Fedratinib induces spleen responses and reduces symptom burden in patients with myeloproliferative neoplasm (MPN)-associated myelofibrosis (MF) and low platelet counts, who were either ruxolitinib-naïve or were previously treated with ruxolitinib. *Blood*. 2019;134(suppl 1); abstract 668.
193. Harrison CN, Mesa RA, Jamieson C, et al. Case series of potential Wernicke's encephalopathy in patients treated with fedratinib. *Blood*. 2017;130(suppl 1): abstract 4197.
194. Harrison CN, Schaap N, Vannucchi AM, et al. Fedratinib in patients with myelofibrosis previously treated with ruxolitinib: an updated analysis of the JAKARTA2 study using stringent criteria for ruxolitinib failure. *Am J Hematol.* 2020;95(6):594-603.
195. Kröger N, Holler E, Kobbe G, et al. Allogeneic stem cell transplantation after reduced-intensity conditioning in patients with myelofibrosis: a prospective, multicenter study of the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Blood*. 2009;114(26):5264-5270.
196. Kröger NM, Deeg JH, Olavarria E, et al. Indication and management of allogeneic stem cell transplantation in primary myelofibrosis: a consensus process by an EBMT/ELN International Working Group. *Leukemia*. 2015;29(11):2126-2133.
197. Gagelmann N, Ditschowski M, Bogdanov R, et al. Comprehensive clinical-molecular transplant scoring system for myelofibrosis undergoing stem cell transplantation. *Blood.* 2019;133(20):2233-2242.
198. Mesa RA, Kiladjian J-J, Catalano JV, et al. SIMPLIFY-1: a phase III randomized trial of momelotinib versus ruxolitinib in Janus kinase inhibitor-naïve patients with myelofibrosis. *J Clin Oncol*. 2017;35(34):3844-3850.
199. Harrison CN, Vannucchi AM, Platzbecker U, et al. Momelotinib versus best available therapy in patients with myelofibrosis previously treated with ruxolitinib (SIMPLIFY 2): a randomized, open-label, phase 3 trial. *Lancet Haematol*. 2018;5(2):e73-e81.
200. Mesa RA, Vannucchi AM, Mead A, et al. Pacritinib versus available therapy for the treatment of myelofibrosis irrespective of baseline cytopenias (PERSIST-1): an international randomized, phase 3 trial. *Lancet Haematol*. 2017;4(5):e225-e236.
201. Mascarenhas J, Hoffman R, Talpaz M, et al. Pacritinib vs best available therapy, including ruxolitinib, in patients with myelofibrosis: a randomized clinical trial. *JAMA Oncol.* 2018;4(5):652-659.
202. Gerds AT, Vannucchi AM, Passamonti F, et al. A phase 2 study of luspatercept in patients with myelofibrosis-associated anemia. *Blood*. 2019;134(suppl 1); abstract 557.
203. Mascarenhas J. Komrokji RS, Martino B, et al. Favorable overall survival with imetelstat treatment correlates with other clinical benefits in intermediate-2 or high-risk myelofibrosis relapsed/refractory to Janus kinase inhibitor. Presented at: 25th Congress of the European Hematology Association (EHA25), June 12, 2020; virtual only. Abstract EP1107.
204. Verstovsek S, Talpaz, M, Wadleigh M, et al. A randomized, double blind phase 2 study of 3 different doses of PRM-151 in patients with myelofibrosis who were previously treated with or ineligible for ruxolitinib. *HemaSphere.* 2019;3(S1):367, abstract S828.
205. Bose P, Verstovsek S. Management of myelofibrosis after ruxolitinib failure. *Leuk Lymphoma*. 2020;61(8):1797-1809.
206. Harrison CN, Garcia JS, Mesa RA, et al. Navitoclax in combination with Ruxolitinib in patients with primary or secondary myelofibrosis: a phase 2 study. Presented at: 25th Congress of the European Hematology Association (EHA25), June 12, 2020; virtual only. Abstract EP1081.
207. Mascarenhas J, Harrison C, Patriarca A, et al. CPI-0610, a bromodomain and extraterminal domain protein (BET) inhibitor, in combination with ruxolitinib, in JAK inhibitor treatment naïve myelofibrosis patients: update from MANIFEST phase 2 study. Presented at: 25th Congress of the European Hematology Association (EHA25), June 12, 2020; virtual only. Abstract EP1084.
208. Valent P, Klion AD, Horny HP, et al. Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. *J Allergy Clin Immunol.* 2012;130(3):607-612, e609.
209. Cools J, DeAngelo DJ, Gotlib J, et al. A tyrosine kinase created by fusion of the *PDGFRA* and *FIP1L1* genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med.* 2003;348(13):1201-1214.
210. Reiter A, Gotlib J. Myeloid neoplasms with eosinophilia. *Blood.* 2017;129(6):704-714.
211. Gotlib J, Cools J, Malone JM 3rd, et al. The FIP1L1-PDGFRalpha fusion tyrosine kinase in hypereosinophilic syndrome and chronic eosinophilic leukemia: implications for diagnosis, classification, and management. *Blood.* 2004;103(8):2879-2891.
212. Pardanani A, Verstovsek S. Hypereosinophilic syndrome, chronic eosinophilic leukemia, and mast cell disease. *Cancer J.* 2007;13(6):384-391.
213. Weller PF, Bubley GJ. The idiopathic hypereosinophilic syndrome. *Blood.* 1994;83(10):2759-2779.
214. Ogbogu PU BB, Butterfield JH, et al. Hypereosinophilic syndrome: a multicenter, retrospective analysis of clinical characteristics and response to therapy. *J Allergy Clin Immunol.* 2009;124(6):1319-25.e3.
215. Pardanani A, Ketterling RP, Li CY, et al. FIP1L1-PDGFRA in eosinophilic disorders: prevalence in routine clinical practice, long-term experience with imatinib therapy, and a critical review of the literature. *Leukemia Res.* 2006;30(8):965-970.
216. Jovanovic JV, Score J, Waghorn K, et al. Low-dose imatinib mesylate leads to rapid induction of major molecular responses and achievement of complete molecular remission in FIP1L1-PDGFRA-positive chronic eosinophilic leukemia. *Blood.* 2007;109(11):4635-4640.
217. Mejia R, Nutman TB. Screening, prevention, and treatment for hyperinfection syndrome and disseminated infections caused by *Strongyloides stercoralis*. *Curr Opin Infect Dis.* 2012;25(4):458-463.
218. Fauci AS, Harley JB, Roberts WC, et al. NIH Conference. The idiopathic hypereosinophilic syndrome. Clinical, pathophysiologic, and therapeutic considerations. *Ann Intern Med.* 1982;97(1):78-92.
219. Sakamoto K, Erdreich-Epstein A, deClerck Y, et al. Prolonged clinical response to vincristine treatment in two patients with idiopathic hypereosinophilic syndrome. *Am J Pediatr Hematol/Oncol.* 1992;14(4):348-351.
220. Lee JH, Lee JW, Jang CS, et al. Successful cyclophosphamide therapy in recurrent eosinophilic colitis associated with hypereosinophilic syndrome. *Yonsei Med J.* 2002;43(2):267-270.
221. Bourrat E, Lebbe C, Calvo F. Etoposide for treating the hypereosinophilic syndrome. *Ann Intern Med.* 1994;121(11):899-900.
222. Jabbour E, Verstovsek S, Giles F, et al. 2-Chlorodeoxyadenosine and cytarabine combination therapy for idiopathic hypereosinophilic syndrome. *Cancer.* 2005;104(3):541-546.
223. Legrand F, Renneville A, MacIntyre E, et al. The spectrum of *FIP1L1-PDGFRA*-associated chronic eosinophilic leukemia: new insights based on a survey of 44 cases. *Medicine (Baltimore).* 2013;92(5):e1-e9.
224. Baccarani M, Cilloni D, Rondoni M, et al. The efficacy of imatinib mesylate in patients with *FIP1L1-PDGFR*alpha-positive hypereosinophilic syndrome. Results of a multicenter prospective study. *Haematologica.* 2007;92(9):1173-1179.

225. David M, Cross NC, Burgstaller S, et al. Durable responses to imatinib in patients with *PDGFRB* fusion gene-positive and *BCR-ABL*-negative chronic myeloproliferative disorders. *Blood.* 2007;109(1):61-64.
226. Cheah CY, Burbury K, Apperley JF, et al. Patients with myeloid malignancies bearing *PDGFRB* fusion genes achieve durable long-term remissions with imatinib. *Blood.* 2014;123(23):3574-3577.
227. Klion AD, Robyn J, Maric I, et al. Relapse following discontinuation of imatinib mesylate therapy for *FIP1L1/PDGFRA*-positive chronic eosinophilic leukemia: implications for optimal dosing. *Blood.* 2007;110(10):3552-3556.
228. Macdonald D, Reiter A, Cross NCP. The 8p11 myeloproliferative syndrome: a distinct clinical entity caused by constitutive activation of *FGFR1*. *Acta Haematol.* 2002;107(2):101-107.
229. Verstovsek S, Subbiah V, Masarova L, et al. Treatment of the myeloid/lymphoid neoplasm with *FGFR1* rearrangement with FGFR1 inhibitor. *Ann Oncol.* 2018;29(8):1880-1882.
230. Verstovsek S VA, Rambladi A, Gotlib J, et al. Interim results from Fight-203, a phase 2, open-label, multicenter study evaluating the efficacy and safety of pemigatinib (INCB054828) in patients with myeloid/lymphoid neoplasms with rearrangement of fibroblast Growth Factor Receptor 1 (*FGFR1*). *Blood.* 2018;132(suppl 1):690.
231. Rothenberg ME, Klion AD, Roufosse FE, et al. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. *N Engl J Med.* 2008;358(12):1215-1228.
232. Roufosse FE, Kahn JE, Gleich GJ, et al. Long-term safety of mepolizumab for the treatment of hypereosinophilic syndromes. *J Allergy Clin Immunol.* 2013;131(2):461-467, e461-465.
233. Roufosse F, Kahn JE, Rothenberg ME, Wardlaw AJ, et al. Efficacy and safety of mepolizumab in hypereosinophilic syndrome: A phase III, randomized, placebo-controlled trial. J Allergy Clin Immunol. 2020 Dec;146(6):1397-1405. doi: 10.1016/j.jaci.2020.08.037. Epub 2020 Sep 18. PMID: 32956756.
234. Kuang FL, Fay MP, Ware J, et al. Long-term clinical outcomes of high-dose mepolizumab treatment for hypereosinophilic syndrome. *J Allergy Clin Immunol Pract.* 2018;6(5):1518-1527, e1515.
235. Kuang FL, Legrand F, Makiya M, et al. Benralizumab for *PDGFRA*-negative hypereosinophilic syndrome. *N Engl J Med.* 2019;380(14):1336-1346.
236. Verstovsek S, Tefferi A, Kantarjian H, et al. Alemtuzumab therapy for hypereosinophilic syndrome and chronic eosinophilic leukemia. *Clin Cancer Res.* 2009;15(1):368-373.
237. Strati P, Cortes J, Faderl S, et al. Long-term follow-up of patients with hypereosinophilic syndrome treated with alemtuzumab, an anti-CD52 antibody. *Clin Lymph Myeloma Leuk.* 2013;13(3):287-291.
238. Panch SR, Bozik ME, Brown T, et al. Dexpramipexole as an oral steroid-sparing agent in hypereosinophilic syndromes. *Blood.* 2018;132(5):501-509.
239. Maxson JE, Gotlib J, Pollyea DA, et al. Oncogenic *CSF3R* mutations in chronic neutrophilic leukemia and atypical CML. *N Engl J Med.* 2013;368(19):1781-1790.
240. Corey SJ, Burkhardt AL, Bolen JB, et al. Granulocyte colony-stimulating factor receptor signaling involves the formation of a three-component complex with Lyn and Syk protein-tyrosine kinases. *Proc Natl Acad Sci U S A.* 1994;91(11):4683-4687.
241. Fleischman AG, Maxson JE, Luty SB, et al. The *CSF3R* T618I mutation causes a lethal neutrophilic neoplasia in mice that is responsive to therapeutic JAK inhibition. *Blood.* 2013;122(22):3628-3631.
242. Pardanani A, Lasho TL, Laborde RR, et al. *CSF3R* T618I is a highly prevalent and specific mutation in chronic neutrophilic leukemia. *Leukemia.* 2013;27(9):1870-1873.
243. Elliott MA, Hanson CA, Dewald GW, Smoley SA, Lasho TL, Tefferi A. WHO-defined chronic neutrophilic leukemia: a long-term analysis of 12 cases and a critical review of the literature. *Leukemia.* 2005;19(2):313-317.
244. Elliott MA, Pardanani A, Hanson CA, et al. *ASXL1* mutations are frequent and prognostically detrimental in *CSF3R*-mutated chronic neutrophilic leukemia. *Am J Hematol.* 2015;90(7):653-656.
245. Piliotis E, Kutas G, Lipton JH. Allogeneic bone marrow transplantation in the management of chronic neutrophilic leukemia. *Leuk Lymph.* 2002;43(10):2051-2054.
246. Gotlib J, Maxson JE, George TI, et al. The new genetics of chronic neutrophilic leukemia and atypical CML: implications for diagnosis and treatment. *Blood.* 2013;122(10):1707-1711.
247. Stahl M, Xu ML, Steensma DP, et al. Clinical response to ruxolitinib in *CSF3R* T618-mutated chronic neutrophilic leukemia. *Ann Hematol.* 2016;95(7):1197-1200.
248. Gunawan AS, McLornan DP, Wilkins B, et al. Ruxolitinib, a potent JAK1/JAK2 inhibitor, induces temporary reductions in the allelic burden of concurrent *CSF3R* mutations in chronic neutrophilic leukemia. *Haematologica.* 2017;102(6):e238-e240.
249. Dao KT, Gotlib J, Deininger MMN, Oh ST, et al. Efficacy of Ruxolitinib in Patients With Chronic Neutrophilic Leukemia and Atypical Chronic Myeloid Leukemia. J Clin Oncol. 2020 Apr 1;38(10):1006-1018. doi: 10.1200/JCO.19.00895. Epub 2019 Dec 27. PMID: 31880950; PMCID: PMC7106977.
250. Garcia-Montero AC, Jara-Acevedo M, Teodosio C, et al. *KIT* mutation in mast cells and other bone marrow hematopoietic cell lineages in systemic mast cell disorders: a prospective study of the Spanish Network on Mastocytosis (REMA) in a series of 113 patients. *Blood.* 2006;108(7):2366-2372.
251. Lemmon MA, Pinchasi D, Zhou M, et al. Kit receptor dimerization is driven by bivalent binding of stem cell factor. *J Biol Chem.* 1997;272(10):6311-6317.
252. Furitsu T, Tsujimura T, Tono T, et al. Identification of mutations in the coding sequence of the proto-oncogene c-kit in a human mast cell leukemia cell line causing ligand-independent activation of c-kit product. *J Clin Invest.* 1993;92(4):1736-1744.
253. Sperr WR, Kundi M, Álvarez-Twose I, et al. International prognostic scoring system for mastocytosis (IPSM): a retrospective cohort study. *Lancet Haematol.* 2019;6(12):e638-e649.
254. Jawhar M, Schwaab J, Álvarez-Twose I, et al. MARS: Mutation-Adjusted Risk Score for advanced systemic mastocytosis. *J Clin Oncol.* 2019;37(31):2846-2856.
255. Pardanani A, Lasho TL, Reichard KK, et al. World Health Organization class-independent risk categorization in mastocytosis. *Blood Cancer J.* 2019;9(3):29.
256. Pardanani A, Shah S, Mannelli F, et al. Mayo Alliance Prognostic System for mastocytosis: clinical and hybrid clinical-molecular models. *Blood Adv.* 2018;2(21):2964-2972.
257. Jawhar M, Schwaab J, Hausmann D, et al. Splenomegaly, elevated alkaline phosphatase and mutations in the *SRSF2/ASXL1/RUNX1* gene panel are strong adverse prognostic markers in patients with systemic mastocytosis. *Leukemia.* 2016;30(12):2342-2350.
258. Schwaab J, Schnittger S, Sotlar K, et al. Comprehensive mutational profiling in advanced systemic mastocytosis. *Blood.* 2013;122(14):2460-2466.
259. Jawhar M, Schwaab J, Schnittger S, et al. Additional mutations in *SRSF2, ASXL1* and/or *RUNX1* identify a high-risk group of patients with *KIT* D816V(+) advanced systemic mastocytosis. *Leukemia.* 2016;30(1):136-143.
260. Pardanani A, Lasho T, Elala Y, et al. Next-generation sequencing in systemic mastocytosis: derivation of a mutation-augmented clinical prognostic model for survival. *Am J Hematol.* 2016;91(9):888-893.
261. Naumann N, Jawhar M, Schwaab J, et al. Incidence and prognostic impact of cytogenetic aberrations in patients with systemic mastocytosis. *Genes Chromosomes Cancer.* 2018;57(5):252-259.

262. Lim KH, Tefferi A, Lasho TL, et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. *Blood.* 2009;113(23):5727-5736.
263. Georgin-Lavialle S, Lhermitte L, Dubreuil P, et al. Mast cell leukemia. *Blood.* 2013;121(8):1285-1295.
264. National Comprehensive Cancer Network. Systemic Mastocytosis (Version 1.2020). Accessed May 31, 2020. http://www.nccn.org/professionals/physician_gls/pdf/mastocytosis.pdf
265. Kaplan AP. Clinical practice. Chronic urticaria and angioedema. *N Engl J Med.* 2002;346(3):175-179.
266. Worobec AS. Treatment of systemic mast cell disorders. *Hematol/Oncol Clin North Am.* 2000;14(3):659-687.
267. Carter MC, Robyn JA, Bressler PB, et al. Omalizumab for the treatment of unprovoked anaphylaxis in patients with systemic mastocytosis. *J Allergy Clin Immunol.* 2007;119(6):1550-1551.
268. Casassus P, Caillat-Vigneron N, Martin A, et al. Treatment of adult systemic mastocytosis with interferon-alpha: results of a multicentre phase II trial on 20 patients. *Br J Haematol.* 2002;119(4):1090-1097.
269. Lortholary O VJ, Feger F, et al. Efficacy and safety of cladribine in adult systemic 64 mastocytosis: a French multicenter study of 33 patients. *Blood.* 2004;104(11):661.
270. Barete S, Lortholary O, Damaj G, et al. Long-term efficacy and safety of cladribine (2-CdA) in adult patients with mastocytosis. *Blood.* 2015;126(8):1009-1016; quiz 1050.
271. Ustun C, Gotlib J, Popat U, et al. Consensus opinion on allogeneic hematopoietic cell transplantation in advanced systemic mastocytosis. *Biol Blood Marrow Transplant.* 2016;22(8):1348-1356.
272. Pardanani A, Brockman SR, Paternoster SF, et al. *FIP1L1-PDGFRA* fusion: prevalence and clinicopathologic correlates in 89 consecutive patients with moderate to severe eosinophilia. *Blood.* 2004;104(10):3038-3045.
273. Gotlib J, Kluin-Nelemans HC, George TI, et al. Efficacy and safety of midostaurin in advanced systemic mastocytosis. *N Engl J Med.* 2016;374(26):2530-2541.
274. DeAngelo DJ, George TI, Linder A, et al. Efficacy and safety of midostaurin in patients with advanced systemic mastocytosis: 10-year median follow-up of a phase II trial. *Leukemia.* 2018;32(2):470-478.
275. Jawhar M, Schwaab J, Naumann N, et al. Response and progression on midostaurin in advanced systemic mastocytosis: *KIT* D816V and other molecular markers. *Blood.* 2017;130(2):137-145.
276. DeAngelo DJ, Reiter A, Radia D, et al. CT023 – PATHFINDER: Interim analysis of avapritinib (ava) in patients (pts) with advanced systemic mastocytosis (AdvSM). Abstract #CT023; American Association for Cancer Research Annual Meeting, April, 2021.
277. DeAngelo DJ, Quiery A, Radia D, et al. Clinical activity in a phase 1 study of Blu-285, a potent, highly-selective inhibitor of *KIT* D816V in advanced systemic mastocytosis (AdvSM). *Blood.* 2017;130(suppl 1): abstract 2.
278. Gotlib J RD, George T, Robinson W, et al. Avapritinib induces responses in patients with advanced systemic mastocytosis (AdvSM), regardles of prior midostuaurin therapy. Presented at: 25th Congress of the European Hematology Association (EHA25), June 12, 2020; virtual only. Abstract EP1079.
279. Akin C EH, Gotlib J, Sabato V, et al. Results from PIONEER: A randomized, double-blind, placebo-controlled, phase 2 study of Avapritinib in patients with Indolent Systemic Mastocytosis (ISM). 25th Congress of the European Hematology Association (EHA25), 12 June 2020; abstract EP1082.
280. Hartmann K, Siebenhaar F, Oude Elberink H, et al. Avapritinib reduced cutaneous symptoms and mast cell burden in patients with indilent systemic mastocytosis in the PIONEER study. European Academy of Allergy and Clinical Immunology (EAACI) Digital Congress, 12 June 2020; Abstract 1832.
281. Lortholary O, Chandesris MO, Bulai Livideanu C, et al. Masitinib for treatment of severely symptomatic indolent systemic mastocytosis: A randomised, placebo-controlled, phase 3 study. *Lancet.* 2017;389(10069):612-620.

Section II

Lymphoma and Myeloma

Section Editor: Nathan H. Fowler

7 Follicular Lymphoma

8 Marginal Zone and Other Small Cell Lymphomas

9 Aggressive B-Cell Lymphomas

10 Mantle Cell Lymphoma

11 Nodal Peripheral T-Cell Lymphoma

12 Cutaneous Lymphomas

13 Hodgkin Lymphoma

14 Systemic Immunoglobulin Light Chain Amyloidosis

15 Waldenström Macroglobulinemia

16 Multiple Myeloma

17 Cellular Therapy for Lymphoma

This page intentionally left blank

7 Follicular Lymphoma

Paolo Strati
Jillian R Gunther
L. Jeffrey Medeiros
Loretta J. Nastoupil

KEY CONCEPTS

- Patients with early-stage follicular lymphoma (FL) can experience prolonged remissions with radiation therapy, particularly in the presence of stage I disease and lesions smaller than 3 cm; as such, surveillance should be reserved only to patients who are not candidates for radiation.
- High tumor burden in patients with FL is defined by the presence of one or more Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria; these include: significant lymphadenopathies (one >7 cm or three each >3 cm), splenomegaly, impending organ compromise, pleural effusion, elevated circulating lymphoma cells, and cytopenia. Among patients with advanced-stage FL, those with high tumor burden should be considered for active treatment; in the presence of low tumor burden, observation or single-agent rituximab are potential management strategies.
- Both chemoimmunotherapy and immunotherapy (with lenalidomide) are potential treatment options for patients with advanced-stage, high tumor burden FL; pretreatment positron emission tomography–computed tomography (PET-CT) scan may identify patients who would benefit from an anthracycline-based regimen.
- PET-CT scan performed at the end of chemoimmunotherapy is considered prognostic. Response to frontline therapy may inform pursuit of maintenance therapy given retrospective data suggesting the largest impact of maintenance rituximab observed among those achieving a partial response to frontline chemoimmunotherapy.
- Patients with FL who progress within 24 months from the initiation of frontline chemoimmunotherapy may have a shorter overall survival; these patients should be evaluated for clinical trials with novel agents or cellular therapy

INTRODUCTION

Follicular lymphoma (FL) is a neoplasm composed of centrocytes and centroblasts that are derived from the germinal center of lymphoid follicles.[1] Most cases of FL have a diffuse pattern but these neoplasms rarely have an entirely diffuse pattern. Being derived from germinal center B cells, these neoplasms commonly express CD10, Bcl-6, HGAL, and LMO2 and carry $t^{14;18}$(q32;q21).

Importantly, knowledge of FL has increasing led to the recognition of variants of FL (e.g. in situ follicular neoplasia) as well as distinct types of FL, the latter including primary cutaneous follicle center cell lymphoma, pediatric-type follicular lymphoma, and follicular lymphoma with *IRF4* rearrangement.

In this chapter we focus on the common form of FL that represents about 80-85% of all cases of FL.

EPIDEMIOLOGY

FL, the second most commonly occurring lymphoma in the United States, represents 22% of all B-cell non-Hodgkin lymphomas (NHLs)[2] and 80% of all indolent B-cell lymphomas. FL occurs almost exclusively in adults, with an equal frequency in men and women. The incidence rates are highest among Caucasians, and median age at diagnosis is approximately 63 years.[3] In the United States, from 2012-2016, the number of new cases of FL was 2.7 per 100,000 men and women per year after age-adjustment. The number of deaths was 0.5 per 100,000 men and women per year.[4] Risk of FL increased in persons who have a first-degree relative with NHL or who worked as a spray painter and among women with Sjögren syndrome.[3] About 2% to 3% of patients with FL

per year undergo transformation to aggressive B-cell lymphoma, usually diffuse large B-cell lymphoma (DLBCL), with a life-time risk of 11%. However not all cases are typically biopsy-proven, diagnosis of transformation being sometimes based on clinical, laboratory and radiological features, and this number may need minor adjustment.[5] Survival for patients with FL is improving, with a median survival of 8 to 10 years in the pre-rituximab era[6-8]; while in the more modern era, the median survival of FL patients has been reported to be greater than 18 years, with a 5-year overall survival (OS) of 88.4% in the United States between 2009 and 2015.[4,9]

CLINICAL FEATURES

Patients with FL most often present with asymptomatic lymphadenopathy. Constitutional symptoms such as fever, drenching night sweats, and significant weight loss occur in approximately 15% of patients. Patients may have symptoms related to lymph node enlargement, especially when there are bulky masses. Other symptoms can include fatigue and, occasionally, end-organ consequences, such as obstructive uropathy or bone marrow compromise. Central nervous system (CNS) disease is rare. Urgent situations, such as superior vena cava syndrome or spinal cord compression, are rare, in part related to the usual slow pace of growth of lymphadenopathy in FL. Spontaneous regression of lymphadenopathy can occur in FL patients. Such regressions, however, are usually partial and are typically short-lived. The potential of FL to wax and wane provides one of several clues that suggest that host immune surveillance can play an important role in the disease course. Consequently, FL has been a prime focus for immunotherapy approaches.

Approximately 80% to 90% of patients with FL present with advanced-stage disease (stage III or IV) with generalized lymphadenopathy. The bone marrow is involved in approximately 50% of patients. Clinical features suspicious for transformation to DLBCL include rapidly progressive lymphadenopathy, systemic (B) symptoms, localized pain, and a rise in serum lactate dehydrogenase (LDH) level. While elevated β2-microglobulin may be secondary to renal insufficiency and does not typically raise concern for transformation, in the rituximab era it has shown to play a prognostic role, and has been incorporated in novel prognostic models (see below).

HISTOLOGIC, IMMUNOPHENOTYPIC, AND MOLECULAR FEATURES

In lymph nodes, the normal architecture is partially or completely replaced by FL, which typically forms follicles, but rarely can have a diffuse pattern. FL is composed of centrocytes (small-cleaved cells) and centroblasts (large-noncleaved cells). The method currently recommended in the World Health Organization (WHO) classification for grading FL is based on counting centroblasts.[6,10] In grade 1 FL, centroblasts are rare, less than 5 per ×400 microscopic field. Grade 2 FL contains 5 or more but less than 15 centroblasts per ×400 microscopic field. Grade 3 FL Has more than 15 centroblasts per ×400 microscopic field are present. Importantly, this system was proposed initially when most microscopes had a smaller field of view. With newer microscopes that have a larger filed of view these counts need to be adjusted. The WHO classification states that there is no prognostic benefit derived from distinguishing grade 1 from grade 2 cases and designates these tumors as FL grade 1-2. In contrast, grade 3 cases of FL are subdivided into A and B categories. In grade 3A FL, more than 15 centroblasts per ×400 microscopic field are present. In grade 3B cases, sheets of centroblasts are present with rare or absent centrocytes.[6] Recent data suggest that FL grade 3B has many features in common with DLBCL, although some features of indolent FL are also present.[11]

Histologic concordance is not uncommon in patients with FL. In the 1970s when staging laparotomy was performed for FL patients, discordance of grade between anatomic sites was observed in 20-30% of patients.[12] Currently, histologic discordance between the bone marrow and lymph node may be observed most often. Typically the bone marrow shows low-grade FL and the lymph node may show grade 3 FL or even DLBCL.[13]

Follicular lymphoma is a neoplasm of mature B-cell lineage. Most grade 1 and 2 tumors express surface immunoglobulin (Ig), but a subset of FLs, mostly grade 3, may be Ig negative. All FLs express pan B-cell markers and typically express Ig and B-cell antigens at high density ("bright" immunofluorescence by flow cytometry). These neoplasms also express the germinal center-associated markers CD10, Bcl-6, *HGAL*, and *LMO2* and are negative for T-cell antigens. Bcl-2 is expressed in 80% to 90% of FLs but can be negative, most often in grade 3 neoplasms.[6] Because Bcl-2 is negative in reactive germinal centers, this marker is helpful in making a differential diagnosis (Fig. 7–1).

With conventional cytogenetic analysis, approximately 75% of FL cases grow in culture and can be successfully karyotyped. The cytogenetic hallmark of FL is $t^{14;18}$(q32;q21), which is identified in 80% to 90% of cases. A small subset of FLs lack the t,$^{14;18}$ suggesting that a minor pathway of follicular lymphomagenesis may exist that is independent of $t^{14;18}$. This appears to apply particularly to grade 3B nodal FL, FLs arising in extranodal sites (such as skin), and rare FLs that occur in children, which commonly lack the $t^{14;18}$.

As a result of the $t^{14;18}$, *BCL2* on chromosome 18q21 is translocated adjacent to the joining region of (*IGH*) on chromosome 14q32. *BCL2* is dysregulated by being placed under the influence of *IGH* regulatory elements

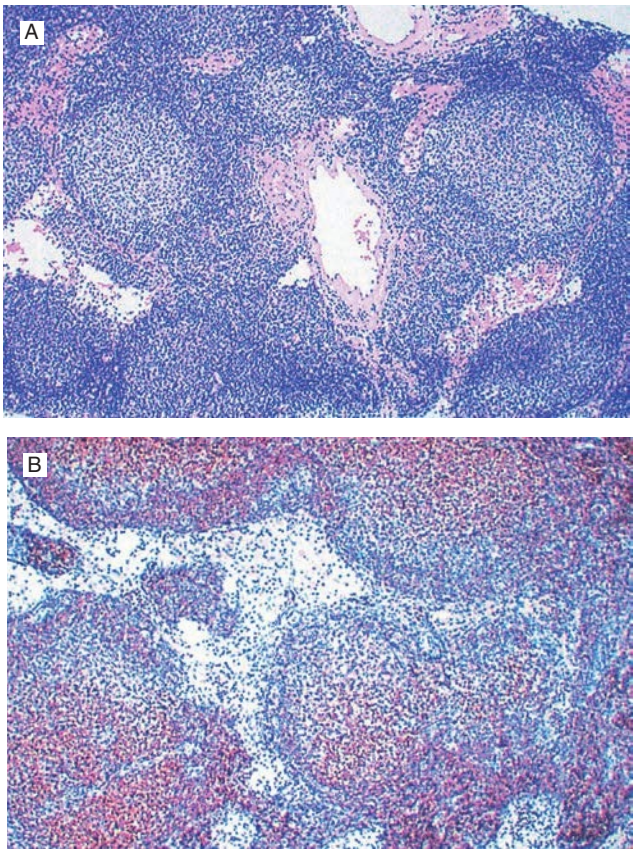


FIGURE 7–1 Follicular lymphoma, grade 1. A. In this needle biopsy specimen, neoplastic follicles partially replace architecture. B. The neoplastic cells are Bcl-2 positive, supporting lymphoma (A, hematoxylin-eosin, ×100; B, Bcl-2 immunostain ×100).

(enhancer region). Insights about the role of the *BCL2* in FL were a gateway to the identification of a large family of proapoptotic and antiapoptotic genes, which play a role in a wide variety of hematopoietic and solid neoplasms.[14–16]

The breakpoints on chromosome 18 are primarily clustered at two sites: the major and minor breakpoint cluster regions, involved in 50% to 60% and 10% to 20% of cases, respectively.[17] Other breakpoint clusters also are described; for example, the intermediate cluster region (ICR). The ICR is involved in approximately 5% of cases; there may be geographic variations in the frequencies of $t^{14;18}$ breakpoints.[18]

The Bcl-2 protein is a 25-kDa molecule that is overexpressed in FL and protects cells from programmed cell death (apoptosis).[14,15,19] Inhibition of apoptosis prolongs cell life, resulting in an expanded compartment of B cells, thereby providing more opportunity for additional molecular defects, which presumably are involved in histologic transformation. The presence of the $t^{14;18}$ alone appears to be insufficient for neoplastic transformation. The $t^{14;18}$ has been identified in rare cells in the tonsils and lymph nodes of normal individuals without clinical evidence of lymphoma.[20] In this regard, recent data show that alternative antiapoptotic proteins, such as Bcl-w (encoded by *BCL2L2*), may also play a crucial role in the pathogenesis of FL.[21]

Other cytogenetic abnormalities have been reported in FL. Of these, trisomy 7 and 18, abnormalities of 3q27-28 and 6q23-26, and 17p deletions are most frequent. Abnormalities of 3q27-28 involve *BCL6* and most often occur in the form of translocations. Secondary cytogenetic and molecular genetic abnormalities also have been extensively studied, including in the context of transformation of FL to DLBCL.[22–24]

The second most common genomic aberration observed in FL is represented by inactivating mutations of *KMT2D* (*MLL2*), found in about 80% of FL cases. These mutations interfere with the ability of KMT2D/MLL2 to activate gene transcription through H3K4 methylation. Although less frequent, mutations of other histone modifiers are also observed, including *CREBBP, EZH2*, *MEF2B*, and *EP300*, suggesting that overall epigenetic dysregulation combined with dysregulated apoptosis may be responsible for the transformation of germinal center B cells into FL cells.[25–28]

In addition, disruption of the epigenome can also alter the tumor immune microenvironment: mutations in CREBBP, for example, are associated with a signature of decreased antigen presentation characterized by reduced transcript and protein abundance of MHC class II on tumor B cells, because of its role in promoting class II transactivator–dependent transcriptional activation of these genes.[29]

The importance of the immunologic microenvironment in the clinical behavior of FL has been an area of intensive study; reduced intratumoral infiltration by host immune cells is associated with a more aggressive clinical course.[30] Gene expression profiling methods have shown molecular signatures attributable to subsets of T cells and macrophages in FLs, the former associated with a milder and the latter with more aggressive clinical features.[31–34] In light of these findings, multiple attempts are ongoing, aimed at characterizing the phenotype of tumor-associated macrophages with a more pronounced protumoral function, using markers such as CD163 and CD172 (or SIRPα).[35–38]

IN SITU FOLLICULAR NEOPLASIA

This lesion, previously known as "follicular lymphoma in situ," is thought to be a preneoplastic stage of FL.[39] Most often, in situ follicular neoplasia (ISFN) is an incidental finding that occurs in lymph nodes excised for a variety of reasons (eg, axillary lymph nodes in a patient with breast carcinoma). The overall frequency of ISFN is low, approximately 2%.

Morphologically, ISFN is difficult to recognize in routine tissue sections stained with hematoxylin-eosin. The lymph node architecture is normal, with widely scattered follicles that are of normal size and inconspicuous. The germinal centers have a sharp peripheral margin and are monotonous, composed almost exclusively of centrocytes, a morphologic clue to the diagnosis of ISFN.[40] Immunohistochemical analysis is essential for the recognition of ISFN. The germinal center cells are strongly positive for Bcl-2 and CD10.[40,41] Typically, Bcl-2 expression by the ISFN cells is brighter than the expression level by mantle zone cells surrounding the germinal center. The cells of ISFN also express pan B-cell antigens and other germinal center B-cell markers, such as *BCL6*, *HGAL*, and *LMO2*.

Cytogenetic and molecular studies have shown that the cells of ISFN carry $t^{14;18}$(q32;q21) and monoclonal *IGH* and Ig light chain gene rearrangements. Array comparative genomic hybridization and other methods performed on ISFN lesions have shown that the cells of ISFN carry $t^{14;18}$ but have relatively few secondary genetic abnormalities, in contrast with fully developed FL.[42] *EZH2* mutations have been detected in ISFN, suggesting this is another early lesion in FL pathogenesis.

Evidence of overt lymphoma at another anatomic site also is present in a small subset of patients with ISFN.[40] In addition, some patients with ISFN subsequently have development of a histologically discordant type of lymphoma. These cases suggest that ISFN could be a marker of genetic instability or a marker of genetic predisposition to lymphoma. Lymphomas most often reported in association with ISFN include classical Hodgkin lymphoma, splenic marginal zone lymphoma, and small lymphocytic lymphoma/chronic lymphocytic lymphoma.[41]

In aggregate, the data suggest that ISFN is a neoplastic process representing an early step in FL pathogenesis that is unlikely to affect patient survival if it is an isolated finding. However, because a subset of some patients with ISFN also have or may develop overt lymphoma at other anatomic sites, staging studies are indicated. If ISFN is the only disease discovered, overtreatment is to be avoided.

DIAGNOSTIC WORKUP AND STAGING

Clinical evaluation requires a comprehensive history, including age; sex; presence of B symptoms (fevers, chills, drenching night sweats, unexplained weight loss of >10% of body mass over 6 months, pruritus); fatigue; and a history of malignancy. Physical examination should include identification and measurement of all accessible lymph node sites, including epitrochlear and occipital lymph nodes, and assessment of the abdomen for splenomegaly or hepatomegaly.

The diagnosis is best established by an excisional lymph node biopsy to provide adequate tissue for assessment of lymph node architecture. The most easily accessible lymph node may not be the most informative or representative one. For example, if a small peripheral lymph node shows grade 1 FL but the patient has a large abdominal mass, a high serum lactate dehydrogenase (LDH) level, elevated standardized uptake value (SUV) on PET scan, and other features suggestive of transformation, then an additional biopsy to exclude higher-grade disease should be considered, because this would influence the selection of appropriate therapy. Core needle biopsies guided by radiographic or imaging techniques may be performed on masses that are not easily accessible. Fine-needle aspiration can be misleading for initial diagnosis; complete classification may not be possible because the limited tissue sample prevents the assessment of architecture, and there is the possibility of sampling error. In the initial staging evaluation, fine-needle aspiration may play a role in documenting and defining sites of involvement.

Once the diagnosis of FL is established, patients should undergo testing to determine stage, assess prognostic risk factors, and evaluate their general health. A complete blood cell count may show anemia or thrombocytopenia, which can result from bone marrow involvement or occasionally from hypersplenism or autoimmune problems. Leukemic involvement can occur in 10% of patients. Serum LDH and β_2-microglobulin (B2M) levels may be elevated and are of prognostic significance. Bilateral bone marrow biopsies with unilateral aspiration are recommended for the staging workup because of the patchy nature of involvement. In FL, the bone marrow characteristically shows a paratrabecular pattern of involvement (Fig. 7–2). Because the lymphoma cells are associated with stroma and are not easily aspirated, bone marrow aspirate smears assessed by routine light microscopy may not be informative. Flow cytometry and molecular assessment (eg, polymerase chain reaction [PCR]) of aspirate material can increase the sensitivity of bone marrow assessment, but in the absence of morphologic abnormalities, positive PCR or flow findings are traditionally not taken as evidence to warrant assignment of stage IV.[43] For example, it is well established that patients at Ann Arbor stage I or II can have cells with the $t^{14;18}$ detected in the peripheral blood or bone marrow by PCR.

Imaging studies should include neck and chest CT for delineation of lymphadenopathy. Abdominal and pelvic CT scans are essential for assessing lymphadenopathy as well as organomegaly. PET using

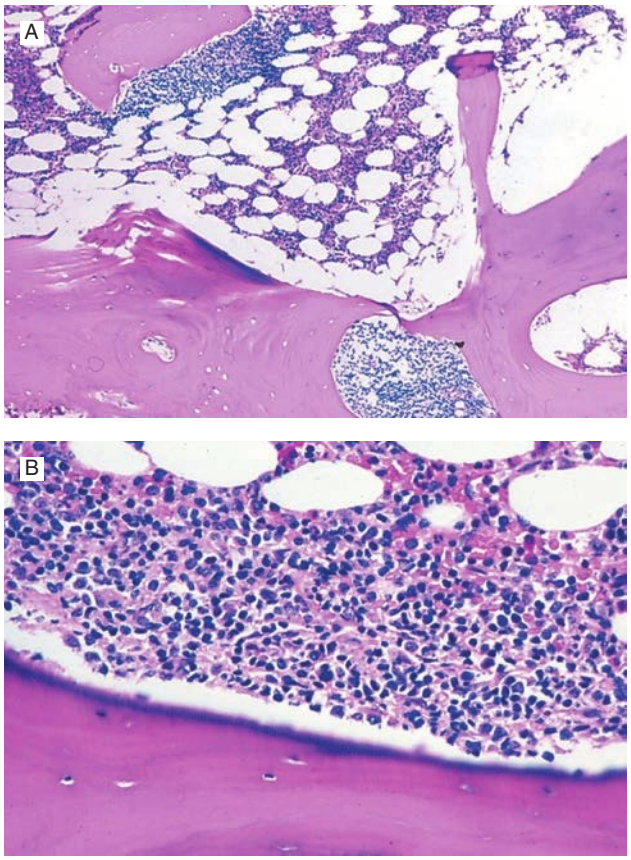


FIGURE 7–2 Follicular lymphoma involving bone marrow. A. The neoplasm is infiltrating the bone marrow with a paratrabecular pattern. B. Neoplastic small-cleaved cells adjacent to bone are seen in this field (A, B, hematoxylin-eosin; A, ×100; B, ×400).

fluorine-18 fluorodeoxyglucose (FDG) combined with CT scan (PET-CT) is a useful tool for assessing patients with FDG-avid lymphomas. Compared with CT scans, PET-CT can improve the accuracy of staging for nodal and extranodal sites and leads to a change in stage in 10% to 30% of patients, more often upstaging these patients.[44] In addition, PET-CT can help identify areas at risk for transformation, as each unit increase in SUV is associated with a 1.25-times increased risk of transformation.[45,46] Recent data show that, even in absence of histologic evidence of transformation, baseline elevated SUV and total metabolic tumor volume may be a surrogate marker for more aggressive biologic features and may help guide treatment selection.[47–50] Improving staging accuracy is important to ensuring patients are appropriately treated. Although most lymphomas are FDG avid, there is great variability in FDG uptake.[46,50,51] Imaging by PET can be less reliable in indolent lymphomas. Therefore, adoption of PET scanning for staging patients with indolent lymphoma has not been embraced to the same extent that it has been for DLBCL and Hodgkin lymphoma. Recent consensus guidelines recommend the use of PET-CT for staging in clinical practice, and clinical trials for patients with FL, and may be used to select the best site to perform biopsy.

PROGNOSTIC FACTORS

The prognostic importance of distinguishing grade 1 or 2 FL from the more aggressive grade 3 FL is well accepted. However, most investigators have not found a clear difference in long-term survival between patients with grades 1 and 2 FL, although older literature suggested that FL grade 2 (nodular mixed-cell lymphoma, in older nomenclature) was more prone to early progression than grade 1 if therapy was deferred.[52] Higher degrees of nodularity have been associated in some reports with improved outcome. An increased proliferation rate is associated with a poorer prognosis, although Ki-67 is not yet acknowledged as an independent prognostic or predictive factor.[53,54]

Variables shown to correlate with survival in patients with FL include tumor burden, host factors, and response to therapy. Tumor burden is estimated according to GELF criteria, by assessing presence of B symptoms, number and size of nodal disease, splenomegaly, compression syndrome, presence of pleural or peritoneal effusions, leukocytosis, and cytopenias.

The International Prognostic Index (IPI) was devised for aggressive lymphomas and consists of five variables, increased risk being associated with: (1) age older than 60 years, (2) Eastern Cooperative Oncology Group performance status 3–4, (3) Ann Arbor stage III–IV, (4) more than one extranodal involvement, and (5) elevated serum LDH level.[55] The IPI is also a useful predictor of survival in patients with indolent B-cell lymphomas. One important limitation of this system is that only about 10% of the patients fall into the high-risk group, and most of these patients have poor performance status and would be poor candidates for aggressive therapy.

Partly for that reason, a Follicular Lymphoma International Prognostic Index (FLIPI) was developed. Initially, an eight-parameter model was proposed, including age 60 years of age or older, male gender, Ann Arbor stages III and IV, at least 5 nodal sites, bone marrow involvement, serum LDH level greater than normal, hemoglobin level lower than 12 g/dL, and lymphocytes at least 1000/mL. However, a simplified version of this model was found to be comparably predictive, using the five parameters of age, Ann Arbor stage, serum LDH, hemoglobin level, and number of nodal sites.[56] This prognostic model separates patients into three prognostic groups: good risk, with 0 to 1 factors; intermediate risk, with 2 factors; and poor risk, with 3 or more factors. The overall five-year survival rate was

90% for the good-risk group, 78% for the intermediate-risk group, and 53% for the poor-risk group.[56] The validity of the FLIPI model has been demonstrated in rituximab-treated patients.[57] A FLIPI-2 model was developed through the prospective collection of prognostic data, producing a five-factor model that incorporates age (>60 years adverse), hemoglobin level (<12 g/dL adverse), serum B2M level (adverse if above normal range), bone marrow (adverse if involved), and size of lymphadenopathy (>6 cm adverse), which has not been validated.[58]

There are more similarities than differences in these models. For instance, the importance of serum B2M was shown in the univariate analyses of both the IPI and FLIPI datasets, but the B2M data were collected prospectively only in the FLIPI-2 report. The importance of sampling the bone marrow, as shown in the FLIPI-2 report, deserves particular emphasis, because practice patterns indicate that the important data offered are often not collected. Easily applied models such as the IPI, FLIPI, or FLIPI-2 can provide a framework for selecting the timing or intensity of therapy, and can facilitate the interpretation of clinical trials, by providing a tool to assess for disparities in patient selection when results of various trials are compared (Table 7–1).

Recently, a model combining the mutational status of seven genes relevant both to FL and the microenvironment (*EZH2, ARID1A, MEF2B, EP300, FOX01, CREBBP, and CARD11*) with the FLIPI has been produced, and termed *m7-FLIPI*. Although not extensively used, it has been shown to be superior to the FLIPI score to identify very high-risk patients.[59]

At the time of relapse, favorable predictors for survival in patients with FL include having achieved a complete response with initial therapy, having had a durable remission of more than 24 months after initial therapy, and being less than 60 years of age. Progression of disease within 24 months from the type of chemoimmunotherapy used as frontline treatment (POD24), in particular, has been shown to be the strongest predictor of long-term outcome in these patients.[60,61]

Table 7–1 Prognostic Models for Lymphoma

	Model		
Prognostic Factor	***IPI***	***FLIPI***	***FLIPI-2***
Age	✓	✓	✓
PS	✓		
Stage	✓	✓	
No. of E sites	✓		
Bone marrow			✓
No. of nodal sites		✓	
Size of nodes			✓
LDH	✓	✓	
Hgb		✓	✓
B2M			✓

B2M, serum β-2-microglobulin; Hgb, hemoglobin; PS, performance status.

POSTTREATMENT MONITORING

An international working group has recommended end-of-treatment assessment and defined response criteria for NHL. These criteria have been updated recently, with important modifications, including incorporation of PET-CT.[44] In FDG-avid FL, PET-CT should be used for response assessment, using the five-point scale (1, no uptake above background; 2, uptake ≤mediastinum; 3, uptake >mediastinum but ≤liver; 4, uptake moderately >liver; 5, uptake markedly higher than liver and/or new lesions). The criteria based on PET-CT eliminate the complete response unconfirmed criteria and improve the prognostic value of a partial response (PR). A complete metabolic response using PET-CT (5-point scale scores of 1–3), even with a persistent mass, is considered a complete remission (CR). With CT-based assessment, a complete radiologic response is determined by nodal masses regressing to 1.5 cm or less in the longest diameter and no extralymphatic sites of disease. In FL, multiple studies have shown the association between posttreatment response assessment by PET-CT scan and risk of relapse, justifying its use in this setting.[62–65]

Bone marrow reevaluation is performed to confirm clinical remission if the bone marrow involvement was initially positive.

Although the monitoring of patients with molecular studies is not currently considered standard practice, detection of the $t^{14;18}$/*IGH-BCL2* by PCR techniques, used to measure circulating tumor cells, has been useful in the monitoring of subclinical disease. "Molecular remission," the disappearance of cells with $t^{14;18}$ detected by PCR, used to be considered a rarity in patients with FL treated with standard therapy. Gribben et al reported that only 1 of 212 (0.5%) patients achieved molecular remission after conventional chemotherapy.[66] With high-dose therapy and stem cell transplantation (SCT), however, molecular remissions could be attained, and patients with molecular remission experienced more durable remissions. Improvements in therapy have changed this. Even before the advent of anti-CD20 monoclonal antibody (MAb) therapy, more potent chemotherapy regimens were capable of inducing molecular remission in more than half of patients. With the availability of rituximab and obinutuzumab, which can largely eradicate B cells

from the blood and bone marrow, it is now common to see molecular remission. Some recent studies also showed that molecular remission correlates with more durable clinical remission,[67–69] but other studies did not.[70] Finally, novel techniques to assess minimal residual disease in FL are now available for clinical research, measuring circulating free DNA, including droplet digital PCR and targeted capture ultradeep next-generation sequencing (The Cancer Personalized Profiling by Deep Sequencing or CAPP-seq).[71] It is important to note, however, that although their application is quickly progressing in the field of aggressive lymphoma, their use in FL is limited, particularly in patients with low tumor burden disease, because of frequently low quantity of measurable circulating DNA.

SURVEILLANCE IMAGING

There are limited data supporting patient benefit from surveillance imaging for patients with FL. As a consequence, there is considerable variation in practice. Zinzani et al performed one of the only prospective studies of surveillance imaging, which included 78 patients with FL in first CR after induction therapy.[72] Patients received PET-CT scans every 6 months for two years, with annual scans thereafter. The relapse rate was 8% to 10%, as shown by scans performed until 36 months, and decreased after that time. Because the purpose of the study was to describe specificity of scans, the impact on management and subsequent outcome was not reported. Gerlinger et al performed surveillance with annual CT scans and bone marrow evaluation in 71 patients with FL in second or subsequent remission after SCT.[73] Although approximately half of relapses were detected on CT scan, few patients required immediate treatment; there was no difference in OS between patients in whom disease relapse was detected by imaging compared with clinical presentation. They concluded that surveillance imaging was futile in this setting. Surveillance CT scans result in radiation exposure, patient anxiety, and significant healthcare costs, and these issues need to be carefully weighed against any potential benefit. The National Comprehensive Cancer Network guidelines suggest "surveillance CT scans up to every 6 months for the first 2 years following completion of therapy, and not more than annually thereafter." In contrast, the European Society for Medical Oncology guidelines are more conservative, suggesting minimal adequate radiologic or ultrasound investigations every 6 months for two years and annually thereafter. Regular CT scans are not mandatory outside clinical trials, and PET-CT should not be used for surveillance.[74]

TREATMENT OF EARLY-STAGE FOLLICULAR LYMPHOMAS

At diagnosis, approximately 15% to 20% of patients with FL have early-stage disease (stages I and II). Retrospective studies have shown that observation is an option for these patients, with disease in 50% of patients not progressing and remaining untreated when actively followed.[75,76] However, this approach is usually reserved for elderly or comorbid patients unable to tolerate treatment, in light of the limited toxicity of available treatment options. Several series have reported long-term disease-free survival rates of approximately 35% to 50% for stage I to II patients treated with involved-field radiotherapy (RT), so it appears that many of these patients are cured, particularly patients with stage I disease and small disease size (<3 cm).[76–82] Studies with extended-field or total lymphoid RT, in an attempt to increase cure rates, have not shown convincing additional benefit. It is important to note that recent studies have shown that outcomes after RT in PET-CT–staged patients could be better than reported in earlier series, particularly in stage I disease (where cure rate can be as high as 74%), and although longer follow-up is needed, the curative potential of RT for truly localized FL may have been underestimated.[83]

The integration of chemotherapy with involved-field RT has shown promising results in some trials. Investigators at MDACC prospectively treated 85 patients with stage I or II FL with 10 cycles of COP-Bleo (cyclophosphamide, vincristine, prednisone, and bleomycin) or CHOP-Bleo (COP-Bleo plus doxorubicin) and involved-field RT "sandwiched" after the third cycle. The disease-free survival at 5 and 10 years was 80% and 72%, respectively—an apparent improvement over results with RT alone.[84] Analysis of the National LymphoCare Study also demonstrated improvement in progression-free survival (PFS) in patients who received systemic therapy in combination with RT.[85] In addition, a recently published randomized trial showed that systemic therapy with R-CVP after RT reduced relapse outside radiation fields and significantly improved PFS in early-stage FL.[86] Given the effects of RT on the tumor microenvironment—and in particular macrophages,[87] crucial for antibody-dependent cellular cytotoxicity—the combination of RT with rituximab is currently being investigated in clinical trials, particularly in patients with residual disease after RT.

In summary, early-stage FL appears to be potentially curable. The role of RT in these patients is well established, and involved-site RT remains the standard treatment (see Table 7–1). Larger extended-field or involved-field RT techniques targeting nodal regions

are no longer recommended; smaller techniques targeting involved nodal disease, termed *involved-site radiation therapy*, should be used.[81] However, when patients are treated with RT alone (without systemic therapy), the target volumes should be slightly more generous to also include nearby lymph nodes that might contain microscopic disease. These smaller fields have been validated in patients with FL treated with definitive RT, with no significant increase in regional relapses.[25,88] Despite the established role of RT and its endorsement by experts, RT appears to be underutilized in standard clinical practice.[85,89] Total lymphoid RT and combined-modality therapy approaches remain controversial and are seldom used.

MANAGEMENT OF ADVANCED-STAGE FOLLICULAR LYMPHOMAS

For decades, the treatment of patients with advanced-stage FL has been built on two pillars that lean in opposite directions. First, there are numerous effective therapeutic options that can induce remission (Table 7–2); second, relapse appears to be inevitable. If and when therapeutic advances lead to more comprehensive control of FL, then there may be a consensus about early intervention, because a smaller tumor burden would presumably be more easily treatable, analogous to the stage I or II situation. Until then, it is still the case that deferral of therapy is a common consideration for many asymptomatic patients with low tumor burden.

When treatment is appropriate, there are a number of considerations in choosing an initial management strategy. With advances in supportive care, we have seen improvement in the tolerability of chemotherapy and SCT. With a better understanding of B-cell lymphomagenesis and the role of the microenvironment, noncytotoxic therapeutic strategies are being incorporated into frontline clinical trials. The range of therapeutic options for patients with advanced-stage FL remains broad (see Table 7–2). The therapeutic goals continue to focus on minimizing toxicity, providing palliation, and attaining durable CR. Consideration of a clinical trial when available is advisable.

Table 7–2 Standard Frontline Strategies for Follicular Lymphoma

Stages I-II	Deferral of therapy (for older and/or infirm patients) Radiation therapy
Stage III-IV Low tumor burden	Deferral of therapy (if no threatening disease) Rituximab
Stages III-IV High tumor burden	Rituximab-CHOP Obinutuzumab-CHOP Rituximab-bendamustine Obinutuzumab-bendamustine Rituximab-lenalidomide Obinutuzumab-lenalidomide

CHOP, cyclophosphamide, adriamycin, vincristine, and prednisone.

Frontline Treatment of Low Tumor Burden FL

For patients with asymptomatic FL with a low tumor burden, deferment of therapy until development of symptoms or tumor burden becomes high has been accepted based on three randomized trials demonstrating survival rates equivalent to those of patients treated with immediate therapy in the prerituximab era.[90–92] With the long-term safety and efficacy of rituximab established, observation has been challenged in the modern era with rituximab monotherapy in patients with low tumor burden. The goal is to delay the first cytotoxic chemotherapy and to have an impact on health-related quality of life.

The findings of a randomized trial of rituximab versus a watch-and-wait approach in asymptomatic, patients with nonbulky FL suggested that patients who received rituximab monotherapy had a delay in progression compared with those with an initial watch-and-wait approach.[93] Those who received rituximab maintenance after rituximab induction also reported improved quality of life, mainly because of a decrease in anxiety. No significant difference in OS was reported.

The Rituximab Extended Schedule or Retreatment Trial was a randomized cooperative group study evaluating two dosing strategies of rituximab monotherapy in patients with untreated grade I or II FL and low tumor burden.[94] There were 289 patients randomly assigned to receive either rituximab maintenance or retreatment after responding to rituximab induction (4 weekly doses). The median time to treatment failure was similar (3.9 vs 4.3 years), quality of life was similar, and significant toxicity was infrequent among both strategies. For patients with FL with a low tumor burden, rituximab monotherapy followed by a retreatment strategy was associated with less rituximab use while providing comparable disease control to that achieved with a maintenance strategy.

For patients with untreated FL of low tumor burden not eligible for a clinical trial or for more intensive therapy, an initial management strategy of rituximab monotherapy was associated with a delay in the need for cytotoxic therapy, was well tolerated, and was perceived by some to enhance their health-related well-being. Hence, the decision between observation and rituximab monotherapy should be made after a

detailed discussion with the patient about the goals of treatment. Because clinical studies have shown that low levels of vitamin D are associated with worse outcomes in patients with B-cell NHL, and in light of its pleotropic antitumoral effect, the combination of vitamin D with rituximab is currently being investigated in a multicenter phase 3 randomized trial in patients with low tumor burden FL.[95]

Frontline Treatment of High Tumor Burden FL

Several trials have convincingly shown that the addition of rituximab to chemotherapy leads to improved outcomes in FL (Table 7–3). Incorporation of rituximab has become standard. Suitable partners for rituximab in induction regimens include cyclophosphamide, vincristine, and prednisone (CVP); cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); and bendamustine (B). Few randomized studies have been conducted to inform selection of frontline chemoimmunotherapy. Bendamustine-rituximab (BR) has been compared with R-CHOP in two randomized trials: the Study group indolent Lymphomas study in Europe and the BRIGHT study in the United States. In both studies, and with extended follow-up, BR was better tolerated and modestly more effective than R-CHOP.[100,101] Retrospective studies conducted at MDACC, however, show that R-CHOP may be a better frontline option than BR for patients with elevated SUVmax, also in absence of histologic evidence of transformation.[47,48]

A randomized study comparing R-CVP versus R-CHOP versus R-FM (fludarabine and mitoxantrone) reported R-CHOP and R-FM were superior to R-CVP in regard to time to treatment failure and PFS; however, both, particularly R-FM, were associated with a higher rate of adverse events.[102] Therefore, the latter is not currently used in standard practice. To improve the efficacy of chemoimmunotherapy, novel anti-CD20 monoclonal antibodies in combination with chemotherapy have been investigated in patients with high tumor burden FL. In a randomized phase III trial, named the GALLIUM study, obinutuzumab was compared with rituximab in combination with chemotherapy in patients with previously untreated FL; obinutuzumab was associated with a significantly longer PFS, despite a higher incidence of late myelosuppression, particularly when combined with bendamustine.[103]

Although the most common initial management strategy in the United States currently is chemoimmunotherapy, the paradigm is changing.[89] A phase II study conducted at MDACC reported the efficacy and safety of a novel, nongenotoxic strategy of rituximab and lenalidomide in untreated FL with high response rates (overall response rate [ORR] 98%, CR 87%) and manageable toxicity.[104] This study provided the rationale for conducting a large, global phase III, randomized study investigating rituximab chemotherapy (R-CVP, R-CHOP, or BR) versus rituximab-lenalidomide in patients with untreated FL, named the Rituximab Lenalidomide versus Any Chemotherapy (RELEVANCE) study. The primary end points were complete response (confirmed or unconfirmed) at 120 weeks and PFS, though only the former was mature enough and published. Among 1030 randomized patients, rituximab and lenalidomide were not superior to rituximab and chemotherapy, with a CR rate at 120 weeks of 48% and 53%, and a 3-year PFS of 77% versus 78%, respectively.[105] Although the efficacy results were similar, the safety profile differed, with less frequent grade 3 or 4 neutropenia and febrile neutropenia, but high rates of grade 3 or 4 cutaneous reactions in the rituximab and lenalidomide arm. Attempts to improve on this regimen by adding ibrutinib, an oral Bruton tyrosine kinase (BTK) inhibitor, to lenalidomide and rituximab have been limited by toxicity, particularly skin rash.[106,107] Recent data from a phase II study conducted at MDACC show that obinutuzumab in combination with lenalidomide was associated with

Table 7–3 Frontline Rituximab-Plus-Chemotherapy Trials in Indolent Lymphoma

Regimen	Trial Design	% CR	% PR	% FFS (Time)	% Survival (Time)
R-CVP[a]	Phase III	41[a]	40	52 (3 y)[a]	89 (30 mo)
R-CHOP[a]	Phase III	20	77	75 (3 y)[a]	96 (2 y)
R-MCP[a]	Phase III	50[a]	42	71 (4 y)[a]	87 (4 y)[a]
R-Bendamustine[a,b]	Phase III	40[a]	53	58 (4 y)[a]	—
R-FND[c]	Phase III	88	12	76 (3 y)	96 (3 y)
R-FCM	Phase II	83	11	58 (5 y)	89 (5 y)
O-chemotherapy[d]	Phase III	86	20	85 (3 y)	98 (3 y)

[a]Significantly better than comparator arm. For R-CVP, survival benefit noted in 2008 update.
[b]Comparator arm R-CHOP.
[c]Comparator arm FND, followed by rituximab (maintenance).
[d]Comparator R-chemo.

favorable outcomes, with an impressive 2-year PFS of more than 90%, although a direct comparison with the combination of lenalidomide and rituximab is currently missing.[108] In the next few years, chemotherapy-free approaches could potentially become the standard frontline treatment for patients with high tumor burden FL.

MAINTENANCE AND CONSOLIDATION THERAPY

Rituximab maintenance (Table 7–4) has been widely used after frontline chemoimmunotherapy, with the goal of extending the disease-free interval after induction. A randomized study investigated the efficacy of two years of rituximab maintenance after rituximab plus chemotherapy in patients with previously untreated FL, named the (Primary RItuximab and Maintenance) PRIMA study.[62] Rituximab maintenance after chemoimmunotherapy with R-CHOP/R-CVP significantly improved PFS (HR [hazard ratio], 0.55; 95% CI, 0.44–0.68) and was generally well tolerated but had no impact on OS. Retrospective data have recently shown similar findings for patients receiving maintenance rituximab after frontline BR, the greatest benefit reported for patients who had not achieved CR at the end of chemoimmunotherapy.[109] Factors influencing the decision to pursue a maintenance strategy should include consideration of the patient's risk of early relapse, the response to induction therapy, and the financial burden of extended dosing.

A large multicenter, randomized trial of radioimmunotherapy (RIT) consolidation therapy has shown a significant failure-free survival benefit when used after a variety of induction therapy regimens.[110] Notably, the induction therapy included rituximab in only a minority of the patients. Still, the feasibility and impact of such a strategy is noteworthy. Prolongation of disease control was significant in subset analyses of both complete and partial responders to the induction therapy. Patients who attained only partial remission after chemotherapy commonly attained CR after RIT (77%) (Table 7–5).

Other trials have also studied RIT consolidation. A SWOG trial compared CHOP followed by RIT versus R-CHOP in patients with advanced-stage FL.[111] With a follow-up of 4.9 years, there was no significant difference in the two-year PFS (80% vs 76%) or OS (93% vs 97%) rates. With the benefits and safety profile of rituximab as part of induction or as maintenance established, the role of RIT in the modern era is unclear.

Table 7–4 Maintenance Rituximab

		Induction Response		↑ FFS With
	Induction	% CR	% PR	Maintenance[a]
A. Frontline trials	Rituximab	9	58	Yes
	CVP	13	60	Yes
	Various +R	—	—	Yes
B. Frontline retrospective studies	BR	41	18	Yes (for CR patients)
C. Salvage trials	Rituximab	0	28	Yes[b]
	R-CHOP	30	55	Yes
	R-FCM	41	54	Yes

[a]Maintenance schedules and duration variable (see text).
[b]Benefit of maintenance was matched by retreatment at time of progression.

Table 7–5 Consolidation Therapy Approaches

Induction	Consolidation	% CR After Induction	% CR After Consolidation	% CR + PR	% FFS (Time)
CHOP	Rituximab[a]	57	[a]	94	44 (3 y)
FN	Rituximab[a]	68	[a]	96	63 (3 y)
CHOP	Tositumomab	39	69	98	67 (5 y)
Various	Ibritumomab/Y-90	51[b]	87[b]	100[b]	53 (3 y[a])
R-FND	Ibritumomab/Y-90	69	89	89	73 (3 y)
Fludarabine	Tositumomab/I^{131}	9	86	100	60 (5 y)

[a]In these trials, rituximab crossover only for subset who did not attain molecular response: conversion to molecular remission occurred in 74% and 61% in the two trials.
[b]Trial design accepted only CR and PR patients for RIT. FFS measured from study entry, before RIT but after induction chemotherapy.

Table 7–6 Standard Salvage Strategies for Follicular Lymphoma

Chemoimmunotherapy	Rituximab-CHOP Obinutuzumab-CHOP Rituximab-bendamustine Obinutuzumab-bendamustine
Monoclonal antibodies	Rituximab Obinutuzumab
Targeted therapy	Idelalisib (third line) Duvelisib (third line) Copanlisib (third line)
Immunotherapy	Rituximab-lenalidomide Obinutuzumab Lenalidomide
Cellular therapies	Autologous SCT Allogeneic SCT

SCT, stem cell transplant.

SALVAGE THERAPY

There are many effective therapeutic options for patients with relapsed disease, including chemoimmunotherapy, anti-CD20 monoclonal antibodies, targeted agents, immunomodulatory agents, and cellular therapies (Table 7–6).

Chemoimmunotherapy

Numerous non–cross-resistant chemotherapeutic agents can be effective in patients with indolent lymphomas. Typically, those agents not chosen for a patient's frontline treatment are candidates for salvage use. It is notable that retreatment of previously responsive patients with the same agents is a legitimate option. Long-term follow-up studies have shown that second and later responses can be attained, even with the same agents, but the ensuing clinical remissions become progressively more brief. Some physicians advocate the avoidance of the toxicities of certain agents (eg, doxorubicin or the nucleoside analogs) in the frontline setting; their role in the salvage setting is an important consideration.

Monoclonal Antibodies

The efficacy of single-agent rituximab has been demonstrated reproducibly, although most responses to salvage rituximab show PR rather than CR. Attempts at improving the rate of CRs and enhancing the duration of response are evolving.

Newer anti-CD20 MAbs are being investigated, with modifications that theoretically represent enhancements over rituximab, such as fully humanized MAbs as opposed to a chimeric mouse–human construct; MAbs with enhanced capacity for mediation of complement-dependent cytotoxicity; MAbs with enhanced mediation of antibody-dependent cellular cytotoxicity; and other modifications. In this regard, in a phase III randomized study comparing obinutuzumab (combined with bendamustine) followed by single-agent obinutuzumab maintenance to single-agent bendamustine, a significantly longer PFS was observed (29 vs 14 months) with the addition of obinutuzumab; these results led to its FDA approval for patients with rituximab-refractory relapsed FL.[112]

Monoclonal antibodies that target antigens other than CD20 have been developed, including those used alone and as immunotoxins, the latter link a toxin to an antibody that delivers the toxin to the lymphoma cells, analogous to the delivery of isotopes with RIT. These agents include polatuzumab vedotin (targeting CD79b) and tafasitamab (monoclonal antibody targeting CD19). Polatuzumab has been investigated in combination with rituximab in a randomized phase II study (termed ROMULUS) and in combination with obinutuzumab and lenalidomide in a phase I/II study. Tafasitamab has been studied as a single agent in a phase II study; all studies showed a promising safety and efficacy signal.[113–115]

Targeted Agents

Many therapeutic options under study in the past decade have been developed against specific cell growth regulatory pathways. These agents include those targeting the B-cell receptor pathway, such as BTK inhibitors (eg, ibrutinib) and phosphatidylinositol-3-kinase (PI3K) inhibitors (eg, idelalisib); agents targeting apoptosis, such as BCL2 inhibitors (eg, venetoclax); and agents targeting epigenetic regulators, such as EZH2 inhibitors (eg, tazemetostat).

Single-agent ibrutinib has been investigated as a treatment for patients with relapsed FL in one phase I and in two phase II studies; although it was shown to be safe and well tolerated, the ORR was only 21% to 37.5% and the CR rate was only 11% to 12.5%, thus ibrutinib is not currently approved for this indication.[116–118] Acalabrutinib, a more potent and specific oral BTK inhibitor than ibrutinib, is being currently investigated as a single agent and in combination with rituximab in patients with relapsed FL. Although it has been shown to be safe, only more mature follow-up will shed light on its activity in this setting.[119]

The efficacy of the oral PI3Kδ inhibitor idelalisib has been investigated for the treatment of patients with relapsed FL (previously exposed to both rituximab and an alkylating agent) in a phase II study, showing an ORR of 56%, a CR rate of 6%, and a median PFS of 11 months.[120] Similar results have been observed for the oral PI3Kαγ inhibitor duvelisib and the intravenous

PI3Kαγ inhibitor copanlisib.[121,122] Based on the efficacy of these agents, and in light of dis-immune toxicity, more pronounced in less heavily treated patients, all three agents are currently approved for third-line treatment of patients with relapsed FL. In addition, efforts are ongoing to identify potentially safer PI3K inhibitors, such as umbralisib.[123,124]

Despite BCL2 translocation and overexpression being the hallmark of FL, its inhibition with the oral BCL2 inhibitor venetoclax has not been successful, with an ORR of 38% and a CR rate of 15% in the relapsed setting.[125] Multiple attempts are now ongoing to identify alternative antiapoptotic proteins as targets for future trials.[21]

Finally, given the frequency of mutations in genes involved in epigenetic regulation in FL, targeted inhibitors of this pathway have been investigated. Tazemetostat is a first-in-class, selective, oral EZH2 inhibitor that has demonstrated antitumor activity in patients with relapsed FL, independently from the presence of an EZH2 mutation. In a multicenter, open-label phase I/II study including 90 patients with relapsed FL, 45 with mutated EZH2 and 45 with WT EZH2, ORR was 98% and 71%, respectively, with a median PFS of 14 months and 11 months, respectively.[126,127] Based on these data, a new drug application for accelerated approval has been recently submitted to the FDA.

Immunomodulatory Agents

As previously discussed, immune modulation is an attractive approach for patients with indolent lymphoma. The activity of lenalidomide in combination with rituximab has been investigated as treatment for patients with relapsed FL in a key phase II study, yielding an ORR of 76% and a CR rate of 35%.[128] These results were followed by a randomized phase III study, termed the AUGMENT study, in which the combination of lenalidomide and rituximab was compared with single-agent rituximab. The results showed a significantly prolonged duration of response (39 vs 14 months), leading to its FDA approval for this patient population.[129] Obinutuzumab instead of rituximab has been recently investigated in combination with lenalidomide in patients with relapsed FL in two phase II studies, showing an ORR as high as 98%, and a CR rate as high as 72%, representing a viable therapeutic option in clinical practice for these patients.[130]

Enhancement of the endogenous antitumor response by targeting the microenvironment may be achieved with immune checkpoint inhibitors, such as anti-PD1 MAbs. The activity of pidilizumab with rituximab has been investigated in 32 patients with relapsed FL and reported an ORR of 66% and CR rate of 52% with no autoimmune or treatment-related grade 3 or 4 adverse events.[131] An alternative, antitumoral activity can also be achieved through enhancement of the macrophage component of the tumor microenvironment. This aim has been achieved through inhibition of CD47, a "do not eat me" signal that FL cells provide to macrophages. In a phase I/II study employing the combination of 5F9, an intravenous anti-CD47 antibody, and rituximab in patients with relapsed FL, there was an ORR of 71% and a CR rate of 43%, supporting the development of novel ongoing experimental combinations for these patients.[132]

Cellular Therapy

Stem cell transplantation approaches can be arduous but deserve strong consideration in patients with recurrent high-risk FL. Autologous SCT strategies result in substantially more durable remissions than conventional-dose salvage therapy, particularly for patients with POD24.[133,134] Allogeneic SCT is a strategy that is contingent on availability of a donor, and is a complex undertaking that includes substantial risks of treatment-related mortality. Nonetheless, allogeneic SCT not only can result in long-term remission but can potentially lead to cure, presumably through its graft-versus-lymphoma effect. Data suggest that nonmyeloablative allogeneic SCT is associated with less toxicity than conventional myeloablative allogeneic SCT, and augmentation of the conditioning regimen, including incorporation of bendamustine, has resulted in reduced myelosuppression and graft-versus-host disease.[135] With improved tolerance of SCT and the potential for cure, this remains a management strategy for eligible patients, and can be preferred to autologous SCT, particularly in patients with bone marrow involvement. It is important, however, to remember that nonrelapse mortality is significantly higher for allogeneic compared with autologous SCT, and for matched unrelated donors compared with matched-sibling donors.[136] Chimeric antigen receptor (CAR) T-cell therapy may represent a more effective and safer alternative to SCT: two phase II studies investigating its use for patients with relapsed FL have completed accrual, and results are eagerly awaited. Early promising results have been reported for the bispecific antibody mosunetuzumab, bringing together CD3+ T cells to CD20+ FL cells, and triggering antitumoral activity similar to what is observed with the use of chimeric antigen receptor T-cell therapy.[137]

Palliative Treatment

Palliative treatment for patients with FL can include involved-site RT to sites of problematic or painful disease (eg, for obstructive uropathy). In this setting, it is important to consider the use of lower RT doses (eg, 4 Gy), because prior studies have confirmed

high response rates even with low-dose RT.[138] This approach also minimizes treatment-related toxicity. Among chemotherapy options, one historically mild option is chlorambucil. Observation without therapy is also an option, even at the time of initial diagnosis, in patients with active but no threatening or symptomatic disease. The approach of deferral of therapy is common, but it should be done thoughtfully and with monitoring. Older patients are often selected for a "watch-and-wait" strategy, but this option should be weighed against the observation that older patients with FL have a tenfold increased risk of dying within one year compared with age-matched controls.[58]

Finally, consideration of a clinical trial in the setting of relapsed or refractory FL is strongly recommended given the vast trial options available and evolving management strategies, particularly for patients with POD24.

CONCLUSIONS

To date, most advanced-stage indolent B-cell lymphomas, including FL, remain incurable. Novel approaches to therapy continue to be explored, including next-generation MAbs, pathway inhibitors, and immune modulators. These approaches to therapy and novel combinations will likely play an increasingly important role in the management of patients with indolent FL. Allogeneic transplantation in indolent FL continues to be an area of heightened interest, especially with the development of more effective and better tolerated cellular therapies. As emerging therapies become integrated with the best of conventional therapies, it is optimistic that a curative approach for more patients with indolent FL is achievable. Equally promising is widespread use of well-tolerated therapy that is associated with durable disease control, resulting in chronic management. Also worthwhile of clinical exploration is identifying the most effective sequencing of therapy over an individual's disease course. With so many unanswered questions and emerging novel strategies, consideration of clinical trials for FL is strongly recommended to facilitate the translation of important scientific breakthroughs.

MD ANDERSON PRACTICE TIPS

- Although the Follicular Lymphoma International Prognostic Index (FLIPI) score has prognostic value and can help guide frequency of surveillance and stratification strategies for clinical trials, it has no predictive value and should not be used to determine initiation of treatment or treatment selection.
- There is currently no universal agreement about the optimal treatment of patients with FL grade 3A; an elevated Ki-67 (>40%) may help identify those in need of anthracycline-based approaches.
- The selection of bendamustine and rituximab compared with lenalidomide and rituximab as frontline treatment for patients with advanced-stage FL and high tumor burden should be driven by patient comorbid health conditions and preferences (chemotherapy vs immunotherapy; 6 months vs 18 months of treatment; insurance coverage).
- In young patients without significant comorbid health conditions, obinutuzumab should be considered over rituximab in combination with frontline chemoimmunotherapy, given improved survival in the GALLIUM study.
- Elevated SUV on PET-CT scan may identify patients with FL who would benefit from an anthracycline-based regimen.
- Outcomes among patients with FL experiencing disease progression within 24 months of frontline chemoimmunotherapy remain suboptimal, and experimental approaches are preferred in these patients.

REFERENCES

1. Jaffe ES, Harris NL, et al. Follicular lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.* 4th ed. IARC; 2017:266-273.
2. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. *Blood.* 1997;89(11):3909-3918.
3. Linet MS, Vajdic CM, Morton LM, et al. Medical history, lifestyle, family history, and occupational risk factors for follicular lymphoma: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. *J Natl Cancer Inst Monogr.* 2014;2014(48):26-40.
4. National Cancer Institute; Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: NHL — Follicular Lymphoma. Accessed March 22, 2021. https://seer.cancer.gov/statfacts/html/follicular.html
5. Link BK, Maurer MJ, Nowakowski GS, et al. Rates and outcomes of follicular lymphoma transformation in the immunochemotherapy era: a report from the University of Iowa/MayoClinic Specialized Program of Research Excellence Molecular Epidemiology Resource. *J Clin Oncol.* 2013;31(26):3272-3278.
6. Swerdlow SH, Campo E, Pileri SA. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood.* 2016;127(20):2375-2390.
7. Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. *J Clin Oncol.* 1998;16(8):2780-2795.
8. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: summary and description of a working formulation for clinical usage. The Non-Hodgkin's Lymphoma Pathologic Classification Project. *Cancer.* 1982;49(10):2112-2135.
9. Tan D, Horning SJ, Hoppe RT, et al. Improvements in observed and relative survival in follicular grade 1-2 lymphoma during 4 decades: the Stanford University experience. *Blood.* 2013;122(6):981-987.
10. Mann RB, Berard CW. Criteria for the cytologic subclassification of follicular lymphomas: a proposed alternative method. *Hematol Oncol.* 1983;1(2):187-192.
11. Horn H, Schmelter C, Leich E, et al. Follicular lymphoma grade 3B is a distinct neoplasm according to cytogenetic and immunohistochemical profiles. *Haematologica.* 2011;96(9):1327-1334.
12. Chabner BA, Fisher RI, Young RC, et al. Staging of non-Hodgkin's lymphoma. *Semin Oncol.* 1980;7(3):285-291.
13. Conlan MG, Bast M, Armitage JO, et al. Bone marrow involvement by non-Hodgkin's lymphoma: the clinical significance of morphologic discordance between the lymph node and bone marrow. Nebraska Lymphoma Study Group. *J Clin Oncol.* 1990;8(7):1163-1172.
14. Reed JC. Bcl-2-family proteins and hematologic malignancies: history and future prospects. Blood. 2008;111(7):3322-3330.
15. Baliga BC, Kumar S. Role of Bcl-2 family of proteins in malignancy. *Hematol Oncol.* 2002;20(2):63-74.
16. Danial NN, Korsmeyer SJ. Cell death: critical control points. *Cell.* 2004;116(2):205-219.
17. Cleary ML, Galili N, Sklar J. Detection of a second t(14;18) breakpoint cluster region in human follicular lymphomas. *J Exp Med.* 1986;164(1):315-320.
18. Albinger-Hegyi A, Hochreutener B, Abdou MT, et al. High frequency of t(14;18)-translocation breakpoints outside of major breakpoint and minor cluster regions in follicular lymphomas: improved polymerase chain reaction protocols for their detection. *Am J Pathol.* 2002;160(3):823-832.
19. Tsujimoto Y, Finger LR, Yunis J, et al. Cloning of the chromosome breakpoint of neoplastic B cells with the t(14;18) chromosome translocation. *Science.* 1984;226(4678):1097-1099.
20. Ladetto M, Drandi D, Compagno M, et al. PCR-detectable non-neoplastic Bcl-2/IgH rearrangements are common in normal subjects and cancer patients at diagnosis but rare in subjects treated with chemotherapy. *J Clin Oncol.* 2003;21(7):1398-1403.
21. Adams CM, Kim AS, Mitra R, et al. BCL-W has a fundamental role in B cell survival and lymphomagenesis. *J Clin Invest.* 2017;127(2):635-650.
22. Cheung KJ, Shah SP, Steidl C, et al. Genome-wide profiling of follicular lymphoma by array comparative genomic hybridization reveals prognostically significant DNA copy number imbalances. *Blood.* 2009;113(1):137-148.
23. Berglund M, Enblad G, Thunberg U, et al. Genomic imbalances during transformation from follicular lymphoma to diffuse large B-cell lymphoma. *Mod Pathol.* 2007;20(1):63-75.
24. Glas AM, Knoops L, Delahaye L, et al. Gene-expression and immunohistochemical study of specific T-cell subsets and accessory cell types in the transformation and prognosis of follicular lymphoma. *J Clin Oncol.* 2007;25(4):390-398.
25. Morin RD, Mendez-Lago M, Mungall AJ, et al. Frequent mutation of histone-modifying genes in non-Hodgkin lymphoma. *Nature.* 2011;476(7360):298-303.
26. Okosun J, Bodor C, Wang J, et al. Integrated genomic analysis identifies recurrent mutations and evolution patterns driving the initiation and progression of follicular lymphoma. *Nat Genet.* 2014;46(2):176-181.
27. Bodor C, Grossmann V, Popov N, et al. EZH2 mutations are frequent and represent an early event in follicular lymphoma. *Blood.* 2013;122(18):3165-3168.
28. Pasqualucci L, Dominguez-Sola D, Chiarenza A, et al. Inactivating mutations of acetyltransferase genes in B-cell lymphoma. *Nature.* 2011;471(7337):189-195.
29. Green MR, Kihira S, Liu CL, et al. Mutations in early follicular lymphoma progenitors are associated with suppressed antigen presentation. *Proc Natl Acad Sci U S A.* 2015;112(10):E1116-E1125.
30. Tobin JWD, Keane C, Gunawardana J, et al. Progression of disease within 24 months in follicular lymphoma is associated with reduced intratumoral immune infiltration. *J Clin Oncol.* 2019;37(34):3300-3309.
31. Bende RJ, Smit LA, van Noesel CJ. Molecular pathways in follicular lymphoma. *Leukemia.* 2007;21(1):18-29.
32. de Jong D. Molecular pathogenesis of follicular lymphoma: a cross talk of genetic and immunologic factors. *J Clin Oncol.* 2005;23(26):6358-6363.
33. Farinha P, Al-Tourah A, Gill K, et al. The architectural pattern of FOXP3-positive T cells in follicular lymphoma is an independent predictor of survival and histologic transformation. Blood. 2010;115(2):289-295.
34. Dave SS, Wright G, Tan B, et al. Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells. *N Engl J Med.* 2004;351(21):2159-2169.
35. Chen YP, Kim HJ, Wu H, et al. SIRPalpha expression delineates subsets of intratumoral monocyte/macrophages with different functional and prognostic impact in follicular lymphoma. *Blood Cancer J.* 2019;9(10):84.
36. Stevens WBC, Mendeville M, Redd R, et al. Prognostic relevance of CD163 and CD8 combined with EZH2 and gain of chromosome 18 in follicular lymphoma: a study by the Lunenburg Lymphoma Biomarker Consortium. *Haematologica.* 2017;102(8):1413-1423.
37. Kridel R, Xerri L, Gelas-Dore B, et al. The Prognostic Impact of CD163-Positive Macrophages in Follicular Lymphoma: A Study from the BC Cancer Agency and the Lymphoma Study Association. *Clin Cancer Res.* 2015;21(15):3428-3435.

38. Blaker YN, Spetalen S, Brodtkorb M, et al. The tumour microenvironment influences survival and time to transformation in follicular lymphoma in the rituximab era. *Br J Haematol.* 2016;175(1):102-114.
39. Mamessier E, Song JY, Eberle FC, et al. Early lesions of follicular lymphoma: a genetic perspective. *Haematologica.* 2014;99(3):481-488.
40. Jegalian AG, Eberle FC, Pack SD, et al. Follicular lymphoma in situ: clinical implications and comparisons with partial involvement by follicular lymphoma. *Blood*. 2011;118(11):2976-2984.
41. Carbone A, Gloghini A. Emerging issues after the recognition of in situ follicular lymphoma. *Leuk Lymphoma.* 2014;55(3):482-490.
42. Schmidt J, Salaverria I, Haake A, et al. Increasing genomic and epigenomic complexity in the clonal evolution from in situ to manifest t(14;18)-positive follicular lymphoma. *Leukemia.* 2014;28(5):1103-1112.
43. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol.* 1999;17(4):1244.
44. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol.* 2014;32(27):3059-3068.
45. Luminari S, Biasoli I, Arcaini L, et al. The use of FDG-PET in the initial staging of 142 patients with follicular lymphoma: a retrospective study from the FOLL05 randomized trial of the Fondazione Italiana Linfomi. *Ann Oncol.* 2013;24(8):2108-2112.
46. Schoder H, Noy A, Gonen M, et al. Intensity of 18fluorodeoxyglucose uptake in positron emission tomography distinguishes between indolent and aggressive non-Hodgkin's lymphoma. *J Clin Oncol.* 2005;23(21):4643-4651.
47. Strati P, Ahmed MA, Fowler N, et al. Pre-treatment maximum standardized uptake value predicts outcome after frontline therapy in patients with advanced stage follicular lymphoma. *Haematologica.* 2020;105(7):1907-1913.
48. Strati P, Ahmed MA, Nastoupil LJ, et al. Pretreatment SUVmax may influence the clinical benefit of BR over R-CHOP in patients with previously untreated FL. *Leuk Lymphoma.* 2020 Jan 23:1-8.
49. Meignan M, Cottereau AS, Versari A, et al. Baseline metabolic tumor volume predicts outcome in high-tumor-burden follicular lymphoma: a pooled analysis of three multicenter studies. *J Clin Oncol.* 2016;34(30):3618-3626.
50. Noy A, Schoder H, Gonen M, et al. The majority of transformed lymphomas have high standardized uptake values (SUVs) on positron emission tomography (PET) scanning similar to diffuse large B-cell lymphoma (DLBCL). *Ann Oncol.* 2009;20(3):508-512.
51. Weiler-Sagie M, Bushelev O, Epelbaum R, et al. (18)F-FDG avidity in lymphoma readdressed: a study of 766 patients. *J Nucl Med.* 2010;51(1):25-30.
52. Portlock CS, Rosenberg SA. No initial therapy for stage III and IV non-Hodgkin's lymphomas of favorable histologic types. *Ann Intern Med.* 1979;90(1):10-13.
53. Koster A, Tromp HA, Raemaekers JM, et al. The prognostic significance of the intra-follicular tumor cell proliferative rate in follicular lymphoma. *Haematologica.* 2007;92(2):184-190.
54. Martin AR, Weisenburger DD, Chan WC, et al. Prognostic value of cellular proliferation and histologic grade in follicular lymphoma. *Blood*. 1995;85(12):3671-3678.
55. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med.* 1993;329(14):987-994.
56. Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. *Blood*. 2004;104(5):1258-1265.
57. Buske C, Hoster E, Dreyling M, et al. The Follicular Lymphoma International Prognostic Index (FLIPI) separates high-risk from intermediate- or low-risk patients with advanced-stage follicular lymphoma treated front-line with rituximab and the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) with respect to treatment outcome. *Blood*. 2006;108(5):1504-1508.
58. Federico M, Bellei M, Marcheselli L, et al. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. *J Clin Oncol.* 2009;27(27):4555-4562.
59. Pastore A, Jurinovic V, Kridel R, et al. Integration of gene mutations in risk prognostication for patients receiving first-line immunochemotherapy for follicular lymphoma: a retrospective analysis of a prospective clinical trial and validation in a population-based registry. *Lancet Oncol.* 2015;16(9):1111-1122.
60. Casulo C, Byrtek M, Dawson KL, et al. Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: an analysis from the National LymphoCare Study. *J Clin Oncol.* 2015;33(23):2516-2522.
61. Freeman CL, Kridel R, Moccia AA, et al. Early progression after bendamustine-rituximab is associated with high risk of transformation in advanced stage follicular lymphoma. *Blood*. 2019;134(9):761-764.
62. Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. *Lancet.* 2011;377(9759):42-51.
63. Luminari S, Biasoli I, Versari A, et al. The prognostic role of post-induction FDG-PET in patients with follicular lymphoma: a subset analysis from the FOLL05 trial of the Fondazione Italiana Linfomi (FIL). *Ann Oncol.* 2014;25(2):442-447.
64. Trotman J, Fournier M, Lamy T, et al. Positron emission tomography-computed tomography (PET-CT) after induction therapy is highly predictive of patient outcome in follicular lymphoma: analysis of PET-CT in a subset of PRIMA trial participants. *J Clin Oncol.* 2011;29(23):3194-3200.
65. Dupuis J, Berriolo-Riedinger A, Julian A, et al. Impact of [(18)F]fluorodeoxyglucose positron emission tomography response evaluation in patients with high-tumor burden follicular lymphoma treated with immunochemotherapy: a prospective study from the Groupe d'Etudes des Lymphomes de l'Adulte and GOELAMS. *J Clin Oncol.* 2012;30(35):4317-4322.
66. Gribben JG, Neuberg D, Barber M, et al. Detection of residual lymphoma cells by polymerase chain reaction in peripheral blood is significantly less predictive for relapse than detection in bone marrow. *Blood*. 1994;83(12):3800-3807.
67. Pott C, Sehn LH, Belada D, et al. MRD response in relapsed/refractory FL after obinutuzumab plus bendamustine or bendamustine alone in the GADOLIN trial. *Leukemia.* 2020;34(2):522-532.
68. Johnson PW, Swinbank K, MacLennan S, et al. Variability of polymerase chain reaction detection of the bcl-2-IgH translocation in an international multicentre study. *Ann Oncol.* 1999;10(11):1349-1354.
69. van Oers MH, Tonnissen E, Van Glabbeke M, et al. BCL-2/IgH polymerase chain reaction status at the end of induction treatment is not predictive for progression-free survival in relapsed/resistant follicular lymphoma: results of a prospective randomized EORTC 20981 phase III intergroup study. *J Clin Oncol.* 2010;28(13):2246-2252.
70. Darby AJ, Lanham S, Soubeyran P, et al. Variability of quantitative polymerase chain reaction detection of the bcl-2-IgH translocation in an international multicenter study. *Haematologica.* 2005;90(12):1706-1707.

71. Delfau-Larue MH, van der Gucht A, Dupuis J, et al. Total metabolic tumor volume, circulating tumor cells, cell-free DNA: distinct prognostic value in follicular lymphoma. *Blood Adv.* 2018;2(7):807-816.
72. Zinzani PL, Stefoni V, Tani M, et al. Role of [18F]fluorodeoxyglucose positron emission tomography scan in the follow-up of lymphoma. *J Clin Oncol*. 2009;27(11):1781-1787.
73. Gerlinger M, Rohatiner AZ, Matthews J, et al. Surveillance investigations after high-dose therapy with stem cell rescue for recurrent follicular lymphoma have no impact on management. *Haematologica.* 2010;95(7):1130-1135.
74. Dreyling M, Ghielmini M, Rule S, et al. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2016;27(suppl 5):v83-v90.
75. Advani R, Rosenberg SA, Horning SJ. Stage I and II follicular non-Hodgkin's lymphoma: long-term follow-up of no initial therapy. *J Clin Oncol*. 2004;22(8):1454-1459.
76. Soubeyran P, Eghbali H, Trojani M, et al. Is there any place for a wait-and-see policy in stage I0 follicular lymphoma? A study of 43 consecutive patients in a single center. *Ann Oncol.* 1996;7(7):713-718.
77. Gospodarowicz MK, Bush RS, Brown TC, et al. Prognostic factors in nodular lymphomas: a multivariate analysis based on the Princess Margaret Hospital experience. *Int J Radiat Oncol Biol Phys.* 1984;10(4):489-497.
78. MacManus MP, Hoppe RT. Is radiotherapy curative for stage I and II low-grade follicular lymphoma? Results of a long-term follow-up study of patients treated at Stanford University. *J Clin Oncol*. 1996;14(4):1282-1290.
79. Wilder RB, Jones D, Tucker SL, et al. Long-term results with radiotherapy for Stage I-II follicular lymphomas. *Int J Radiat Oncol Biol Phys.* 2001;51(5):1219-1227.
80. Guadagnolo BA, Li S, Neuberg D, et al. Long-term outcome and mortality trends in early-stage, Grade 1-2 follicular lymphoma treated with radiation therapy. *Int J Radiat Oncol Biol Phys.* 2006;64(3):928-934.
81. Campbell BA, Voss N, Woods R, et al. Long-term outcomes for patients with limited stage follicular lymphoma: involved regional radiotherapy versus involved node radiotherapy. *Cancer.* 2010;116(16):3797-3806.
82. Lo AC, Campbell BA, Pickles T, et al. Long-term outcomes for patients with limited stage follicular lymphoma: an update of a population-based study. *Int J Radiat Oncol*. 2019;105(1):S33-S34.
83. Brady JL, Binkley MS, Hajj C, et al. Definitive radiotherapy for localized follicular lymphoma staged by (18)F-FDG PET-CT: a collaborative study by ILROG. *Blood*. 2019;133(3):237-245.
84. Seymour JF, Pro B, Fuller LM, et al. Long-term follow-up of a prospective study of combined modality therapy for stage I-II indolent non-Hodgkin's lymphoma. *J Clin Oncol*. 2003;21(11):2115-2122.
85. Friedberg JW, Byrtek M, Link BK, et al. Effectiveness of first-line management strategies for stage I follicular lymphoma: analysis of the National LymphoCare Study. *J Clin Oncol*. 2012;30(27):3368-3375.
86. MacManus M, Fisher R, Roos D, et al. Randomized trial of systemic therapy after involved-field radiotherapy in patients with early-stage follicular lymphoma: TROG 99.03. *J Clin Oncol*. 2018;36(29):2918-2925.
87. Klug F, Prakash H, Huber PE, et al. Low-dose irradiation programs macrophage differentiation to an iNOS(+)/M1 phenotype that orchestrates effective T cell immunotherapy. *Cancer Cell.* 2013;24(5):589-602.
88. Illidge T, Specht L, Yahalom J, et al. Modern radiation therapy for nodal non-Hodgkin lymphoma-target definition and dose guidelines from the International Lymphoma Radiation Oncology Group. *Int J Radiat Oncol Biol Phys.* 2014;89(1):49-58.
89. Friedberg JW, Taylor MD, Cerhan JR, et al. Follicular lymphoma in the United States: first report of the national LymphoCare study. *J Clin Oncol*. 2009;27(8):1202-1208.
90. Ardeshna KM, Smith P, Norton A, et al. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. *Lancet.* 2003;362(9383):516-522.
91. Young RC, Longo DL, Glatstein E, et al. The treatment of indolent lymphomas: watchful waiting v aggressive combined modality treatment. *Semin Hematol.* 1988;25(2 suppl 2):11-16.
92. Brice P, Bastion Y, Lepage E, et al. Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol*. 1997;15(3):1110-1117.
93. Ardeshna KM, Qian W, Smith P, et al. Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial. *Lancet Oncol.* 2014;15(4):424-435.
94. Kahl BS, Hong F, Williams ME, et al. Rituximab extended schedule or re-treatment trial for low-tumor burden follicular lymphoma: eastern cooperative oncology group protocol e4402. *J Clin Oncol*. 2014;32(28):3096-3102.
95. Borchmann S, Cirillo M, Goergen H, et al. Pretreatment vitamin D deficiency is associated with impaired progression-free and overall survival in Hodgkin lymphoma. *J Clin Oncol.* 2019;37(36):3528-3537.
96. Herold M, Haas A, Srock S, et al. Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy followed by interferon maintenance prolongs survival in patients with advanced follicular lymphoma: an East German Study Group Hematology and Oncology Study. *J Clin Oncol.* 2007;25(15):1986-1992.
97. Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood.* 2005;106(12):3725-3732.
98. Marcus R, Imrie K, Solal-Celigny P, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. *J Clin Oncol*. 2008;26(28):4579-4586.
99. McLaughlin P, Hagemeister FB, Rodriguez MA, et al. Safety of fludarabine, mitoxantrone, and dexamethasone combined with rituximab in the treatment of stage IV indolent lymphoma. *Semin Oncol.* 2000;27(6 suppl 12):37-41.
100. Rummel M, Kaiser U, Balser C, et al. Bendamustine plus rituximab versus fludarabine plus rituximab for patients with relapsed indolent and mantle-cell lymphomas: a multicentre, randomised, open-label, non-inferiority phase 3 trial. *Lancet Oncol.* 2016;17(1):57-66.
101. Flinn IW, van der Jagt R, Kahl B, et al. First-line treatment of patients with indolent non-Hodgkin lymphoma or mantle-cell lymphoma with bendamustine plus rituximab versus R-CHOP or R-CVP: results of the BRIGHT 5-year follow-up study. *J Clin Oncol*. 2019;37(12):984-991.
102. Federico M, Luminari S, Dondi A, et al. R-CVP versus R-CHOP versus R-FM for the initial treatment of patients with advanced-stage follicular lymphoma: results of the FOLL05

trial conducted by the Fondazione Italiana Linfomi. *J Clin Oncol*. 2013;31(12):1506-1513.
103. Marcus R, Davies A, Ando K, et al. Obinutuzumab for the first-line treatment of follicular lymphoma. *N Engl J Med.* 2017;377(14):1331-1344.
104. Fowler NH, Davis RE, Rawal S, et al. Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: an open-label, phase 2 trial. *Lancet Oncol.* 2014;15(12):1311-1318.
105. Morschhauser F, Fowler NH, Feugier P, et al. Rituximab plus lenalidomide in advanced untreated follicular lymphoma. *N Engl J Med.* 2018;379(10):934-947.
106. Ujjani CS, Jung SH, Pitcher B, et al. Phase 1 trial of rituximab, lenalidomide, and ibrutinib in previously untreated follicular lymphoma: Alliance A051103. *Blood*. 2016;128(21):2510-2516.
107. Nastoupil LJ, Lee HJ, Hagemeister FB, et al. Safety and efficacy of ibrutinib in combination with rituximab and lenalidomide in previously untreated subjects with follicular and marginal zone lymphoma: an open label, phase II study. *Blood*. 2018;132(suppl 1):447.
108. Nastoupil LJ, Westin JR, Hagemeister FB, et al. Results of a phase II study of obinutuzumab in combination with lenalidomide in previously untreated, high tumor burden follicular lymphoma (FL). *Blood*. 2019;134(suppl 1):125.
109. Hill BT, Nastoupil L, Winter AM, et al. Maintenance rituximab or observation after frontline treatment with bendamustine-rituximab for follicular lymphoma. *Br J Haematol.* 2019;184(4):524-535.
110. Morschhauser F, Radford J, Van Hoof A, et al. Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma. *J Clin Oncol*. 2008;26(32):5156-5164.
111. Press OW, Unger JM, Rimsza LM, et al. Phase III randomized intergroup trial of CHOP plus rituximab compared with CHOP chemotherapy plus (131)iodine-tositumomab for previously untreated follicular non-Hodgkin lymphoma: SWOG S0016. *J Clin Oncol*. 2013;31(3):314-320.
112. Sehn LH, Chua N, Mayer J, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. *Lancet Oncol.* 2016;17(8):1081-1093.
113. Diefenbach C, Kahl BS, Banerjee L, et al. Polatuzumab vedotin plus obinutuzumab and lenalidomide in patients with relapsed/refractory follicular lymphoma: primary analysis of the full efficacy population in a phase Ib/II trial. *Blood*. 2019;134(suppl 1):126.
114. Morschhauser F, Flinn IW, Advani R, et al. Polatuzumab vedotin or pinatuzumab vedotin plus rituximab in patients with relapsed or refractory non-Hodgkin lymphoma: final results from a phase 2 randomised study (ROMULUS). *Lancet Haematol.* 2019;6(5):e254-e265.
115. Jurczak W, Zinzani PL, Gaidano G, et al. Phase IIa study of the CD19 antibody MOR208 in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. *Ann Oncol.* 2018;29(5):1266-1272.
116. Advani RH, Buggy JJ, Sharman JP, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. *J Clin Oncol*. 2013;31(1):88-94.
117. Bartlett NL, Costello BA, LaPlant BR, et al. Single-agent ibrutinib in relapsed or refractory follicular lymphoma: a phase 2 consortium trial. *Blood*. 2018;131(2):182-190.
118. Gopal AK, Schuster SJ, Fowler NH, et al. Ibrutinib as treatment for patients with relapsed/refractory follicular lymphoma: results from the open-label, multicenter, phase II DAWN study. *J Clin Oncol*. 2018;36(23):2405-2412.
119. Fowler NH, Coleman M, Stevens DA, et al. Acalabrutinib alone or in combination with rituximab (R) in follicular lymphoma (FL). *J Clin Oncol.* 2018;36(15).
120. Gopal AK, Kahl BS, de Vos S, et al. PI3Kdelta inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med.* 2014;370(11):1008-1018.
121. Dreyling M, Santoro A, Mollica L, et al. Phosphatidylinositol 3-kinase inhibition by copanlisib in relapsed or refractory indolent lymphoma. *J Clin Oncol*. 2017;35(35):3898-3905.
122. Flinn IW, Miller CB, Ardeshna KM, et al. DYNAMO: a phase II study of duvelisib (IPI-145) in patients with refractory indolent non-Hodgkin lymphoma. *J Clin Oncol*. 2019;37(11):912-922.
123. Lunning M, Vose J, Nastoupil L, et al. Ublituximab and umbralisib in relapsed/refractory B-cell non-Hodgkin lymphoma and chronic lymphocytic leukemia. *Blood*. 2019;134(21):1811-1820.
124. Nastoupil LJ, Lunning MA, Vose JM, et al. Tolerability and activity of ublituximab, umbralisib, and ibrutinib in patients with chronic lymphocytic leukaemia and non-Hodgkin lymphoma: a phase 1 dose escalation and expansion trial. *Lancet Haematol.* 2019;6(2):e100-e109.
125. Davids MS, Roberts AW, Seymour JF, et al. Phase I first-in-human study of venetoclax in patients with relapsed or refractory non-Hodgkin lymphoma. *J Clin Oncol*. 2017;35(8):826-833.
126. Italiano A, Soria JC, Toulmonde M, et al. Tazemetostat, an EZH2 inhibitor, in relapsed or refractory B-cell non-Hodgkin lymphoma and advanced solid tumours: a first-in-human, open-label, phase 1 study. *Lancet Oncol.* 2018;19(5):649-659.
127. Morschhauser F, Tilly H, Chaidos A, et al. Phase 2 multicenter study of tazemetostat, an EZH2 inhibitor, in patients with relapsed or refractory follicular lymphoma. *Blood*. 2019;134(suppl 1):123.
128. Leonard JP, Jung SH, Johnson J, et al. Randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma: CALGB 50401 (Alliance). *J Clin Oncol*. 2015;33(31):3635-3640.
129. Leonard JP, Trneny M, Izutsu K, et al. AUGMENT: a phase III study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. *J Clin Oncol.* 2019;37(14):1188-1199.
130. Fowler NH, Nastoupil LJ, Chin C, et al. A phase I/II study of lenalidomide plus obinutuzumab in relapsed indolent lymphoma. *Blood*. 2019;134(suppl 1):348.
131. Westin JR, Chu F, Zhang M, et al. Safety and activity of PD1 blockade by pidilizumab in combination with rituximab in patients with relapsed follicular lymphoma: a single group, open-label, phase 2 trial. *Lancet Oncol.* 2014;15(1):69-77.
132. Advani R, Flinn I, Popplewell L, et al. CD47 blockade by Hu5F9-G4 and rituximab in non-Hodgkin's lymphoma. *N Engl J Med.* 2018;379(18):1711-1721.
133. Jurinovic V, Metzner B, Pfreundschuh M, et al. Autologous stem cell transplantation for patients with early progression of follicular lymphoma: a follow-up study of 2 randomized trials from the German Low Grade Lymphoma Study Group. *Biol Blood Marrow Transplant.* 2018;24(6):1172-1179.
134. Rohatiner AZ, Freedman A, Nadler L, et al. Myeloablative therapy with autologous bone marrow transplantation as consolidation therapy for follicular lymphoma. *Ann Oncol.* 1994;(5 suppl 2):143-146.
135. Khouri IF, Wei W, Korbling M, et al. BFR (bendamustine, fludarabine, and rituximab) allogeneic conditioning for chronic lymphocytic leukemia/lymphoma: reduced myelosuppression and GVHD. *Blood*. 2014;124(14):2306-2312.

136. Smith SM, Godfrey J, Ahn KW, et al. Autologous transplantation versus allogeneic transplantation in patients with follicular lymphoma experiencing early treatment failure. *Cancer*. 2018;124(12):2541-2551.
137. Schuster SJ, Bartlett NL, Assouline S, et al. Mosunetuzumab induces complete remissions in poor prognosis non-Hodgkin lymphoma patients, including those who are resistant to or relapsing after chimeric antigen receptor T-cell (CAR-T) therapies, and is active in treatment through multiple lines. *Blood*. 2019;134(suppl 1):6.
138. Hoskin PJ, Kirkwood AA, Popova B, et al. 4 Gy versus 24 Gy radiotherapy for patients with indolent lymphoma (FORT): a randomised phase 3 non-inferiority trial. *Lancet Oncol*. 2014;15(4):457-463.

8 Marginal Zone and Other Small Cell Lymphomas

Melody Becnel
Felipe Samaniego

KEY CONCEPTS

- Marginal zone lymphoma (MZL) is an indolent B-cell non-Hodgkin lymphoma composed of three subtypes: extranodal (mucosal-associated lymphoid tissue [MALT] lymphoma), splenic, and nodal.
- MALT lymphoma, the most common subtype, is composed of gastric and nongastric MALT and is often associated with infectious organisms such as *Helicobacter pylori*.
- Nongastric MALT is often associated with inflammatory conditions such as Sjögren syndrome and Hashimoto thyroiditis.
- Translocations well characterized in MALT lymphomas include t(11;18), t(14;18), t(1;14), and t(3;14). No unique recurrent chromosomal abnormalities are noted in nodal MZL. *MYD88* L265P mutations (as seen in Waldenström macroglobulinemia) have been identified in 10% to 20% of cases of splenic MZL.
- WHO classification restricts small lymphocytic lymphoma (SLL) to tumors involving lymph nodes with the same B-cell immunophenotype as CLL without leukemic involvement and considers SLL to be the nodal or tissue counterpart of chronic lymphocytic leukemia (CLL).
- Abnormalities of the *p53* or *MYC* genes correlate with increased risk of histologic transformation (Richter syndrome) and poorer prognosis in CLL/SLL.

MARGINAL ZONE LYMPHOMA

Marginal zone lymphoma (MZL) is the second most common B-cell–indolent non-Hodgkin Lymphoma (NHL; <10% of NHL cases in adults). MZL generally presents at a median age of 60 years old, and women have a slightly increased propensity toward MZL developing compared with men.[1,2] There are three subtypes of MZL: extranodal MZL of mucosa-associated lymphoid tissue (MALT lymphoma), which represents 7% to 8% of all NHLs; nodal marginal zone lymphoma, which represents approximately 2% of all NHLs; and splenic B-cell marginal zone lymphoma (SMZL), representing less than 1% of all NHLs.[3,4] Splenic MZL can be associated with circulating lymphocytes with villous cytoplasmic projections. The entity previously described as splenic lymphoma with villous lymphocytes is, in most cases, SMZL.

Extranodal Marginal Zone B-Cell Lymphoma

Clinical Features

Patients with MALT lymphoma present with extranodal disease that is often localized (stage I-E or II-E). There may be a history of infection or autoimmune disease, which are conditions that lead to chronic B-cell receptor activation.[5] Peripheral lymph node involvement is uncommon in patients with MALT lymphoma. The most common site of involvement is the stomach, but numerous other extranodal locations can be involved, including lung, skin, orbit, salivary glands, other parts of the gastrointestinal tract, thyroid gland, and other rare sites.[2] Dissemination occurs in up to 30% of cases, most often in patients with nongastric MALT lymphoma, and dissemination generally occurs to other extranodal sites. In patients with nongastric

MALT lymphomas, subclinical gastric involvement is not uncommon. The bone marrow is involved in only 10% to 20% of patients.

The stomach is the best-studied site of involvement. Patients often present with signs and symptoms suggestive of peptic ulcer disease, such as epigastric pain and dyspepsia. Anemia, weight loss, and gastrointestinal bleeding can be seen in patients with more advanced disease. *Helicobacter pylori* is present in the gastric mucosa of many patients with MALT lymphoma. Antibiotic elimination of *H pylori* has resulted in regression of MALT lymphoma in more than half of treated patients.[6,7] Thus, *H pylori* is thought to be essential to lymphomagenesis in gastric MALT lymphoma.

In nongastric MALT lymphomas, symptoms are related to the anatomic site involved. Disseminated disease is generally more common in these patients than in patients with gastric MALT lymphoma. Despite the higher frequency of stage IV disease, the five-year survival rate is 90% when treated with a variety of therapies.[2,5]

Histologic Features

Four findings are present in most MALT lymphomas: a population of neoplastic small lymphoid (centrocyte-like) cells that may have monocytoid features, occasional large lymphoid cells (blasts), lymphoepithelial lesions, and reactive lymphoid follicles (Figs. 8–1 through 8–3).[4]

The neoplastic small lymphoid cells exhibit a range of cytologic appearances. In some cases, the cells resemble small lymphocytes with or without plasmacytoid differentiation. In other cases, the neoplasm appears biphasic: one component is a population of small lymphoid cells, and the other is a population of cells with extensive plasmacytoid differentiation, resembling mature plasma cells (see Fig. 8–3). In some cases, the cells have markedly irregular nuclear contours and resemble small cleaved cells. All of these cell types may have abundant pale cytoplasm, imparting a

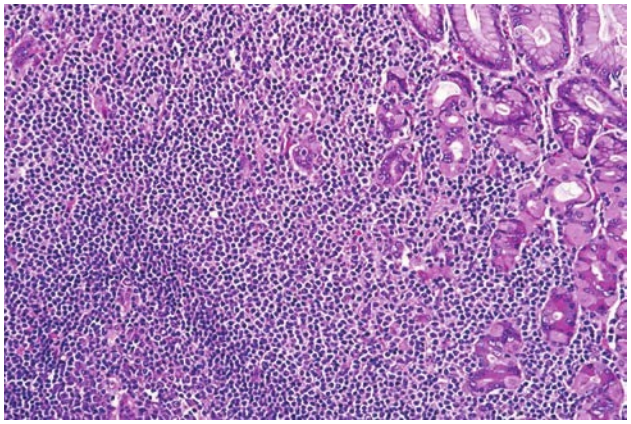


FIGURE 8–1 **Extranodal marginal zone B-cell lymphoma of MALT (MALT lymphoma) involving the stomach. The neoplasm partially replaces gastric mucosa and infiltrates epithelium. A reactive follicle is present at the bottom left of the field.**

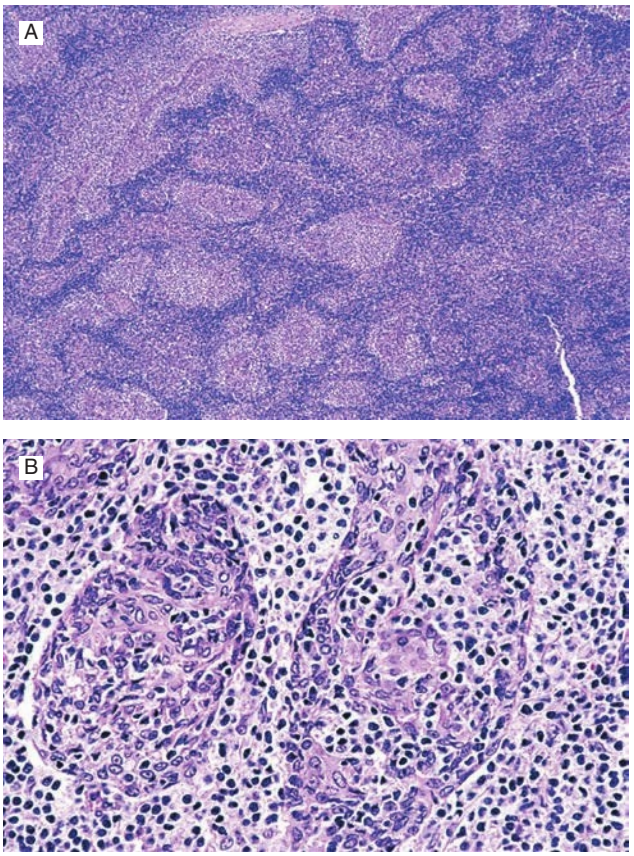


FIGURE 8–2 **A MALT lymphoma of a salivary gland. A. The neoplastic cells have a pale (monocytoid) low-power appearance and surround ducts. B. Lymphoepithelial lesions are prominent in this case (A, B, hematoxylin and eosin; A, ×20; B, ×400).**

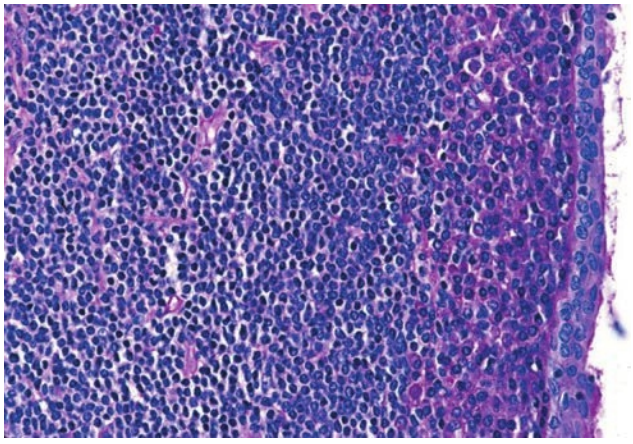


FIGURE 8–3 **A MALT lymphoma of the conjunctiva. In this field, the neoplasm has a biphasic pattern, with the subepithelial portion exhibiting extensive plasmacytoid differentiation (periodic acid–Schiff, ×400).**

Table 8–1 Translocations and Gene Abnormalities in MALT

Translocation	Tissues Involved	Genes Involved
t(11;18)	15%–40% of MALT, most commonly present in lung and stomach MALT	*BIRC3*, *MALT1* to form a fusion gene
t(14;18)	In 15%–20% of MALT; seen in nongastrointestinal MALT lymphoma	Juxtaposes *IGH* and *MALT1*, causing overexpression of *MALT1*
t(1;14)	In 1%–2% of MALT; seen in lung and stomach	Juxtaposes *BCL10* and *IGH*, truncating *BCL10* and causing loss of proapoptotic function
t(3;14)	Most commonly present in MALT of skin, thyroid, and ocular adnexal site	Juxtaposes *FOXP1* and *IGH*, causing overexpression of *FOXP1*

monocytoid appearance. In most MALT lymphomas, occasional large lymphoid cells (blasts) are also present. However, when large cells are numerous and form confluent sheets, the neoplasm has evolved to diffuse large B-cell lymphoma.[4]

The small neoplastic cells have a marked tendency to infiltrate epithelium, forming so-called lymphoepithelial lesions (see Fig. 8–2). In well-formed lesions, aggregates of neoplastic cells are found within the epithelium. Reactive lymphoid follicles are also usually present in MALT lymphomas, generally surrounded by neoplastic small lymphoid cells. Neoplastic cells can also accumulate in these follicles (termed *colonization*), imparting a vaguely nodular appearance at low-power magnification.[4]

Anatomic site–specific histologic findings are also observed in MALT lymphomas, involving chronic antigenic stimulation caused by the presence of either an infectious organism or autoimmune disease. For example, normal lymphoid tissue is not usually present in the stomach. However, some forms of MALT are acquired in response to *H pylori* infection. *Chlamydia psittaci, Borrelia burgdorferi*, and *Campylobacter jejuni* are other infectious agents that have been associated with orbital, skin, and small intestinal MALT lymphomas, respectively, although the data linking *B burgdorferi* to skin lymphomas do not appear to be strong. Like the stomach, normal lymphoid tissue is also poorly developed in the lung. However, two inflammatory diseases are frequently associated with lung MALT lymphoma: Sjögren syndrome and lymphoid interstitial pneumonia. Similarly, MALT lymphomas of the salivary gland are usually associated with Sjögren syndrome, and Hashimoto thyroiditis usually precedes MALT lymphoma of the thyroid gland.[8,9]

Immunophenotypic, Cytogenetic, and Molecular Features

The MALT lymphomas express monotypic immunoglobulin (Ig) light chain, pan–B-cell antigens, and Bcl-2. These tumors typically do not express IgD, CD10, CD21, CD23, Bcl-6, cyclin D1, or T-cell antigens, including CD5. Four chromosomal translocations are well characterized in MALT lymphomas: t(11;18), t(14;18), t(1;14), and t(3;14). The frequency of these translocations varies by anatomic site of the lymphoma, and each translocation results in dysregulation of specific genes (see Table 8–1).[8,10] Vinatzer et al identified additional chromosomal translocations or partner genes in MALT lymphomas, including t(1;14)/*IGH-CNN3*, t(5;14)/*IGH-ODZ2*, t(3;14)/*IGH-BCL6*, t(9;14)/*IGH-JMJD2C*, and t(6;7)(q25;q11).[8] The translocations alter signaling associated with proliferation or inhibit apoptosis. Activation of NF-κB may be a final common pathway in MALT lymphomas. API2-MALT1 is known to activate NF-κB. Similarly, overexpression of MALT1 or BCL10, by binding with each other, can form a complex in the cell and act to activate NF-κB.[11]

Workup and Management

The diagnosis of gastric MALT lymphoma and presence of *H pylori* is established by endoscopy, with multiple biopsies obtained from abnormal and normal mucosa.[6] Endoscopic ultrasound and computed tomography scans may also be helpful in determining the depth of the lesion and for staging. Early-stage disease can be successfully treated initially with antibiotic therapy, with complete regression in 35% to 100% of patients with a low rate of recurrence.[6,11] Therefore, the recommended therapy for stage I or II disease is a standard regimen of antibiotic therapy for *H pylori* with follow-up endoscopy two to three months later to document *H pylori* eradication. If patients remain *H pylori*–positive, a second-line anti-*Helicobacter* regimen is administered until the patient tests negative for *H pylori*. The time between *H pylori* eradication and complete remission of gastric MALT lymphoma varies and can take longer than one year. More extensive disease, as documented by endoscopic ultrasound demonstrating lymphoma involvement beyond the mucosa and in regional nodes, is less likely to respond

to antibiotic therapy.[6,12] Lack of response has been correlated with the presence of the t(11;18) translocation.[9]

Surgery, radiotherapy (RT), chemotherapy, and anti-CD20 monoclonal antibody therapy have been used for both gastric and nongastric types of MALT lymphomas and other MZLs. The treatment of choice is dependent on the site and stage of disease and the patient's clinical presentation. Surgery and RT are prime therapeutic approaches for localized MALT lymphoma, including gastric MALT lymphoma that does not respond adequately to antibiotic therapy and *H pylori*–negative disease.[12] Chemotherapy and monoclonal antibody therapy are also options for advanced-stage MZL. Conconi et al studied rituximab in patients with MALT lymphoma and found significant clinical activity in both untreated and relapsed patients.[13] By extrapolation from small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL) data, combinations that include nucleoside analogues have been explored.[14] In recent years, nonchemotherapy treatment approaches have been explored, such as the use of the ibrutinib, a Bruton tyrosine kinase inhibitor that was FDA approved in 2017 for the treatment of MZL, and the immunomodulatory agent lenalidomide in combination with rituximab, which was FDA approved in 2019.[15–17] In addition, other targeted agents such as PI3 kinase inhibitors such as umbralisib (FDA granted breakthrough therapy designation.) and copanlisib have been explored.[18] The best systemic treatment option is not clear, but therapy for relapsed or extensive disease should be approached in the same manner as relapsed follicular lymphoma (refer to Chapter 7, Indolent Follicular Lymphomas).[9,12]

Nodal Marginal Zone Lymphoma

Clinical Features and Management

Patients with nodal MZL typically present with peripheral or para-aortic lymphadenopathy and bone marrow involvement. The five-year overall and failure-free survival rates are lower for patients with nodal MZL compared with patients with MALT lymphoma (56% vs 81% and 28% vs 65%, respectively). The majority of effective treatment regimens and outcomes of patients with nodal MZL are similar to that of patients with advanced follicular lymphoma (FL).

Histologic, Immunophenotypic, and Molecular Features

Nodal MZLs have a propensity to involve the marginal zones of a lymph node. In most cases, however, the neoplasm also expands into the perifollicular compartments with sparing of germinal centers, or it may completely replace lymph node architecture. The

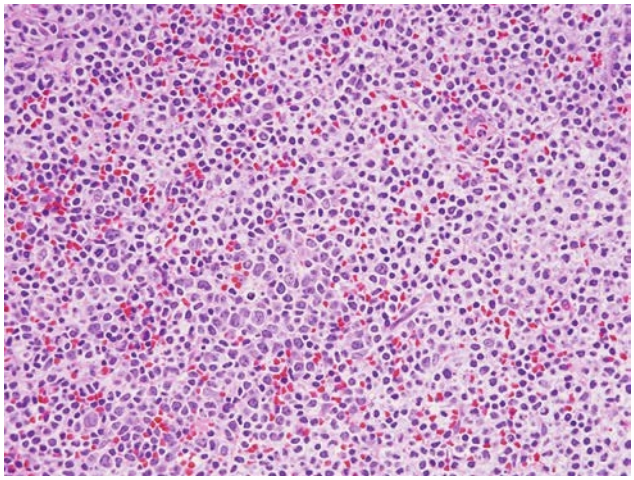


FIGURE 8–4 Nodal marginal zone lymphoma. In this field, the neoplastic cells have abundant pale cytoplasm and surround a reactive germinal center composed of large cells (center of field) (hematoxylin and eosin, ×400).

cytologic features of nodal MZL are the most distinctive aspect of this neoplasm. The tumor cell cytoplasm is relatively abundant and pale, with well-delineated cell borders (Fig. 8–4). The tumor cell nuclei are small, chromatin is relatively clumped, and mitotic figures are infrequent. Rare large cells are also present.[5]

Nodal MZLs are mature B-cell neoplasms that express monotypic Ig, pan–B-cell antigens, and Bcl-2. These tumors do not express CD10, CD21, CD23, BCL6, cyclin D1, or T-cell antigens, including CD5. Conventional cytogenetics and fluorescence in situ hybridization (FISH) studies have identified a variety of abnormalities, most often trisomy.[3] However, there are no unique recurrent chromosomal abnormalities in nodal MZL. The t(11;18), t(14;18), and t(1;14) have not been identified in nodal MZL5.

Splenic Marginal Zone Lymphoma

Clinical Features and Management

Patients with SMZL usually present with splenomegaly, cytopenias, and circulating malignant lymphocytes. They commonly have modest abdominal lymphadenopathy and bone marrow involvement. Monoclonal gammopathy, usually of IgM type, can be observed in 10% to 20% of patients. Peripheral lymphadenopathy and B-type symptoms are uncommon. The clinical course is indolent, with the five-year overall survival rate ranging from 65% to 78%.[19]

Approximately one third of patients with SMZL will never require therapy. Splenectomy is indicated in patients with symptomatic splenomegaly or cytopenias secondary to hypersplenism. If splenectomy is contraindicated, low-dose splenic irradiation may

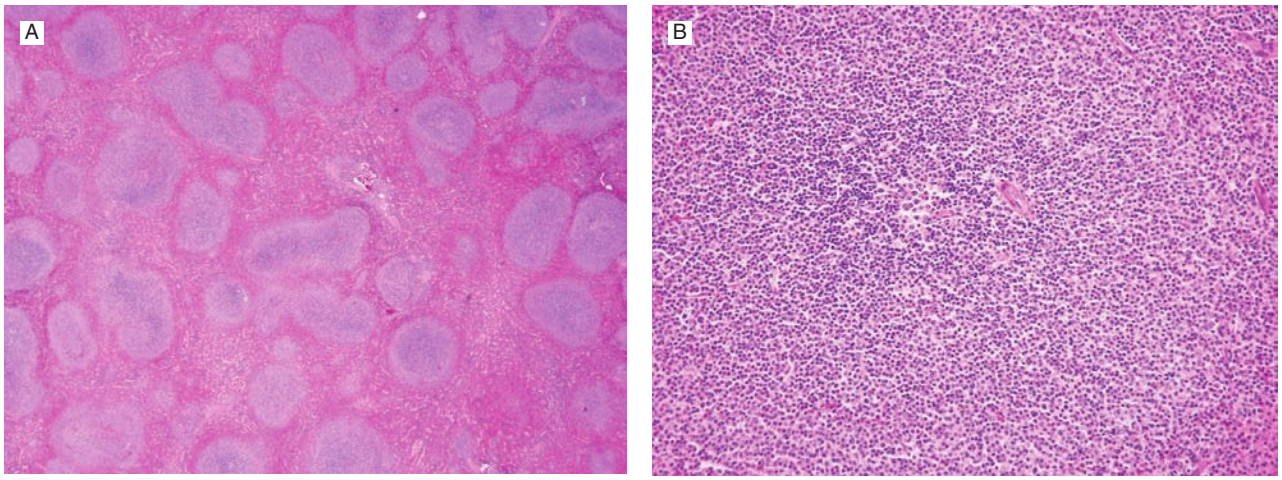


FIGURE 8–5 **Splenic marginal zone lymphoma. A. At low power, the white pulp of the spleen is markedly expanded by lymphoma, which has a biphasic pattern. B. One white pulp nodule at higher magnification (A, B, hematoxylin and eosin; A, ×20; B, ×200).**

be an alternative. Alkylating agents have been used, but responses are usually partial and not durable. Patients treated with fludarabine demonstrate a higher response rate and longer lasting remission than those treated with alkylating agents. Rituximab has significant activity in SMZL. In addition, in SMZL associated with hepatitis C, treatment of the underlying infection may be sufficient treatment for the lymphoma as well.[19]

Histologic, Immunophenotypic, and Molecular Features

In SMZL, the white pulp is expanded by a neoplasm that initially replaces the marginal and mantle zones and then eventually replaces the white pulp (Fig. 8–5). Lesser red pulp involvement is also usually present. At high-power magnification, the neoplastic cells are small lymphocytes with abundant pale (monocytoid) cytoplasm. The neoplastic cells may exhibit plasmacytoid differentiation. Occasional large lymphoid cells are present. In a peripheral blood smear, the neoplastic cells can have villous cytoplasmic projections.[19]

Splenic MZL is a mature B-cell neoplasm that expresses monotypic immunoglobulin, pan–B-cell antigens, and Bcl-2. A subset of cases is positive for IgD or CD5 (dim intensity detected by flow cytometry). These neoplasms are negative for CD10, Bcl6, cyclin D1, and T-cell antigens (other than CD5).

Conventional cytogenetics and FISH analysis have identified a variety of abnormalities, most often trisomy of chromosomes 3 and 7. Deletion of 7q is present in approximately 50% of cases. A recent study using array-based comparative genomic hybridization has demonstrated the presence of del(7q36.2) involving the sonic hedgehog (*SHH*) gene and del(7q31.32) involving the protection of telomere 1 (*POT1*) genes in SMZL.[20] *MYD88* L265P mutations have been identified in 10% to 20% of cases of SMZL and correlate with IgM gammopathy.[21]

SMALL LYMPHOCYTIC LYMPHOMA/ CHRONIC LYMPHOCYTIC LEUKEMIA

Small lymphocytic lymphoma represents approximately 7% of all NHLs.[3,4] The WHO classification restricts SLL to tumors involving lymph nodes with the same B-cell immunophenotype as CLL without leukemic involvement and considers SLL to be the nodal or tissue counterpart of CLL.[4] Cases of SLL and CLL combined represent about 12% of all B-cell NHLs.

Clinical Features and Management

Patients with SLL often present with asymptomatic lymphadenopathy. B symptoms are uncommon and are observed in less than 10% of patients. Splenomegaly is common. Bone marrow is often involved, affecting approximately 70% of patients.[3,4] Although the traditional staging systems for SLL and CLL differ, these systems share common features, and the prognosis of patients with SLL is similar to that of patients with CLL.

Management strategies for patients with FL and CLL are often applicable to patients with SLL, but there are some caveats (refer to Chapter 3, Chronic Lymphocytic Leukemia and Associated Disorders, and Chapter 7, Indolent Follicular Lymphomas). For instance, because CD20 is usually expressed at low levels in SLL/CLL, anti-CD20 antibody therapy for SLL may be better modeled on the results of studies in CLL

rather than the results of studies in patients with FL. Nonchemotherapy drug therapy consisting of venetoclax and obinutuzumab is FDA approved for SLL, with an overall response rate of 85%.

Histologic, Immunophenotypic, and Molecular Features

The lymph node architecture is diffuse and usually totally effaced by SLL/CLL4. The neoplastic cells are predominantly small, round lymphocytes. Vague pale areas composed of lymphocytes, prolymphocytes, and paraimmunoblasts, known as proliferation centers (or pseudofollicles), are usually present and are diagnostic of this neoplasm. In 5% to 10% of SLL/CLL cases, residual reactive lymphoid follicles are present, surrounded by neoplasm; this represents the so-called interfollicular pattern of SLL/CLL. In this morphologic variant, proliferation centers can surround benign follicles, mimicking nodal MZL.

The SLL/CLL cells express monotypic immunoglobulin light chain, IgM, usually IgD, pan–B-cell antigens, and Bcl-2. CD23 is usually positive in 90% to 95% of cases, and CD22, CD79B, and FMC7 are negative in most cases. The density of Ig and CD20 antigen expression on the surface of SLL/CLL cells is characteristically low ("dim" immunofluorescence by flow cytometry). These neoplasms almost invariably express the CD5 antigen, a pan–T-cell antigen that is not expressed on normal B cells. Other T-cell antigens are not expressed4. CD38 and ZAP70 are expressed in a subset of cases, and expression correlates with unmutated Ig genes and poorer prognosis.[22] The neoplastic cells are negative for CD10 and Bcl-64.

Conventional cytogenetic analysis has shown chromosomal abnormalities in 50% to 60% of SLL/CLL cases. This low frequency is partly attributable to poor cell growth in culture. Translocations involving the Ig genes are rare in SLL/CLL. The t(14;19)(q32;q13) translocation involving the *BCL3* gene at 19q13 is most common but is present in less than 5% of SLL/CLL cases. The t(14;19) translocation is associated with atypical morphologic or immunophenotypic features and a poorer prognosis.[23]

FISH analysis has shown a higher frequency of abnormalities in SLL/CLL because this technique can assess interphase as well as metaphase nuclei and does not require cell growth in culture. At our center, SLL/CLL cases are routinely assessed by FISH with a panel of probes, including those specific for 6q, 11q (ATM), trisomy 12, 13q14, and 17p (p53). Deletion of the 13q14 locus is the most common abnormality in SLL/CLL. Trisomy 12 is detected in approximately 15% to 20% of cases and appears to be a secondary event, because it is usually found in only a subset of the neoplastic cells.[24] Both del (11q) has been correlated with poorer prognosis. Abnormalities of the *p53* or *MYC* genes correlate with increased risk of histologic transformation (Richter syndrome) and poorer prognosis.

MD ANDERSON PRACTICE TIPS

- Many patients with MZL and SLL present asymptomatically. There are currently no data to suggest that the early initiation of treatment leads to improved overall survival; therefore, a close observation approach is indicated in many patients as is the case with other low-grade lymphomas.
- Patients with gastric MALT often present with symptoms of gastroesophageal reflux disease and abdominal pain. In addition to endoscopic evaluation, *H pylori* testing and advanced imaging is important to determine the extent of disease.
- Localized *H pylori*–positive gastric MALT is treated with triple or quadruple antibiotics targeting *H pylori*. Treatment should be continued until the patient is negative for *H pylori*. More extensive disease and patients with translocation t(11;18) may not respond to antibiotics alone and may need systemic treatment extrapolated from studies of FL.
- Nodal MZL should be treated in the same manner as FL.
- Splenic MZL that is associated with hepatitis C should be first managed by treating the hepatitis C. Rituximab is the treatment of choice in most cases of splenic MZL; splenectomy can be considered in specific circumstances such as symptomatic splenomegaly and refractory cytopenias cause by splenic sequestration.
- In SLL, abnormalities of the *p53* or *MYC* genes correlate with increased risk of histologic transformation (Richter syndrome) and poorer prognosis.

REFERENCES

1. Juárez-Salcedo LM, Castillo JJ. Lymphoplasmacytic lymphoma and marginal zone lymphoma. *Hematol Oncol Clin North Am.* 2019;33(4):639-656.
2. Sindel A, Al-Juhaishi T, Yazbeck V. Marginal Zone lymphoma: state-of-the-art treatment. *Curr Treat Options Oncol.* 2019;20(12):90.
3. The Non-Hodgkin's Lymphoma Classification Project. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. *Blood.* 1997;89(11):3909-3918.
4. Polyatskin IL, Artemyeva AS, Krivolapov YA. [Revised WHO classification of tumors of hematopoietic and lymphoid tissues, 2017 (4th edition):lymphoid tumors]. *Arkh Patol.* 2019;81(3):59-65.
5. Leslie LA, Feldman TA, McNeill A, et al. Contemporary management of nodal and primary splenic marginal zone lymphoma. *Expert Rev Hematol.* 2019;12(12):1011-1022.
6. Steinbach G, Ford R, Glober G, et al. Antibiotic treatment of gastric lymphoma of mucosa-associated lymphoid tissue. An uncontrolled trial. *Ann Intern Med.* 1999;131(2):88-95.
7. Wotherspoon AC, Doglioni C, Diss TC, et al. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of Helicobacter pylori. *Lancet.* 1993;342(8871):575-577.
8. Vinatzer U, Gollinger M, Müllauer L, et al. Mucosa-associated lymphoid tissue lymphoma: novel translocations including rearrangements of ODZ2, JMJD2C, and CNN3. *Clin Cancer Res.* 2008;14(20):6426-6431.
9. Toyoda K, Maeshima AM, Nomoto J, et al. Mucosa-associated lymphoid tissue lymphoma with t(11;18)(q21;q21) translocation: long-term follow-up results. *Ann Hematol.* 2019;98(7):1675-1687.
10. Kaplon H, Muralidharan M, Schneider Z, et al. Antibodies to watch in 2020. *MAbs.* 2020;12(1):1703531.
11. Isaacson PG, Du MQ. MALT lymphoma: from morphology to molecules. *Nat Rev Cancer.* 2004;4(8):644-653.
12. Kobayashi Y. JSH practical guidelines for hematological malignancies, 2018: II. Lymphoma-2. Marginal zone lymphoma (MALT lymphoma/extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue and splenic marginal zone lymphoma). *Int J Hematol.* 2019;110(4):393-405.
13. Conconi A, Martinelli G, Thiéblemont C, et al. Clinical activity of rituximab in extranodal marginal zone B-cell lymphoma of MALT type. *Blood.* 2003;102(8):2741-2745.
14. Samaniego F, Fanale M, Pro B, et al. Pentostatin, cyclophosphamide, and rituximab (PCR) achieve high response rates in indolent B-cell lyphoma without prolonged myelosuppression. *Blood.* 2008;112(11):835-835.
15. Becnel MR, Nastoupil LJ, Samaniego F, et al. Lenalidomide plus rituximab (R(2)) in previously untreated marginal zone lymphoma: subgroup analysis and long-term follow-up of an open-label phase 2 trial. *Br J Haematol.* 2019;185(5):874-882.
16. Noy A, de Vos S, Thieblemont C, et al. Single-agent ibrutinib demonstrates efficacy and safety in patients with relapsed/refractory marginal zone lymphoma: a multicenter, open-label, phase 2 study. *Blood.* 2016;128(22):1213.
17. Leonard JP, Trneny M, Izutsu K, et al. AUGMENT: a phase III study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. *J Clin Oncol.* 2019;37(14):1188-1199.
18. Dreyling M, Morschhauser F, Bouabdallah K, et al. Phase II study of copanlisib, a PI3K inhibitor, in relapsed or refractory, indolent or aggressive lymphoma. *Ann Oncol.* 2017;28(9):2169-2178.
19. Arcaini L, Rossi D, Paulli M. Splenic marginal zone lymphoma: from genetics to management. *Blood.* 2016;127(17):2072-2081.
20. Vega F, Cho-Vega JH, Lennon PA, et al. Splenic marginal zone lymphomas are characterized by loss of interstitial regions of chromosome 7q, 7q31.32 and 7q36.2 that include the protection of telomere 1 (POT1) and sonic hedgehog (SHH) genes. *Br J Haematol.* 2008;142(2):216-226.
21. Martinez-Lopez A, Curiel-Olmo S, Mollejo M, et al. MYD88 (L265P) somatic mutation in marginal zone B-cell lymphoma. *Am J Surg Pathol.* 2015;39(5):644-651.
22. Admirand JH, Rassidakis GZ, Abruzzo LV, et al. Immunohistochemical detection of ZAP-70 in 341 cases of non-Hodgkin and Hodgkin lymphoma. *Mod Pathol.* 2004;17(8):954-961.
23. Huh YO, Schweighofer CD, Ketterling RP, et al. Chronic lymphocytic leukemia with t(14;19)(q32;q13) is characterized by atypical morphologic and immunophenotypic features and distinctive genetic features. *Am J Clin Pathol.* 2011;135(5):686-696.
24. Aoun P, Blair HE, Smith LM, et al. Fluorescence in situ hybridization detection of cytogenetic abnormalities in B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma. *Leuk Lymphoma.* 2004;45(8):1595-1603.

This page intentionally left blank

9 Aggressive B-Cell Lymphomas

Raphael Steiner
Jason R. Westin
Sergej N. Konoplev
Luis E. Fayad
L. Jeffrey Medeiros

KEY CONCEPTS

- Evaluation of pretreatment prognostic factors of diffuse large B-cell lymphoma (DLBCL) includes scores such as the International Prognostic Index (IPI); cell-of-origin (germinal center B-cell subtype [GCB] and activated B-cell [ABC] subtype); genetic profiling (such as fluorescence in situ hybridization studies [FISH] for *MYC* rearrangement, if *MYC* rearrangement is detected, additional FISH studies for *BCL2* and *BCL6* rearrangements should be performed); and immunophenotypic studies (such as *MYC, BCL2*, and *BCL6 expression)*.
- The baseline workup of aggressive B-cell lymphoma should not omit testing for hepatitis B and HIV, echocardiogram, or multigated acquisition scan (if planned therapy with anthracycline), and fertility counseling for eligible patients.
- Besides a clinical trial, the standard-of-care frontline therapy of DLBCL not otherwise specified is still rituximab cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). However, many studies are ongoing to outperform this combination.
- The treatment plan of aggressive B-cell lymphoma should evaluate the potential need for central nervous system (CNS) prophylaxis for patients presenting with the following risk factors: elevated CNS-IPI (age >60 years, Eastern Cooperative Oncology Group [ECOG] Performance Status ≥2, extranodal disease >1 site, stage III/IV, elevated lactate dehydrogenase, kidney/adrenal involvement); extranodal disease with testicular, uterine, breast, epidural, skin involvement); aggressive B-cell lymphoma subtypes (Burkitt lymphoma, double/triple-hit lymphoma/high-grade B-cell lymphoma, double-expressor lymphomas, HIV-associated lymphoma, DLBCL with ABC subtype, intravascular DLBCL, CD5+ DLBCL, IgM-secreting DLBCL).
- The baseline workup of a suspected primary CNS lymphoma should include magnetic resonance imaging (MRI) of the brain and biopsy of the lesion, search for additional disease sites, such as testicular ultrasound for men >60 years old, full ophthalmologic examination including slit-lamp eye examination, spine MRI, positron emission tomography/computed tomography (PET/CT) scan, and bone marrow biopsy.
- The optimal frontline therapy of Burkitt lymphoma has yet to be defined in a prospective randomized trial, but R-CHOP is not an adequate therapy. If a patient cannot be enrolled in a clinical trial, aggressive combination chemotherapy such as R-Hyper-CVAD/MA, R-CODOX-M/IVAC, or DA-EPOCH-R with adequate CNS prophylaxis is recommended.

It is clinically useful to divide B-cell non-Hodgkin lymphomas (NHLs) into indolent and aggressive groups based on their clinical behavior.[1] Patients with indolent NHLs typically have a survival of many years, even if the NHL is untreated, but paradoxically, the NHLs are usually incurable. Patients with aggressive NHL have a survival time measured in weeks to months if untreated yet the NHLs are usually chemosensitive and frequently curable. In this chapter, we focus on the clinical characteristics, pathology, and treatment of aggressive B-cell NHLs.

EPIDEMIOLOGY

Globally, lymphoma incidence rates have declined slightly (0.3% per year) since 2001 in females and since 2004 in males in the US. Earlier, lymphoma incidence

rates increased steadily during the 1970s and 1980s, leveled off in the 1990s, and began a slight decline by the end of that decade. This drop, independent of HIV infection may in part reflect International Classification of Diseases coding changes in 2001, when the World Health Organization (WHO) classification system was first published.[2]

Among mature lymphoid neoplasms, the fastest increase over the 12-year period from 2001 through 2012 was for plasma cell neoplasms. The trend in increasing body size may partly explain this increase, because obesity was steadily increasing over this time period and is a risk factor for plasma cell neoplasms.[2] In 2020, the American Cancer Society estimated that 77,240 individuals would be diagnosed with NHL in the United States during the year, and 19,940 patients would succumb to disease.

Diffuse large B-cell lymphoma (DLBCL), the most common NHL subtype, has an aggressive behavior and is more common in Whites than African Americans in the United States; however, 5-year survival outcomes are worse in African Americans.[3,4]

ETIOLOGY

Most cases of aggressive B-cell NHL do not have a well-defined etiology. Recent work has shown that the lifetime risk for many cancers correlates with the total number of divisions of normal self-renewing cells.[5] The implications of these findings suggest that many cancers may not be caused by hereditable genetic aberrancies, environmental exposures, infectious etiologies, or other known causes, but instead are attributable to a combination of factors that may include chance. For the NHLs that appear to have currently identifiable drivers, there are five groups of drivers: immune suppression (both acquired and primary), infectious agents, toxic exposure, lifestyle, and familial factors (Table 9–1). Moreover, risk factors may be different for children and adults.[2]

Most cases of DLBCL not otherwise specified arise de novo (referred as primary) but can also represent a transformation of an indolent/less aggressive lymphoma, such as chronic lymphocytic leukemia/small lymphocytic lymphoma, follicular lymphoma, marginal zone lymphoma or nodular lymphocyte-predominant Hodgkin lymphoma.[6]

Immunosuppression

The strongest association with aggressive B-cell NHLs is immune suppression, both primary and acquired.[7] Examples of primary immunodeficiency include inherited immune disorders, such as Wiskott-Aldrich syndrome, severe combined immune deficiency, common variable immune deficiency, and ataxia-telangiectasia.[8] These diseases and other inherited disorders are associated with an increased lifetime risk of developing NHL, with aggressive B-cell NHL being most common.

Patients who are immunosuppressed for therapeutic reasons—for example, after organ transplantation—are also at increased risk of NHL, especially if the disease is treated with cyclosporine, azathioprine, prednisone, or monoclonal antibodies for the removal of T cells.[9] A loose association can be drawn between the level of immune suppression and lymphoma risk. Transplant patients treated with the highest doses of immunosuppressive agents, such as heart transplant recipients, are at greater risk of lymphomas developing. These lesions are also more likely to be aggressive and are often extranodal forms. Individuals treated with pharmacologic immune suppression for autoimmune disorders—such as systemic lupus erythematosus, Sjögren syndrome, or rheumatoid arthritis—are also at increased risk for NHL, including the tumor necrosis factor antagonists.[10] A subset of these NHLs is histologically aggressive and associated with Epstein-Barr virus (EBV) infections. These

Table 9–1 Risk Factors Associated With Aggressive Non-Hodgkin Lymphomas

Inherited and acquired immune deficiency
– Wiskott-Aldrich syndrome
– Ataxia-telangiectasia
– Chédiak-Higashi syndrome
– X-linked immunoproliferative disorder
– Severe combined immunodeficiency
– Common variable immune deficiency
– Iatrogenic immune suppression
– Solid organ or bone marrow transplant
Toxic exposures
– Prior chemotherapy
– Phenoxyherbicides
– Dioxin
– Radiation or radiation therapy
Infectious exposures
– Epstein-Barr virus
– Hepatitis C virus
– Human T-cell leukemia/lymphoma virus
– Human herpesvirus type 8 (HHV-8)
– HIV
Lifestyle
– Higher young-adult body mass index
Autoimmune disorders
– Sjögren syndrome
– Celiac sprue
– Systemic lupus erythematosus
– Rheumatoid arthritis

lesions may regress after withdrawal of the immunosuppressive agent, speaking to a complex interaction between the immune system and an immune clonal population.[11]

Infectious Exposure

Infectious agents associated with development of aggressive B-cell NHLs include HIV, EBV, human herpesvirus type 8, and human T-cell lymphotropic virus type 1.[12] The greatest factor involved in the worldwide increase in NHLs, although lessened with the advent of highly active antiretroviral therapy, is HIV infection. The risk of NHL is increased by up to 300% in untreated HIV-infected patients, rising in proportion to the duration of the HIV infection. Although the risk of NHL in HIV-infected patients appears to be decreased by highly active antiretroviral therapy, the relative risk of NHL in these patients remains much higher than that for those not infected with HIV. Aggressive B-cell NHLs can occur in HIV-infected patients at any stage of infection, but the risk increases as CD4 counts drop to $<100 \times 10^3/\mu L$. In addition, Burkitt lymphoma (BL), DLBCL arising in the CNS, and DLBCL–immunoblastic variant are considered as AIDS-defining illnesses.[13–15] Further information can be found in the Chapter 52 on acquired immunodeficiency syndrome–related cancers.

EBV also plays a role in lymphomagenesis, in part because of chronic antigenic stimulation.[16] EBV is virtually always associated with certain types of NHL, such as endemic BL and extranodal T-cell/natural killer (NK)-cell lymphoma of nasal type, with many other NHL types occasionally positive for EBV. Many patients with HIV-related lymphomas are coinfected by EBV, including HIV-associated primary CNS lymphoma, which is infected in essentially 100% of cases.[17]

Hepatitis C virus has been associated with different types of B-cell NHL, notably marginal zone lymphomas, lymphoplasmacytic lymphoma, and DLBCL.[18,19]

Human herpesvirus type 8 (HHV8) is associated with primary effusion lymphoma (PEL), which tends to occur in HIV-infected patients, but also occurs less often in endemic geographic regions (eg, sub-Saharan Africa). Human T-cell lymphotropic virus type 1 is integrated into the genome of the neoplastic cells of adult T-cell lymphoma/leukemia.

Toxic Exposure

Environmental and occupational exposures to toxins are associated with an increased risk of NHL. Herbicides have been implicated.[20] Occupations held by individuals reported to be at increased risk for NHL include farming, metalworking, forestry, aircraft maintenance, woodworking, and dry cleaning. One of the common exposures in these industries is the use of organic solvents.[21]

Lifestyle and Family History

Higher body mass index in young adults has been described as a risk factor for DLBCL.[19] Family history of NHL is also a potential risk factor for some types of NHL. Individuals who have relatives with NHL may be at a slightly higher risk of acquiring NHL, but data are inconclusive and mechanisms are unclear.[22]

CLINICAL PRESENTATION

The clinical presentation of patients with aggressive B-cell NHL varies substantially based on histologic type and anatomic site of disease. The likelihood of B symptoms, including fever greater than 38 °C, night sweats, or weight loss more than 10% of body weight in the preceding 6 months, increases with NHL aggressiveness.[23] Approximately 13% to 53% of patients present with these B symptoms, often with fatigue, malaise, and pruritus, although these are less common initially.[24]

Most patients present with painless lymphadenopathy, which is often first treated with antibiotics for presumed infection and then eventually lymph nodes are biopsied when lymphadenopathy fails to regress. The most common scenario involves a diagnosis based on examination of peripheral lymph nodes, which may be detectable before internal lymph nodes become enlarged and cause symptoms. Peripheral lymph nodes are not usually painful, unless they enlarge rapidly or are massive. Symptoms vary with the anatomic site of internal lymphadenopathy. Patients with mediastinal lymphadenopathy frequently experience cough, chest pain, and, less commonly, superior vena cava syndrome. Patients with large nodal masses in the abdomen or retroperitoneum frequently experience pain, abdominal fullness, or early satiety. Retroperitoneal lymphadenopathy can cause back pain and discomfort.

Extranodal disease is common in patients with aggressive NHL. The most common extranodal sites are the gastrointestinal (GI) tract, tonsils, and skin, although the frequency of involvement of these sites varies across reports. Disease in the GI tract can manifest as nonspecific symptoms, including gastric obstruction, blood loss with subsequent anemia, or diarrhea. Other extranodal sites include liver, lungs, testes, breasts, ovaries, bones, CNS, and spleen; however, aggressive extranodal NHL may involve nearly any organ system.[23]

CLINICOPATHOLOGIC CHARACTERISTICS

The current WHO classification of lymphoid neoplasms has refined the diagnostic criteria for some entities, detailed the expanding genetic/molecular landscape of numerous lymphoid neoplasms and their clinical correlates, and refers to investigations leading to more targeted therapeutic strategies. This new classification of large B-cell lymphomas is illustrated in Table 9–2.[1,25] Most cases of DLBCL are designated as not otherwise specified (NOS). However, about 20% of cases, are designated as specific variants of DLBCL. These variants, are specified on the basis of distinctive morphologic or immunophenotypic findings or distinctive biological or clinical issues associated with their diagnoses.[26]

Table 9–2 2016 WHO Classification of Large B-Cell Lymphoma

DLBCL, NOS
Morphological variants
Centroblastic
Immunoblastic
Anaplastic
Other rare variants
Molecular subtypes
Germinal center B-cell subtype
Activated B-cell subtype
Other lymphomas of large B-cells
T-cell/histiocyte-rich large B-cell lymphoma
Primary diffuse large B-cell lymphoma of the central nervous system
Primary cutaneous DLBCL, leg type
EBV-positive DLBCL, NOS
DLBCL associated with chronic inflammation
EBV-positive mucocutaneous ulcer
Lymphomatoid granulomatosis
Large B-cell lymphoma with IRF4 rearrangement
Primary mediastinal (thymic) B-cell lymphoma
Intravascular large B-cell lymphomas
ALK-positive large B-cell lymphoma
Plasmablastic lymphoma
HHV8-positive diffuse large B-cell lymphoma
Primary effusion lymphoma
High-grade B-cell lymphoma
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements
High-grade B-cell lymphoma, NOS
B-cell lymphoma, unclassifiable
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and
Classic Hodgkin lymphoma

DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; HHV, human herpesvirus; NOS, not otherwise specified.
Reproduced with permission from from Swerdlow SH, Campo E, Harris NL, et al: *WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues*, 4th ed. IARC, *Lyon*; 2017.

Diffuse Large B-Cell Lymphoma, Not Otherwise Specified

Epidemiology

DLBCL–NOS is the most common type of lymphoma and accounts for approximately 25% of all NHLs in the developed world.[2]

DLBCL–NOS occurs mainly in adults, with a median age in the sixth decade of life. Men are affected slightly more often than women.[2]

Clinical Presentation

B-type symptoms or bulky disease occurs in one-third of patients. Nodal presentation is most common, but extranodal sites are involved in approximately 40% of patients (Figs. 9–1 and 9–2), and more than one-third of patients have more than one extranodal site of disease.[27] Slightly more than half of patients have stage III or IV disease. Bone marrow involvement occurs in approximately 10% to 20% of patients.[27] DLBCL uncommonly involves privileged sites, such as the testes and CNS, of which the latter portends a poorer prognosis.

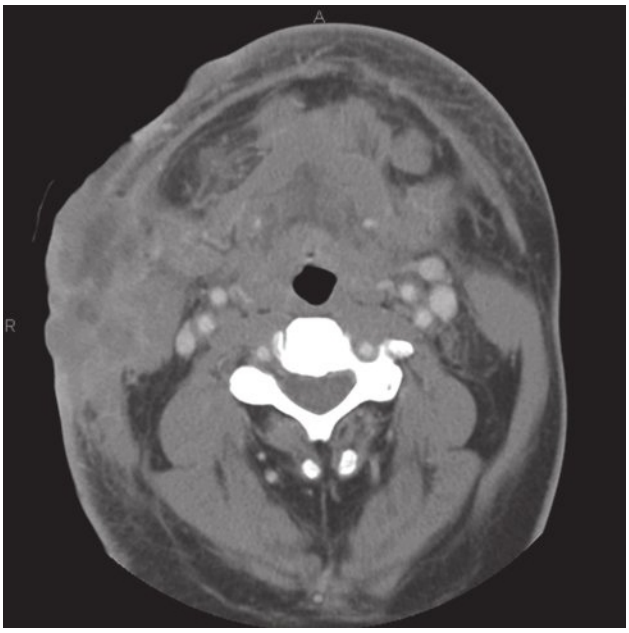


FIGURE 9–1 Computed tomography scan showing diffuse large B-cell lymphoma with extensive lymph node involvement in the neck.

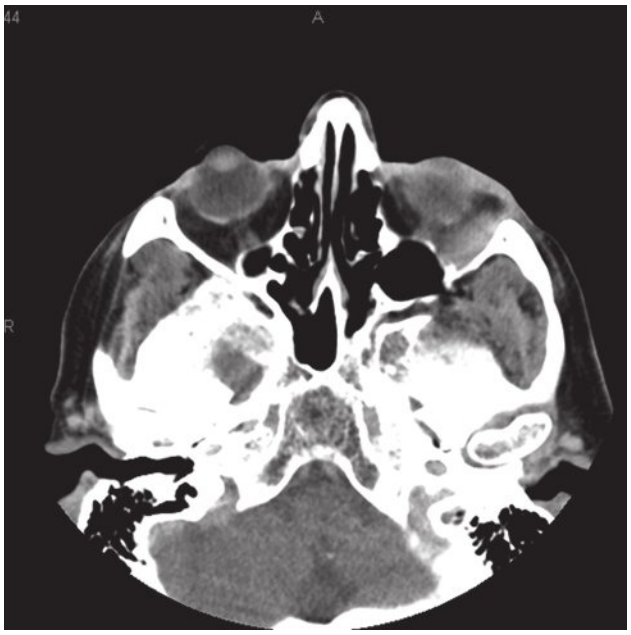


FIGURE 9–2 **Computed tomography scan showing diffuse large B-cell lymphoma as a periorbital mass.**

Interestingly, patients with limited-stage DLBCL tend to present a pattern of continuing relapse after completion of therapy, likely a result of biological differences between limited- and advanced-stage lymphoma.[28]

Microscopic Morphology

DLBCL is defined as a neoplasm with a diffuse growth pattern composed of medium-size or large B cells whose nuclei are the same size as, or larger than, the nuclei of normal macrophages, or more than twice the size of normal lymphocytes.[25]

Morphologic, biologic, and clinical studies have subclassified DLBCLs into subtypes and distinct entities, as illustrated in Table 9–2. However, there remain many cases that may be biologically heterogeneous, for which there are no universally accepted criteria for subdivisions. These cases are classified as DLBCL–NOS (Figs. 9–3 and 9–4).[25]

The most common morphologic variant is the centroblastic variant. Centroblasts are medium to large lymphoid cells with oval to round, vesicular nuclei containing fine chromatin and two to four membrane-bound nucleoli.

The immunoblastic variant (Fig. 9–5) represents about 10% of all cases of DLBCL–NOS and is composed of more than 90% immunoblasts, defined as a large cell with a central round nucleus and a prominent single, centrally located nucleolus. One study demonstrated that DLBCL with immunoblastic variant more often demonstrated *MYC* rearrangement (13 of 39

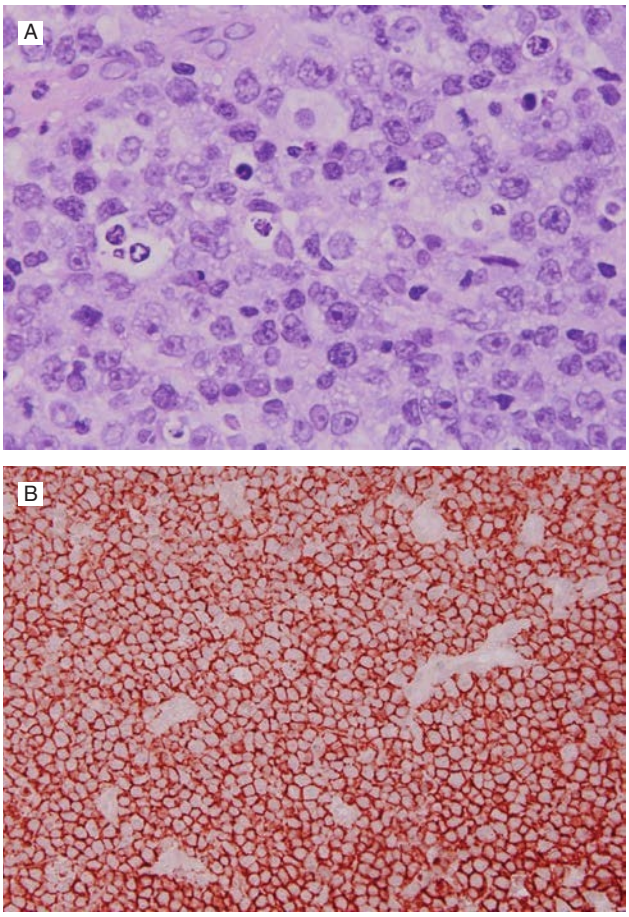


FIGURE 9–3 **Diffuse large B-cell lymphoma. A. The neoplastic cells are large with vesicular chromatin and are arranged in a diffuse pattern. B. The neoplastic cells are positive for CD20. (A, hematoxylin-eosin, ×1000; B, immunohistochemistry, ×400.)**

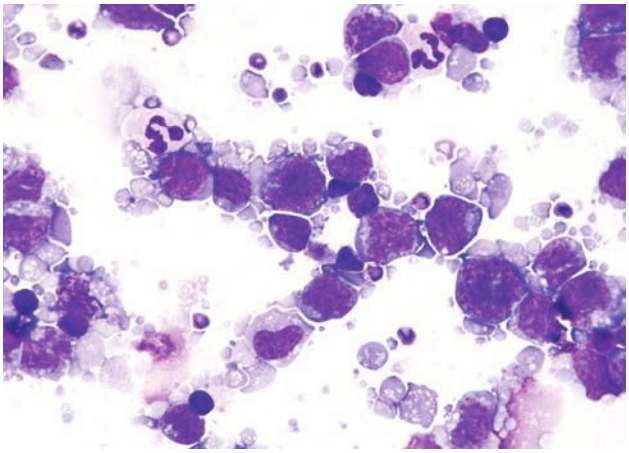


FIGURE 9–4 **Diffuse large B-cell lymphoma. Fine-needle aspiration of cervical lymph node. The neoplastic cells are large (compared with neutrophils in field) with abundant basophilic cytoplasm (Wright-Giemsa, ×1000).**

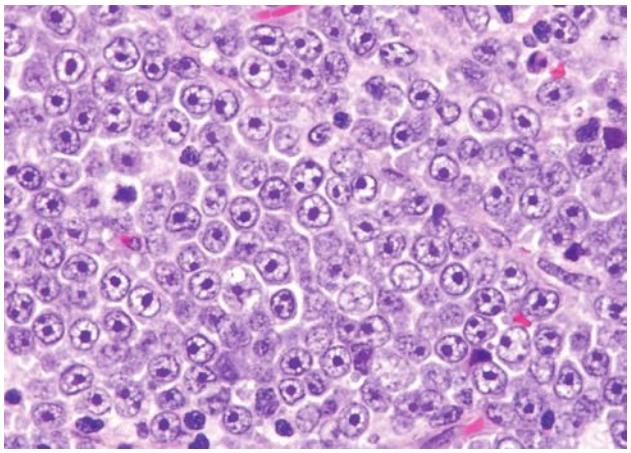


FIGURE 9–5 Diffuse large B-cell lymphoma, immunoblastic variant. The neoplastic cells are large with prominent central nucleoli imparting a "target-like" appearance (hematoxylin-eosin, ×1000).

immunoblastic DLBCLs including 10 with *MYC* rearrangement as a single hit compared with 5 of 68 non-immunoblastic DLBCLs).[29] Some studies have found an adverse impact of immunoblastic morphology.

The anaplastic variant represents 2% to 3% of all cases of DLBCL and is characterized by large to very large cells with bizarre pleomorphic nuclei, which may resemble partially Hodgkin/Reed-Sternberg cells or the neoplastic cells of anaplastic large cell lymphoma. CD30 is often expressed by the neoplastic cells of the anaplastic variant.[25]

There are also rare morphologic variants including cases with myxoid stroma, fibrillary matrix, signet ring morphology, spindle-cell morphology, and microvillous morphology (by electron microscopy). Because of the rarity of those variants, their clinical significance is unclear, but occasionally these unusual morphologic features might create diagnostic challenges.

Immunophenotype

Immunophenotypic studies have shown that DLBCLs are of mature B-cell lineage. Approximately two-thirds of cases express monotypic immunoglobulin (Ig). These tumors express pan–B-cell markers such as CD19, CD20, CD22, CD79a, and PAX5, although occasionally the neoplasm might demonstrate an aberrant loss of one of the pan–B-cell markers. About 60% to 70% of DLBCL–NOS cases express BCL2, and a 40% to 60% subset is positive for CD10 and BCL6. The Ki-67 proliferation index is high, usually more than 40% and may be even as high as more than 90% in some cases. p53 is expressed in more than 50% of cells in 20% to 60% of cases.[25] Immunohistochemistry also can be used to determine cell of origin (COO; see below).

MYC, BCL2, and Double-Expressor Lymphoma

Immunohistochemistry is also commonly used to detect MYC expression in DLBCL cases. MYC is detected in 30% to 50% of cases of DLBCL using a 40% cutoff (which is most commonly used in the literature). MYC expression correlates loosely with the presence of *MYC* rearrangement. Concomitant expression of BCL2 (50% cutoff) and MYC occurs in 20% to 35% of cases of DLBCL, and this is known as a double-expressor phenotype or "double-expressor lymphoma." The incidence of double protein expression is estimated to be 19% to 34%.[30] Most of these tumors do not carry *MYC/BCL2* chromosomal alterations. In most studies, the double-expressor lymphomas are more frequently of the ABC subtype and have a worse outcome than other DLBCL–NOS, but they offer a better outcome than aggressive B-cell lymphoma with rearrangements of *MYC* and *BCL2* and/or *BCL6*. Overall, double expression of MYC and BCL2 proteins without gene aberrations is be considered a prognostic indicator in DLBCL–NOS, but is not considered a separate category.[1,31–34]

Genetic Profile

Common somatic mutations in DLBCL are inactivating mutations of *TP53* and genes involved in immunosurveillance (*B2M*, *CD58*), alterations in epigenetic regulators (*CREBBP/EP300*, *KMT2D/C* [*MLL2/3*], *MEF 2B*), and oncogenic activation of *BCL6*.[1]

DLBCLs are heterogeneous at the molecular level. A subset of cases carries the t(14;18)(q32;q21) involving *BCL2*, as shown by conventional cytogenetic or molecular studies.[35,36] Another subset of DLBCLs has translocations or other abnormalities involving *BCL6* at chromosome 3q27. *BCL6* is rearranged in approximately 20% to 40% of DLBCLs, more often in tumors arising at extranodal sites.[37] *MYC* translocation occurs in 10% to 15% of DLBCL cases.

Cell of Origin

The WHO classification recommends determining the COO in all cases of DLBCL. The best approach is to use gene expression profiling (GEP) methods, which requires fresh tissue to extract RNA. A number of studies using this approach was published about 20 years ago, but the most popular system classified cases into germinal center B-cell (GCB), activated B-cell (ABC), and an unclassified group, the latter representing about 15% of all cases. This COO classification not only defined subgroups with distinct biology and pathogenesis, but in many studies (but not all) identified groups of patients with different outcomes after therapy.[38]

Although the COO classification was an important first step, more recent studies have shown the limitations of this system, which is not sufficiently precise. Studies by Schmitz and colleagues and Chapuy et al. showed four and five groups, respectively and a recent study by Conley et al showed six groups, with one divided into two subgroups: MCD, N1, A53, BN2, EZB MYC+, and EZB MYC–. Analysis of genetic pathways suggested that MCD and BN2 DLBCLs rely on "chronic active" B-cell receptor signaling that will be amenable to therapeutic targeted inhibition.[39,40] Outside a clinical trial, these genetic groups do not have currently therapeutic consequences.

Nevertheless, in our opinion, this system will likely be refined and applied to cases of DLBCL in routine practice, although this approach may take some time to institute. Recent technologies such as Nanostring assays (Nanostring) will likely facilitate this progress.[41]

Because gene expression profiling is not available in many laboratories, immunohistochemistry surrogates are considered acceptable using markers such as CD10, MUM-1, BCL6, GCET1, and FOXP1. The most popular system is the one proposed by Hans and colleagues, which used CD10, MUM-1, and BCL6, and subclassifies DLBCL groups into germinal center B-cell subtype (GCB) and non-GCB, with relatively good concordance with GEP.[42,43]

Other Lymphomas of Large B Cells

T-Cell/Histiocyte-Rich Large B-Cell Lymphoma

T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) accounts for less than 5% of DLBCL and is a diffuse neoplasm in which most of the cells are reactive T cells and histiocytes. The large, neoplastic B cells represent less than 10% of all cells in the infiltrate (Fig. 9–6). THRLBCL frequently harbors genetic mutations in *JUNB*, *DUSP2*, *SGK1*, *SOC1*,or *CREBBP*.[26] Patients with THRLBCL commonly have a history of nodular lymphocyte-predominant Hodgkin lymphoma, and THRLBCL may represent a transformation event in some patients.[25,44]

Primary Diffuse Large B-Cell Lymphoma of the Central Nervous System

This entity includes DLBCL arising within the brain, spinal cord, leptomeninges, or eye. It notably excludes lymphomas of the dura, intravascular large B-cell lymphoma, and lymphomas with evidence of systemic disease. Primary DLBCL of the central nervous system (PCNSL) accounts for less than 1% of all NHL and 2.4% to 3% of all brain malignancies. Approximately 20% of patients present with or develop intraocular lesions and 80% to 90% of patients with intraocular

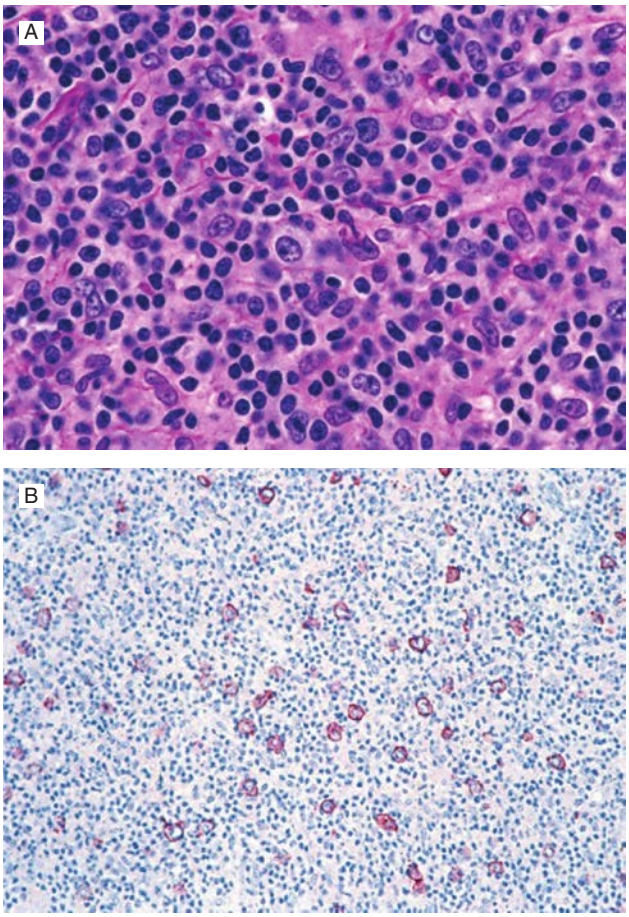


FIGURE 9–6 T-cell/histiocyte-rich large B-cell lymphoma. A. Scattered large neoplastic lymphoid cells in a background of numerous small lymphocytes. B. The large neoplastic cells are positive for CD20, and the small lymphocytes are T cells (immunostain not shown). (A, hematoxylin-eosin, ×630]; B, immunohistochemistry, ×200.)

DLBCL develop contralateral tumors and parenchymal brain lesions. Interestingly, dissemination to extraneural sites is rare.[25]

Patients present focal neurologic deficits in 56% to 70% of cases and other signs and symptoms include mental and behavioral alteration, intracranial pressure symptoms, and seizures.[26]

Although these lymphomas are remarkable for their unique clinical presentation, histologically and at the immunophenotypic level, these neoplasms closely resemble other cases of systemic DLBCL. The neoplasm demonstrates pan–B-cell markers such as CD19, CD20, CD22, CD79a, and PAX5. Most cases are positive for BCL6 and IRF4/MUM1, whereas only a small proportion (<10%) of neoplasms is positive for CD10. The Ki-67 proliferation rate is usually high (>70%), and BCL2 and MYC expression is common (>80%). EBV infection is consistently absent. Central nervous system (CNS) DLBCLs show a high prevalence of *MYD88*

mutations and *CDKN2A* biallelic loss and alteration of the B-cell receptor/toll-like receptor/NF-κB pathways.[45] PCNSL may be considered a post–germinal center disease associated with the ABC-DLBCL type in origin.[46] Approximately one-third of the cases demonstrate translocations involving *BCL6*.

In HIV-positive patients, DLBCL arising in the brain is an AIDS-defining malignancy. These neoplasms differ from cases of PCNSL in which a history of immunodeficiency is not accepted. In HIV-associated DLBCL of the brain, CD4 counts in affected patients are commonly less than 50 cells/μL. The neoplastic cells often have immunoblastic cytologic features and are positive for EBV.[47] However, the incidence of DLBCL in patients living with HIV has declined with widespread adoption of antiretroviral therapy.[48]

Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type

Primary cutaneous diffuse large B-cell lymphoma, leg type (PCLBCL-LT), as the name suggests, presents as cutaneous lesions without extracutaneous disease. PCLBCL-LT, originally described in the lower extremities, presents in legs in 85% to 90% of patients. However, all skin sites may be affected. PCLBCL-LT accounts for 4% of all primary cutaneous B-cell lymphomas.[25,49] Lesions are often red or blue-red and eventually become diffuse and ulcerated. Histologic sections show diffuse sheets of monotonous neoplastic cells, often with immunoblastic morphology with frequent mitotic figures.[50] The neoplastic cells are positive for CD20, CD79a, BCL2, IRF4/MUM1, FOXP1, and monotypic Ig. Up to 80% of cases are MYC positive and about two-thirds of cases have a double-expressor immunophenotype. Fluorescence in situ hybridization (FISH) studies can show rearrangements of *MYC i*n up to one-third of cases.[26,51]

Epstein-Barr Virus–Positive Diffuse Large B-Cell Lymphoma, Not Otherwise Specified

This nomenclature replaces EBV-positive DLBCL of the elderly because this neoplasm may occur in younger patients. However, this lymphoma occurs usually in individuals older than 50 years, with a peak in the eighth decade of life. This neoplasm accounts for 10% to 15% of DLBCLs among Asian and Latin American patients and less than 5% of Western patients. The increased incidence of this lymphoma in the elderly is believed to be related to physiologic immunosenescence. Histologically, these neoplasms have a diffuse pattern and show a spectrum of features, and two morphologic variants are recognized: polymorphous, with a broad range of B-cell maturation in the reactive background, and monomorphous, which contains mostly large cells.[1,25] Geographical necrosis is common, and the neoplastic cells usually have a non–GCB immunophenotype. The lymphoma cells express B-cell markers such as CD19, CD20, CD22, and CD79. CD30 is expressed in about 40% of cases.[52]

The prognosis of EBV-positive DLBCL tends to be significantly worse in older adult patients than in young-adult patients.[53]

Diffuse Large B-Cell Lymphoma Associated With Chronic Inflammation

The prototype DLBCL associated with chronic inflammation (DLBCL-CI) is known as pyothorax-associated lymphoma. These neoplasms typically develop in patients with a longstanding (often >10 years) history of therapeutically-induced pyothorax as part of treatment for pulmonary tuberculosis. These neoplasms are often large with a poor prognosis. This type of lymphoma occurs worldwide but appears to be more common in Japan and China.[25]

A second group of cases included in the DLBCL-CI are very different. These neoplasms are small, often microscopic in size, and arise at sites of chronic inflammation, such as chronic osteomyelitis, metallic implant insertion, surgical mesh implantation, and chronic skin venous ulcer.[54] Another name proposed for these neoplasms is fibrin-associated lymphoma.

DLBCL-CI (both groups) is composed of large cells with centroblastic, immunoblastic, or, less commonly, anaplastic features.[26] Most cases express CD20 and CD79a; some cases show CD30 expression. Many cases show plasmacytic differentiation; in some cases the plasmacytic differentiation becomes so prominent that the neoplasm shows loss of CD20 and/or CD79a and acquires IRF/MUM1 and CD138. DLBCL-CI are uniformly EBV-positive and are believed to arise from post–germinal center B cells in a hypoxic and perhaps immune protected environment.

Epstein-Barr Virus–Positive Mucocutaneous Ulcer

EBV-positive mucocutaneous ulcer (EMCU) presents with isolated circumscribed ulcerative lesions, typically in patients with age-related or iatrogenic immunosuppression. EMCU is associated with defective host immunosurveillance of EBV infection. The lesions are most common in the oral mucosa but may also occur in the skin or in the GI tract. The lesions contain a polymorphous inflammatory infiltrate mixed with scattered EBV-infected B cells, which frequently include cells resembling Hodgkin/Reed-Sternberg cells morphologically and immunophenotypically (CD30+, CD15+/–).[25,55,56]

Lymphomatoid Granulomatosis

Lymphomatoid granulomatosis (LYG) is an angiocentric and angiodestructive lymphoproliferative disease, composed of EBV-positive CD20+ B cells and reactive T cells. This entity is EBV-driven and can present in a subset of patients with underlying immunodeficiency, such as in Wiskott-Aldrich syndrome, X-linked lymphoproliferative syndrome, and other conditions linked to immunodeficiency.

Patients with LYG typically present with extranodal disease, almost always in the lungs, followed by the CNS, skin, liver, mediastinum, adrenal glands, kidneys, and breasts. Bone marrow and lymph node involvement are rare.[57]

Histologically, LYG is characterized by atypical large B cells in a pleomorphic background of lymphocytes, plasma cells, and histiocytes. Angiocentricity and necrosis are common. Histologic grading of LYG ranges from I to III and is based on the number and density of EBV-positive atypical B cells and degree of coagulative necrosis.[58] The clinical behavior ranges from indolent process to aggressive large B-cell lymphoma.[1,59]

Large B-Cell Lymphoma with *IRF4* Rearrangement

This neoplasm is characterized by strong expression of MUM1/IRF4 and is associated with chromosome *6p25/IRF4* rearrangement. The histologic pattern can be follicular, follicular and diffuse, or entirely diffuse. These neoplasms represent 0.05% of all cases of DLBCL, and affected patients are usually children and younger adults with a median age of 12 years (range, 4–79).

Patients generally present with localized disease involving head and neck lymph nodes or components of Waldeyer ring. These neoplasms are composed of medium or large cells that can exhibit blastoid features, usually without starry-sky pattern. BCL-6 and CD10 are usually positive, supporting a germinal center B-cell immunophenotype.[25,26]

Primary Mediastinal (Thymic) B-Cell Lymphoma

Primary mediastinal (thymic) B-cell lymphoma (PMBL) accounts for 2% to 3% of all NHLs and 6% to 10% of all DLBCL. The median age of diagnosis is 35 to 37 years, and women are affected more than men.[60] Patients present with an often-bulky mediastinal mass, potentially leading to compressive symptoms, including superior vena cava syndrome. The lymphoma cells have round or pleomorphic nuclei and Reed-Sternberg–like cells may be observed occasionally. The lymphoma cells are positive for pan–B-cell antigens, BCL-6 (~95%), MUM-1/IRF-4 (~95%), and MYC (~65%); CD30 is positive in approximately 80% of cases but is usually weak and heterogeneous. PD-L1/PD-L2 is positive in approximately 50% to 75%. CD10 positivity is less common (~25%).

Major pathways involved in the pathogenesis of PMBL include the NF-κB, cell cycle dysregulation, apoptosis, JAK-STAT, and immune evasion pathways. Major genetic alterations involving the NF-κB pathway include amplification of *REL* (~75%) and *BCL11A* (~50%). Gains/amplification of chromosome 9p24.1, the site of *JAK2* as well as *PD-L1* and *PD-L2*, are also common (~70%).[25,26] Decreased expression of HLA molecules, CD58, and other immune recognition molecules on the surface of the lymphoma cells as a result of molecular alterations (eg, mutations, translocations of *CIITA*) are also common.

Intravascular Large B-Cell Lymphoma

Intravascular large B-cell lymphoma (IVLBCL) is a rare neoplasm that is mostly confined within the lumina of small- to medium-sized blood vessels, particularly capillaries (Fig. 9–7). In general, larger blood arteries and veins are not involved. There are three clinical variants of IVLBCL: classic, hemophagocytic syndrome–associated, and cutaneous. Patients with the classic form (mostly present in Western countries) present nonspecifically with B symptoms and organ-related manifestations, particularly involving the CNS and the skin. The hemophagocytic syndrome–associated form is characterized by pancytopenia, hepatosplenomegaly, multiorgan failure, and bone marrow involvement. An isolated cutaneous variant, identified invariably in Western females, is characterized by restriction of the tumor to the skin and is associated with a better prognosis. The lymphoma cells express pan–B-cell markers and most cases have a complex karyotype, with chromosome 1 commonly involved in 72% of cases.[25,26]

ALK-Positive Large B-Cell Lymphoma

ALK-positive large B-cell lymphoma (ALK+ LBCL) accounts for less than 1% of all cases of DLBCL. These neoplasms are more common in young men (median age, 43 years) and present with nodal and/or extranodal disease. Approximately 60% of patients present with stage III/IV disease. By definition, the neoplastic cells express ALK and have a plasmablastic phenotype, positive for plasma cell–associated markers that are usually positive, including CD138, VS38, IMUM-1/IRF-4, XBP-1, and BLIMP-1. Other pan–B-cell markers (CD20, CD79a, and PAX5) are usually negative or show only focal and weak expression. IPI score and Ann Arbor stage are significant risk factors.[61,62]

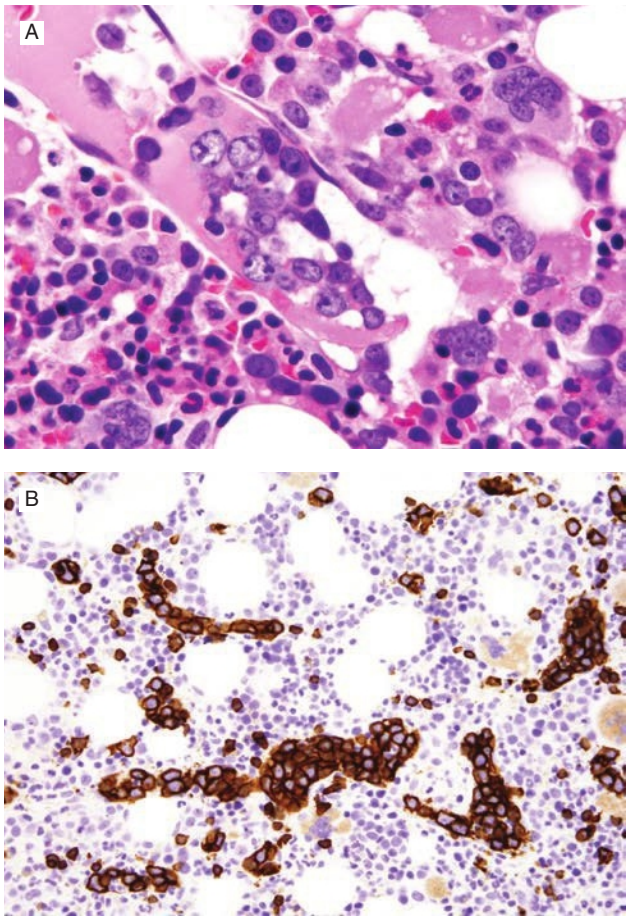


FIGURE 9–7 Intravascular large B-cell lymphoma involving bone marrow. A. Large neoplastic cells are present with a small blood vessel. B. The anti-CD20 antibody highlights numerous large neoplastic cells within many blood vessels. (A, hematoxylin-eosin, ×1000; B, immunohistochemistry, ×400.)

Plasmablastic Lymphoma

Plasmablastic lymphoma (PBL) represents less than 1% of all cases of DLBCL and occurs commonly in the setting of immunodeficiency. PBL commonly presents in patients with HIV infection and represents approximately 3% of HIV-related lymphomas. PBL can also occur in patients after allogeneic transplant and in patients with other forms of immunodeficiency, including physiologic immunosenescence. The most frequent sites of involvement include the oral/nasal cavity and the GI tract.

PBL is composed of immunoblast- or plasmablast-like cells with variable degrees of plasmacytic differentiation. The neoplastic cells are usually positive for plasma cell markers such as CD38, CD138, IRF/MUM1, BLIMP1, and cytoplasmic Ig, and negative for CD45 (LCA) and most pan–B-cell markers. Many cases show expression of CD30 and Epithelial Membrane Antigen (EMA). CD79a is positive in 40% to 50% of cases. The Ki-67 proliferation rate is usually over 90%. In situ hybridization for EBV-encoded RNA (EBER) is positive in about 70% of cases.[25,26]

HHV8-Positive Diffuse Large B-Cell Lymphoma, Not Otherwise Specified

HHV8+ DLBCL–NOS is an extremely aggressive and rare disease. Approximately 50% of patients are HIV+. Notably, patients with HIV+ HHV8+ multicentric Castleman disease are at 15 times higher risk of developing HHV8+ DLBCL. However, most often, HHV8+ DLBCL–NOS arises in association with HHV8+ multicentric Castleman disease, but very rarely neoplasms present de novo without known Castleman disease. Lymphadenopathy occurs in about 80% of patients and disseminated disease, hepatomegaly, and splenomegaly may occur. Moreover, coexistent Kaposi sarcoma may occur. Patients have an aggressive clinical course and often a poor prognosis. HHV8+ DLBCL is composed of sheets of plasmablasts that disrupt normal architecture, sometimes with a background of multicentric Castleman disease. In addition to HHV8, the lymphoma cells are positive for cytoplasmic IgM and lambda. HHV8 virus induces B-cell receptor revision to lambda, with CD20, CD38, CD45, or CD79a positive in subsets of cases. Unlike PEL, HHV8+ DLBCL–NOS are EBV-negative.[25,26]

Primary Effusion Lymphoma

PEL is a human herpesvirus 8 (HHV8)-driven malignancy that involves the pleural, pericardial, or peritoneal cavities without usually forming a mass. Extracavitary PEL refers to a solid neoplasm that has characteristics similar to conventional PEL.

In the United States, most PEL patients are HIV-positive adult men; few are HIV-negative patients, notably in the posttransplant or physiologic immunosenescence setting. Patients with conventional PEL present with symptoms associated with an effusion. The GI tract and lymph nodes are most frequently involved by extracavitary PEL.

PEL cells are pleomorphic, resembling immunoblasts, plasmablasts, or anaplastic cells with Hodgkin/Reed-Sternberg–like features. Moreover, PEL cells usually lack pan–B-cell markers such as CD19, CD20, and CD79a, but are positive for HHV8, MUM-1/IRF-4 (up to 100%), CD38 (up to 100%), CD45 (>80%), CD138 (35%–75%), and CD30 (>50%). These neoplasms have an ABC/non-GCB immunophenotype. Interestingly, extracavitary PEL more often expresses CD20 or CD79a.[25,26]

Table 9–3 Diagnostic Table for the Differential Diagnosis of High-Grade B-Cell Lymphomas

		B-Lymphoblastic Leukemia/Lymphoma	HGBL, NOS	DLBCL	HGBL DHL/THL	BL
Morphology	**Blastoid**	Yes	Yes		Yes	
	DLBCL			Yes	Yes	
	DLBCL/BL		Yes		Yes	Yes
	BL					Yes
IHC	**TdT**	Positive	Negative			
	CD10	Positive				Positive
	BCL6	Negative				Positive
	CCND1	Negative	Negative			
	BCL2					Negative
	Ki-67					~100%
FISH	**No DH**		Yes	Yes		
	SH MYC-IG					Yes
	DH/TH	Yes			Yes	

BL, Burkitt lymphoma; CCND1, c-terminal Cyclin D1; DH(L), double-hit (lymphoma); DLBCL, diffuse large B-cell lymphoma; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; HGBL, NOS, high-grade B-cell lymphoma, not otherwise specified; SH MYC-IG, single-hit with IG/MYC fusion but no translocation involving BCL2, BCL6, or CCND1; TdT, Terminal deoxynucleotidyl transferase; TH(L), triple-hit (lymphoma).
Data from Swerdlow SH, Campo E, Harris NL, et al: *WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues*, 4th ed. IARC, *Lyon*; 2017 and Swerdlow SH, Campo E, Pileri SA, et al: The 2016 revision of the World Health Organization classification of lymphoid neoplasms, *Blood* 2016 May 19;127(20):2375-2390.

High-Grade B-Cell Lymphoma

High-grade B-cell lymphoma (HGBL) is a subset of very aggressive tumors with features intermediate between DLBCL and BL, or with a blastoid appearance, as illustrated in Table 9–3.

High-Grade B-Cell Lymphoma, With *MYC* and *BCL2* and/or *BCL6* Rearrangements

HGBL with *MYC* and *BCL2* and/or *BCL6* rearrangements, also called "double-hit lymphoma" and "triple-hit lymphoma" (DHL and THL), are aggressive lymphomas that account for around 7% to 10% of DLBCL.

Similar to DLBCL, these lymphomas present mostly in the sixth to seventh decade of life. More than half of patients present with Ann Arbor stage IV and more than one extranodal site of disease, notably with CNS involvement in up to 45% of cases.

At least half of DHL and THL have the morphology of DLBCL–NOS, and starry-sky macrophages may be present. The number of mitotic figures and apoptotic figures are highly variable, occasionally with a somewhat low (50%–70%) Ki-67 proliferation index. Another subset of DHL and THL shows a morphology with features intermediate between DLBCL and BL. For these cases, starry-sky macrophages are generally present, with many mitotic figures. Other cases of DHL and THL can have a blastoid cytomorphology. Unlike B-cell lymphoblastic leukemia/lymphoma, staining for terminal deoxynucleotidyl transferase is negative and, unlike the blastoid variant of mantle cell lymphoma, cyclin D1 is negative (Table 9–3, Fig. 9–8).

These lymphomas are of mature B-cell lineage with expression of CD19, CD20, CD79a, and PAX5. Rearrangements, usually as a result of translocations, occur in *MYC* (chromosome 8q24), *BCL2* (chromosome 18q21), and/or *BCL6* (chromosome 3q27). These lymphomas are predominantly observed in the GCB subset of DLBCL. Lymphoma with both *MYC* and *BCL6* translocations (*MYC/BCL6*) is likely a different disease biologically compared with DHL with *MYC/BCL2* translocations. Indeed, *MYC/BCL6* lymphoma is much less common and more likely to be of ABC/non-GCB type. Interestingly, *MYC/BCL2* DHL frequently exhibits TP53 mutations, whereas MYC/BCL6-rearranged lymphomas do not. THL has a prognosis comparable with DHL.[30] Most double-hit lymphomas have a double-expressor phenotype, but the reverse is not true.[25]

At MDACC, we routinely perform FISH studies for *MYC* rearrangement on all new cases of DLBCL, irrespective of Ki-67 index. If *MYC* rearrangement is detected, additional FISH studies for *BCL2* and *BCL6* rearrangements are performed. If a lymphoma does not demonstrate *MYC* rearrangement, no additional studies are required.

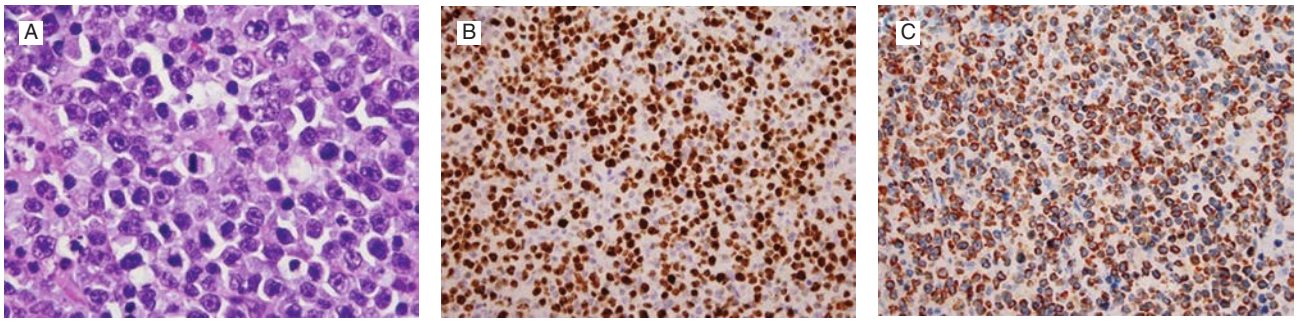


FIGURE 9–8 High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements. Similar to Burkitt lymphoma, the neoplastic cells are intermediate-sized and demonstrate brisk mitotic activity, but unlike Burkitt lymphoma, cells have prominent single nucleoli (A). Although the proliferative rate is similar to Burkitt lymphoma (B), the neoplastic cells strongly express BCL2 (C). In this case, fluorescence in situ hybridization detected both translocations t(8;14) and t(14;18), so-called double-hit lymphoma (lymph node; A, hematoxylin-eosin, ×1000; B, Ki-67 (Mib-1), ×400; C, BCL2, ×400).

High-Grade B-Cell Lymphoma, Not Otherwise Specified

HGBL–NOS is a rare and heterogeneous category with cases that appear with blastoid cells and cases that appear intermediate between DLBCL and BL. About 20% to 35% of cases have a MYC rearrangement, but by definition lack *BCL2* and/or *BCL6* rearrangement (Table 9–3). Some cases show increased copy numbers of *BCL2* or, rarely, amplification of 18q21 involving *BCL2*. In addition, some cases demonstrate *BCL2* rearrangement and increased copy numbers of *MYC* gene.[1,25]

B-Cell Lymphoma, Unclassifiable, With Features Intermediate Between DLBCL and Classic Hodgkin Lymphoma

B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma (cHL) is also known as grey-zone lymphoma (GZL). These neoplasms are very rare and not precisely defined as of this writing. The median age of patients is around 40 years, with males more commonly affected. Mediastinal GZL (MGZL) is most common, and patients present with a large anterior mediastinal mass. Nonmediastinal GZL (NMGZL) often presents in older patients and tends to be a more advanced-stage disease with higher IPI score.[63]

Morphologically, cases of GZL tend to be tumor cell–rich and can be further divided into two subtypes: cases in which the neoplastic cells morphologically resemble Hodgkin and Reed-Sternberg cells, and cases morphologically resembling DLBCL/PMBL. Cases morphologically resembling cHL usually show CD45 (LCA) positivity and strong expression of pan–B-cell markers such as CD20, CD22, CD79a, PAX5, OCT2, and BOB1. Cases morphologically resembling DLBCL/PMBL may show loss of some pan–B-cell markers or CD45 but demonstrate positivity for CD15 and CD30. Immunophenotype does not appear to differ based on presentation with MGZL versus NMGZL disease.[63]

GZL is a highly heterogeneous disease harboring somatic driver events shared with PMBL and cHL. Chromosomal aberrations in GZLs show gains including amplifications in 2p16.1 (*REL/BCL11A* locus) in 33% of all cases, alterations of the *JAK2/PDL2* locus in 9p24.1 in 55%, rearrangement of the *CIITA* locus at 16p13.13 in 27%, and gains of 8q24 (*MYC*) in 27%.[64,65] These lymphomas are often aggressive and resistant to chemotherapy, and patients have worse outcomes than patients with either cHL or PMBL.[64,66]

Burkitt Lymphoma

There are three variants of BL: endemic (African), sporadic (nonendemic), and immunodeficiency-associated. Endemic BL occurs in equatorial Africa and in Papua, New Guinea, and is associated with EBV infection in 95% to 100% of patients. The peak incidence is at 4 to 7 years and the male-to-female ratio is 2–3:1. Jaw and facial bones lesions are present in about 50% of patients. Mesentery, gonads, and CNS are other common sites of presentation.

Sporadic BL occurs worldwide, accounts for 1% to 2% of lymphomas in the United States and is associated with EBV infection in 25% to 40% of patients. Patients are usually in their third decade of life, but there is also an incidence peak in the elderly. The male-to-female ratio is 2–3:1. Clinical presentation most frequently involves the ileocecal region, and less commonly the bone marrow, ovaries, kidneys, breasts or CNS.

BL can also occur in the clinical setting of immunosuppression, including HIV infection (further information in Chapter 52), post transplant, or congenital immune deficiency. In HIV-infected patients, BL appears often when CD4+ T-cell counts are still in the normal range or low, but not extremely low, and the risk of developing BL persists in spite of highly

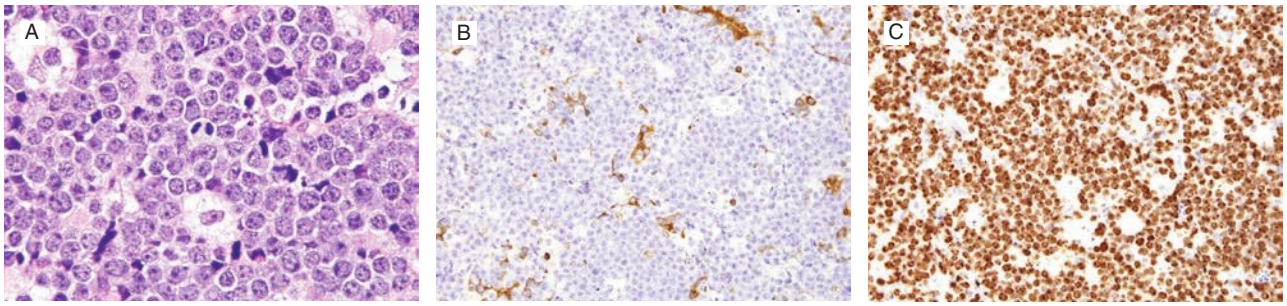


FIGURE 9–9 Burkitt lymphoma. A. The neoplastic cells are intermediate in size, similar to that of benign histiocyte nuclei, with multiple small nucleoli. A "starry-sky" pattern is also seen in this field. B and C. The neoplastic cells are negative for BCL2 (B) and are over 99% positive for Ki-67 (C). (A, hematoxylin-eosin, ×1000; B-C, immunohistochemistry, ×400.)

active antiretroviral therapy. EBV infection occurs in 25% to 40% of cases. A nodal presentation is most common, with occasional bone marrow involvement. CNS dissemination can occur as well.[67] Burkitt leukemia variant tends to involve the CNS at diagnosis or early in the disease course.

In general, all variants of BL show similar morphologic features. At low power, clear tingle-body macrophages in the background of deep-blue lymphoma cells impart a "starry-sky" appearance. The neoplastic cells are typically intermediate in size and relatively homogeneous, with basophilic cytoplasm containing small vacuoles and round nuclei. The neoplastic cells in sporadic cases might be more pleomorphic; the neoplastic cells in immunodeficiency cases can show plasmacytic features. The nuclear chromatin is granular with small nucleoli and recurrent mitoses.

All BL types are of mature B-cell lineage and of GCB origin, expressing surface Ig, pan–B-cell antigens, CD10, and BCL6.[22] Burkitt lymphomas have a very high proliferation rate, approaching 100%, using an antibody specific for Ki-67 (Table 9–3, Fig. **9–9**) and are negative for BCL2. *MYC* translocations are typical of BL; 80% of cases carry the t(8;14)(q24;q32), with the other cases having one of two variant translocations, t(2;8)(p11;q24) or t(8;22) (q24;q11). Common to each of these translocations is involvement of chromosome region 8q24, the site of the *MYC*, which is deregulated. Via these translocations, *MYC* is juxtaposed with the *IGH* or *IGK* or *IGL*. Mutations in the *transcription factor 3* (*TCF3*) or its own negative regulator *ID3* occur in approximately 70% of sporadic and immunodeficiency-related BL and 40% of endemic cases. TCF3 promotes survival and proliferation in lymphoid cells by activating the B-cell receptor/phosphatidylinositol 3-kinase (PI3K) signaling pathways and modulating the expression of cyclin D3, which is also mutated in 30% of BL.[1,25,67]

Burkitt-Like Lymphoma With 11q Aberration

Burkitt-like lymphoma with 11q aberration (BLL-11q) is a lymphoma that closely resembles BL but lacks *MYC* rearrangement and has some other distinctive features. Notably, these neoplasms carry a chromosome 11q alteration characterized by proximal gains and telomeric losses. Compared with BL, BLL-11q have more complex karyotypes, lower levels of MYC expression, a certain degree of cytologic pleomorphism, sometimes a follicular pattern, and frequently a nodal presentation. This malignancy may be closer to HGBCL or DLBCL than to BL.[1,25,68]

STAGING AND INITIAL EVALUATION

General Workup

The Ann Arbor Staging system, developed in 1971 for Hodgkin lymphoma, is used to stage patients with NHL (Table 9–4). Of interest, there does not appear

Table 9–4 Ann Arbor Staging System for Non-Hodgkin Lymphomas[a]

Stage I	Involvement of a single nodal group or extranodal site (I_E)
Stage II	Involvement of two or more nodal groups on the same side of the diaphragm or localized involvement of an extranodal site or organ (II_E) and one or more nodal groups on the same side of the diaphragm
Stage III	Involvement of nodal groups on both sides of the diaphragm, which may be accompanied by localized involvement of an extranodal region or site (III_E) of spleen (III_S) or both (III_{SE})
Stage IV	Diffuse or disseminated involvement of one or more distant extranodal sites

[a]Temperature >38 °C, weight loss more than 10% of body weight in the last 6 months, and night sweats preceding diagnosis are defined as "B" symptoms and designated by the suffix B. Others are designated by the suffix A.

to be any meaningful difference in the outcomes of patients with stage III or IV disease, and thus the purpose of staging is to identify the patients with localized NHL who may benefit from a reduced course of systemic therapy and eventual additional local therapy.[69]

A careful history and physical examination, including findings of systemic symptoms (including B symptoms), is essential. Performance status and comorbid conditions should be assessed. Physical examination should include a complete survey of all external lymph node groups including cervical, supraclavicular, axillary, epitrochlear, inguinal, and popliteal areas. Examination of abdomen for organomegaly is necessary, and in men the testes should be examined. A complete neurologic examination must also be performed. Laboratory evaluation includes a complete blood count with differential diagnosis; lactate dehydrogenase (LDH) level; kidney and liver function tests; albumin, calcium, and uric acid levels; pregnancy testing in women of childbearing age; testing for hepatitis B (especially indicated before rituximab therapy, as the virus may reactivate during or after treatment); hepatitis C; and HIV.[70] Serum protein electrophoresis can be considered in some cases.

Left ventricular function should be assessed by echocardiogram or multigated acquisition scan. Fertility-preserving treatments, such as sperm cryopreservation for males and referral to a fertility specialist for females, should be discussed with eligible patients.[70]

Imaging Studies and Bone Marrow Evaluation for Initial Staging

Based on the recent consensus recommendations for staging and restaging of lymphoma developed by the clinical and imaging working groups of the International Conference on Malignant Lymphomas, fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) scan is recommended as standard practice for staging patients with DLBCL. Indeed, PET/CT is more sensitive, especially for extranodal disease, and improves staging accuracy and subsequent response assessment[69] (Figures 9-10 and 9-11). Moreover, several studies showed that high baseline total metabolic tumor volume negatively impacts outcome in DLBCL patients.[71]

Limitations of PET/CT scan for staging of aggressive lymphoma include the fact that uptake of FDG is not specific to tumors and that infection and inflammatory processes are common false-positive findings on PET scans. As a result, an unexpected FDG-avid lesion that will result in a significant change in management should be confirmed by biopsy. The presence of high normal background activity in an organ—for example, in the kidneys or testes—may also make it difficult to identify abnormal FDG sites in that region. Although there is usually high normal metabolic activity within the brain, CNS lymphomas are often positive on FDG-PET scans, showing greater metabolic activity than the adjacent brain. However, additional imaging with magnetic resonance imaging (MRI) is indicated for confirmation.

Focal bone marrow FDG uptake with or without increased diffuse uptake is more sensitive than bone marrow biopsy (BMB) for infiltration in aggressive B-cell lymphoma and is highly specific. Of note, the pattern of uptake within the bone marrow spaces on FDG-PET is important because a diffuse pattern is commonly seen with activation (eg, with underlying anemia or infection, or after chemotherapy or growth factor treatment), and caution should be taken in interpreting this as diffuse bone marrow involvement by tumor. In contrast, focal or nodular uptake within osseous structures is suspicious

However, low-volume involvement (<10%–20%) and discordant lymphoma may be missed by PET/CT imaging, but these positive BMB/negative PET/CT findings are lower than 10% (Figure 9-12). Therefore, BMB is no longer required when a PET/CT scan demonstrates bone or marrow involvement indicating



FIGURE 9–10 **Positron emission tomography scan showing right cervical lymph nodes involved by diffuse large B-cell lymphoma.**

stage IV, but is appropriate in case of negative PET, when its results would change prognosis and treatment, especially when a shortened number of immunochemotherapy cycles is proposed or as workup of unclear cytopenia.[72]

If bone marrow aspiration and biopsy are performed, bilateral iliac crest assessment is preferred because sensitivity of detection is higher than with unilateral biopsy.[73]

Specific Considerations

Assessment of CNS Disease

Examination of the cerebrospinal fluid (CSF) should be strongly considered for patients with risk factors such as: elevated CNS-IPI[74] (age >60 years, Eastern Cooperative Oncology Group [ECOG] Performance Status ≥2, extranodal disease >1 site, stage III/IV, elevated LDH, kidney/adrenal involvement; low risk (0–1 factors), intermediate risk (2–3 factors), and high risk (≥4 factors). In addition, extranodal disease with involvement of testicular, uterine, breast, epidural, and skin is a risk factor for CNS. Moreover, the following aggressive B-cell lymphoma subtypes, such as BL, double-/triple-hit lymphoma/HGBCL, double-expressor lymphomas, HIV-associated lymphoma, non-GCB DLBCL, intravascular DLBCL, CD5+ DLBCL, PCDLBCL-LT, and IgM-secreting DLBCL,[75] present increased risk of CNS involvement.[76,77]

Evaluation of clinical or radiologic suspicion of primary or secondary CNS lymphoma requires lumbar puncture (unless contraindicated), MRI of the brain and biopsy of the lesion (preferably a stereotactic biopsy). It is important to withhold corticosteroids before biopsy, because they can induce rapid tumor shrinkage and prevent an appropriate diagnosis.[25]

Moreover, in case of suspected PCNSL, a vigorous search for additional disease sites, such as testicular ultrasound for men older than 60 years, full ophthalmologic examination including slit-lamp eye examination, spine MRI, PET/CT, and BMB should be done concurrently, because therapy for CNS and systemic disease will need to account directly for both.[78]



FIGURE 9–11 Extranodal lymphoma on FDG-PET/CT. The patient presented with mediastinal lymphoma; this is easily seen on a maximum intensity projection image from FDG-PET/CT. However, an additional focus is present in the right kidney; although not confirmed by biopsy, the renal lesion disappeared after chemotherapy, and the stage was changed from stage I to stage IV.

Involvement of the Gastrointestinal Tract

Lymphomas of the GI tract, especially in the stomach, require endoscopy for diagnosis unless other disease sites can be found to biopsy. It is especially important that multiple biopsies of different areas of the stomach be obtained because sampling error is frequent. There is no utility to gastrectomy or other surgical management for extranodal disease.

Intravascular Large B-Cell Lymphomas

Standard staging workup usually has a high proportion of false-negative results because of a lack of detectable tumor masses. Random skin biopsies of normal-appearing skin and transbronchial lung biopsy can be necessary. Evaluation for CNS disease is recommended because of the high risk of CNS relapse.[25,81]

Laboratory abnormalities are frequent, particularly high serum LDH and soluble IL-2 receptor levels.[26]

PROGNOSTIC FACTORS

Pretreatment

Prognostic factors in patients with aggressive NHL can be broadly grouped into pretreatment (tumor-related) and treatment-related characteristics. Tumor-related

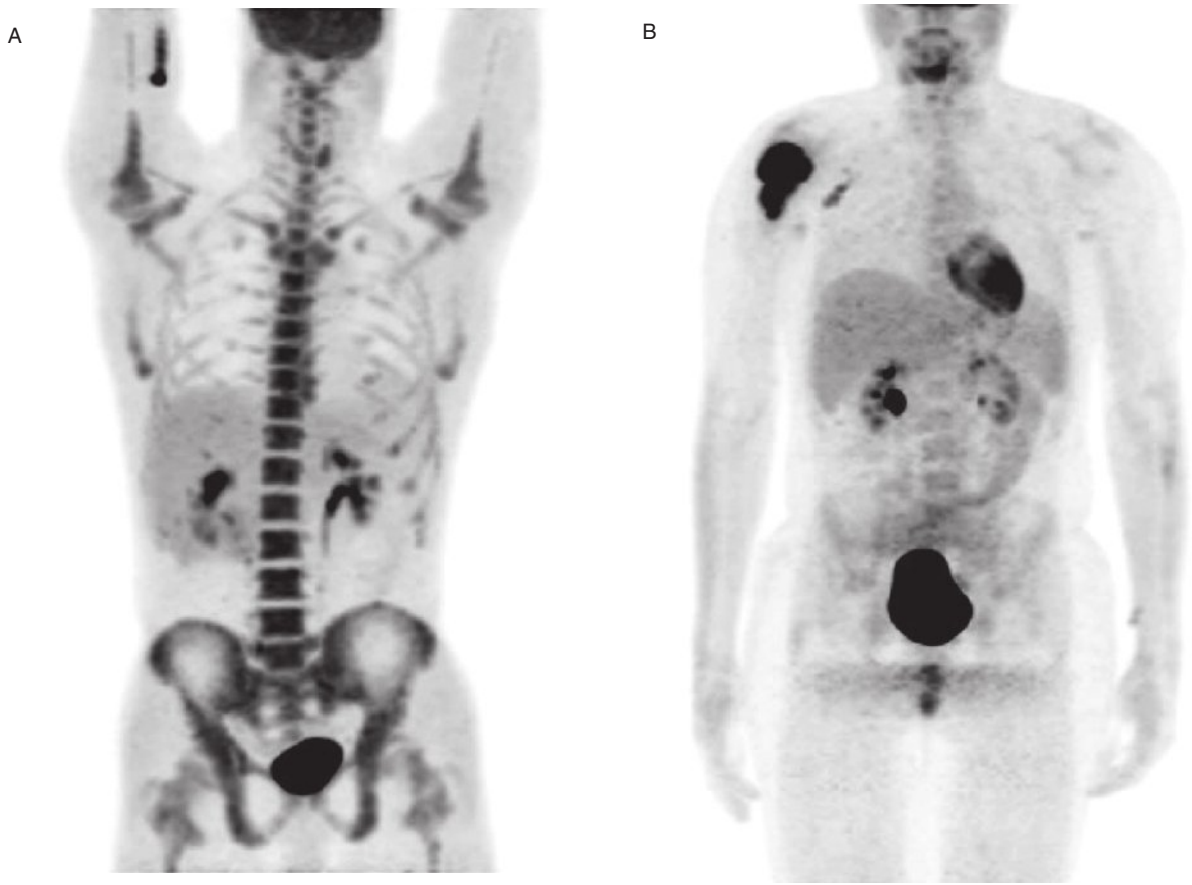


FIGURE 9–12 **Bone and bone marrow uptake on FDG-PET/CT. A. Typical pattern of marrow activation, commonly seen after chemotherapy or with growth factor treatment. This is diffuse but homogenous. In contrast (B), another patient had negative bilateral iliac crest biopsies but had focal activity in a destructive lesion involving the right humerus. Directed biopsy of this site was positive for bone involvement.**

genetic characteristics of importance, as noted earlier, include GCB or non-GCB origin genetic profile and the presence of *MYC* and *BCL2* and/or *BCL6* translocations (double-hit lymphomas).

Other tumor-related characteristics reported to be of prognostic value include a complex karyotype shown by conventional cytogenetics, high proliferation rate (high Ki-67 expression), and BCL2 and/or MYC expression shown by immunohistochemical staining.[1] In addition, a study found that P53 alterations correlated with poorer survival and augmented the negative prognostic effect of MYC rearrangement, expression, or concurrent MYC/BCL2 expression in DLBCL.[80]

High serum LDH level is a measure of anaerobic metabolism and/or cell turnover and tumor bulk and is associated with a lower probability of complete remission and poorer long-term survival in patients with aggressive NHL. Other pretreatment prognostic factors include serum β_2-microglobulin level, stage, number of disease sites, bulky disease, presence of bone marrow involvement, poor performance status, and age.[81] Of these pretreatment factors, age appears to be the most important, with patients over the age of 60 years having lower response rates and higher rates of relapse.[82]

The IPI score remains a widely used prognostic model, despite its not accounting for any tumor-specific biologic features. With rituximab plus chemotherapy–based disease management, the progression-free survival (PFS) and overall survival (OS) rates for DLBCL patients with IPI, age-adjusted IPI, National Comprehensive Cancer Network (NCCN)-IPI and Revised IPI (R-IPI) are shown in Tables 9–5, 9–6, and 9–7.[83,84] Compared with the IPI, the NCCN-IPI better discriminates low- and high-risk subgroups, by refined categorization of age and LDH, and the identification of disease involvement at specific extranodal sites.[84] The NCCN-IPI was shown to better discriminate between patients with poor and favorable OS compared with the IPI/R-IPI.[85] However, even if these data are informative, they are not reliably predictive of outcomes for an individual patient and are not validated in routine practice for choice of therapy. Nearly half of patients will have a poor-risk R-IPI, and of these patients, approximately half will be cured.

Table 9–5 International Prognostic Index and NCCN-IPI

Factors	IPI		NCCN-IPI	
Age, years	>60	1	>40 to ≤60 >60 to <75 ≥75	1 2 3
Serum LDH	>normal	1	LDH ratio >1 to 3 LDH ratio >3	1 2
Performance status	2-4	1	≥2	1
Extranodal disease	>1 site	1	BM, CNS, Liver/GI tract or lung	1
Stage, Ann Arbor	III-IV	1	III-IV	1

BM, bone marrow; CNS, central nervous system; GI, gastrointestinal; IPI, International Prognostic Index; LDH, lactate dehydrogenase; NCCN, National Comprehensive Cancer Network.

Table 9–6 Survival Rates of IPI, Age-Adjusted IPI, and NCCN-IPI for Patients With Diffuse Large B-Cell Lymphoma

International Prognostic Index, Age Adjusted and NCCN-IPI					
Group	**Risk Factors**	**RFS**		**Survival**	
	Score	2 Years (%)	5 Years (%)	2 Years (%)	5 Years (%)
All ages	0–1	79	70	84	73
	2	66	50	66	51
	3	59	49	54	43
	4–5	52	40	34	26
Age adjusted ≤60	0	88	86	90	83
	1	74	66	79	69
	2	62	53	59	46
	3	61	58	37	32
Age adjusted >60 years	0	75	46	80	56
	1	64	45	68	44
	2	60	41	48	37
	3	47	37	31	21
NCCN-IPI risk group	**Score**	**5-year PFS (%)**		**5-year OS (%)**	
Low	0–1	91		96	
Low-intermediate	2–3	74		82	
High-intermediate	4–5	51		64	
High	≥6	30		33	

IPI, International Prognostic Index; NCCN, *National Comprehensive Cancer Network;* OS, overall survival; PFS, progression-free survival; RFS, relapse-free survival

Table 9–7 Survival Rates for Patients With Diffuse Large B-Cell Lymphoma

Revised IPI	No. of Factors Present	% of Patients	4-Year PFS	4-Year OS
Very good	0	10	94	94
Good	1-2	45	80	79
Poor	3-5	45	53	55

IPI, International Prognostic Index; OS, overall survival; PFS, progression-free survival.

Prognostic Factors in Primary Central Nervous System Lymphoma

Age and LDH level are important prognostic factors in patients with HIV-negative primary CNS lymphoma; however, the most important factor is performance status at the time of treatment. Elevated LDH, CSF protein, and tumor mass location(s) are also contributors to prognosis.[86] Many patients can improve their condition by use of corticosteroids and thus be candidates for intensive chemotherapy-based regimens that are potentially curative.

Therapy-Associated Prognostic Factors

An important posttreatment prognostic indicator is tumor response to induction chemotherapy. In patients with aggressive NHL, dramatic response to induction with early complete remission (by the third cycle of therapy) is associated with a superior outcome. FDG-PET has been found to be highly sensitive for the detection of aggressive NHL in posttreatment residual masses, but its ability to detect interim therapy response is controversial.[87] Moskowitz et al found that DLBCL patients with persistent FDG avidity after four cycles of rituximab plus CHOP (R-CHOP) had an 86% false-positive rate (PET/CT positive, biopsy negative for persistent disease).[88] Similar data have been shown by many others, highlighting the need for biopsy confirmation of a positive PET/CT scan before therapeutic decisions.

Patients who fail to achieve at least a good partial response to induction chemotherapy have primary refractory disease and an unfavorable prognosis. Another important indicator of prognosis is duration of remission obtained after induction chemotherapy, because patients with relapses occurring at less than one year have a worse outcome.[89]

APPROACH TO THERAPY

There is a diversity of clinical practice surrounding the preferred treatment approach for patients with aggressive B-cell lymphoma, notably related to its wide pathologies, molecular variations, and clinical behaviors. At MDACC, our preference is that all patients with aggressive B-cell lymphoma be evaluated for a clinical trial at each treatment stage.

Frontline Therapy

Large B-Cell Lymphomas

R-CHOP remains the backbone of therapy for untreated DLBCL. However, the total number of cycles and addition of radiation depends on stage at presentation and tumor bulk. Abundant efforts to improve R-CHOP, including increased dose density with 14-day cycles, the use obinutuzumab in place of rituximab, or intensification of therapy to, for example, dose-adjusted (DA) etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) have been made, but have generally failed to show significant clinical benefits.[90–92] Notably, the phase 3 trial Alliance/CALGB 50303 showed that DA-EPOCH-R was more toxic and did not improve PFS and OS compared with R-CHOP. However, the subgroup analysis showed improvement of PFS for patients with high IPI (3–5) when treated with DA-EPOCH-R.

Treatment Option by Stage

Early-Stage Aggressive Non-Hodgkin B-Cell Lymphoma

Therapy of early (localized) stage I and II includes chemoimmunotherapy with R-CHOP administered alone or combined with radiation therapy (RT; combined modality therapy [CMT]). The choice of chemoimmunotherapy alone versus CMT and number of cycles of systemic therapy are influenced by adverse effects, comorbidities, response to therapy, and personal preference. For instance, for patients in whom RT may cause substantial early toxicity (notably if there is involvement of the oronasopharynx or pelvis) or late toxicity (in young women whose breasts would be in the RT field), treatment with chemoimmunotherapy alone can be favored. Inversely, the lower total dose of doxorubicin of an abbreviated course of chemotherapy associated with CMT may be preferred for a patient with marginal cardiac function.

The following trials studied the optimal therapy of early-stage DLBCL, which has to be tailored according

to adverse features, size of lesion(s) and response to therapy.

The FLYER trial showed that in patients with favorable prognosis (aged 18–60 years, with stage I-II disease, normal serum LDH, ECOG performance status 0–1, and without bulky disease [max tumor diameter <7.5 cm]), four cycles of R-CHOP plus two cycles of rituximab was noninferior to six cycles of R-CHOP (Table 9-8), with relevant reduction of toxic effects. After a median follow-up of 66 months, 3-year PFS was 96% with four cycles of R-CHOP versus 94% with six cycles of R-CHOP.[95]

Moreover, in the SWOG S0014 trial, patients with limited-stage disease and at least one adverse risk factor as defined by the stage-modified IPI (nonbulky stage II disease, age >60 years, WHO performance status of 2, or elevated serum LDH) treated with three cycles of R-CHOP plus one cycle of rituximab followed by 40–46 Gy of involved-field radiation therapy (IFRT) showed 2-year PFS of 93% and 4-year PFS of 88%. This study highlighted a pattern of continuing relapse likely related likely to biologic differences between limited- and advanced-stage lymphoma.[28,94]

In addition, some studies, such as RICOVER-60/RICOVER-noRTh (6 cycles of R-CHOP plus 2 cycles of rituximab followed by IFRT of 36 Gy to sites of initial bulky [≥7.5 cm] disease and extralymphatic involvement) report that adding RT to chemoimmunotherapy may improve outcomes for patients with bulky disease; however, this is not well proven.[95]

Alternatively, the NCTN Study S1001 proposed PET-directed therapy to improve outcomes and decrease toxicities. After three cycles of R-CHOP, patients with nonbulky (<10 cm), stage I/II, untreated DLBCL had an interim PET after cycle 3. Patients with negative PET scan results (Deauville 1–3, interim [i] PET-negative) proceeded with one additional cycle of R-CHOP. Patients with positive PET scan results (Deauville 4–5, iPET-positive) were initiated 36 Gy of IFRT, plus an additional boost to FDG-avid area up to 9 Gy, within 5 weeks of the third cycle of R-CHOP. This was followed by ibritumomab tiuxetan three to six weeks after completing IFRT. NCTN S1001 demonstrated that 89% of patients maintained excellent outcomes after four founds of R-CHOP with PET-directed therapy. Only 11% of patients were iPET-positive and required radiation, but they also had excellent outcomes. Together with the FLYER trial in younger patient, this NCTN trial may establish a new standard approach to limited-stage disease for the majority of patients.[96]

Advanced-Stage Aggressive Non-Hodgkin Lymphoma

For patients with advanced-stage lymphoma, six cycles of immunochemotherapy are the standard of care, as established by different trials. In the MInT study, with patients aged 18–60 years with maximal IPI I in stage II–IV disease, or who had stage I disease with bulk, received six cycles of R-CHOP. Bulky and extranodal sites received additional radiotherapy. After a median

Table 9–8 Most Commonly Used Chemotherapeutic Regimens in Aggressive B-Cell Lymphomas

Regimen	Dose/Route	Days	Interval
Frontline			
R-CHOP			
Cyclophosphamide	750 mg/m² IV	1	21 days
Doxorubicin	50 mg/m² IV	1	
Prednisone	100 mg PO	1–5	
Vincristine	1.4 mg/m² IV	1	
Rituximab	375 mg/m² IV	1	
Salvage **(first salvage, pre-autologous SCT)**			
R-ICE			
Rituximab	375 mg/m² IV	1	14–21 days
Ifosfamide	5 g/m² IV CI	2	
Mesna concurrent with ifosfamide	5 g/m² IVCI 2 over 24 h, then 2 g/m² over 12 h	2–3	
Carboplatin[a]	Maximum 800 mg	2	
Etoposide	100 mg/m² IV	2–4	
GCSF	5 µg/kg/day SC	7–14	

[a]Calculate carboplatin dose using Calvert equation: AUC = 5 g/mL/min; dose = 5 × [25+Cl_{cr}] capped at 800 mg.

follow-up of 34 months, the 3-year event-free survival (EFS) was 79% and 3-year OS was 93%.[97]

Treatment Options by Cell of Origin

Multiple studies have shown that patients with the ABC disease subtype have significantly poorer outcomes with standard up front similar therapy, compared with GCB disease. For instance, in a study of 344 patients with DLBCL treated with R-CHOP that used the Lymph2Cx assay on the paraffin-embedded tissue to identify COO, the 5-year PFS was 48% versus 73%, and 5-year OS was 56% versus 78%, respectively in ABC disease compared with GCB disease.[38,98]

Efforts to improve up front therapy in ABC-DLBCL have combined biologic agents, including ibrutinib,[99] bortezomib,[100] or lenalidomide[101] with R-CHOP with varying success. These agents were chosen for their synthetic lethality specific to the ABC disease, driven by dysregulation and constitutive activation of B-cell receptor signaling, leading to downstream activation of the NF-κB) pathway and uncontrolled gene transcription and cellular survival and proliferation.[98] Alternatively, the Smart Start trial with rituximab, ibrutinib, and lenalidomide alone and combined with chemotherapy in patients with ABC-DLBCL achieved impressive results with 1-year PFS of 92.5% and 1-year OS of 96.5%. Instead, the more intensive R-ACVBP regimen (rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone, followed by consolidation with methotrexate, has demonstrated superiority to R-CHOP, but vindesine is not available in the United States.[102] Nevertheless, frontline R-CHOP is still considered the standard of care regardless of COO type. Patients with non-GCB DLBCL should be referred for trials investigating novel therapies.

CNS Prophylaxis

The incidence of CNS relapse among patients with DLBCL is only around 5% in unselected cohorts.[103] However, in high-risk patients, such as those with adrenal/kidney involvement, estimates as high as 36% have been reported (25% at time of diagnosis, 75% at time of relapse).[104] Patients with CNS relapse may have indications of occult disease at diagnosis. Indeed, CSF diagnostic sensitivity is low. Nevertheless, the overall consequence of CNS relapse is often devastating, and for most patients, the median OS is typically only a few months, highlighting the need to accurately identify at-risk patients, screen for CNS disease, and develop safe and effective treatment/prophylaxis strategies.[76]

There are several approaches for risk stratification, prophylaxis methods, and diagnostic tools related to CNS prophylaxis in patients with aggressive B-cell lymphoma.

The CNS-IPI represents a robust risk model but does not integrate high-risk CNS biomarkers such as rearrangement of MYC and BCL2 (DHL), at-risk extranodal sites such as testicles, or subtypes such as IVDLBCL. A retrospective population-based database of patients with DLBCL treated with R-CHOP demonstrated the following two-year CNS relapse risk estimates: CNS-IPI low risk, 0.8%; intermediate risk, 3.9%; and high risk, 12.0%.[76]

There is no prospective study integrating all the previously described risk factors for CNS disease. However, it can be considered reasonable to give CNS prophylaxis to the following patients: any patient with CNS-IPI score of at least 4, any patient with testicular or breast involvement, any patient with DHL/THL, any patient with HIV-associated aggressive B-cell NHL; BL; intravascular DLBCL; plasmablastic lymphoma; PEL; CNS-IPI score of at least 2 *and* adrenal/kidney/uterine/skin involvement; or double-expressor lymphoma (DEL) and/or ABC/non-GCB. Consider as well CNS prophylaxis for patients with CD5+ DLBCL and IgM-secreting DLBCL.[76,105]

Considering the most recent evidence, systemic CNS prophylaxis with 2 to 4 cycles high-dose methotrexate (HDMTX) 3–3.5 g/m^2 is the preferred option with early integration if feasible, typically on days 10 to 15 of R-CHOP.[106,107] Nephrotoxicity is typically the main limiting factor affecting feasibility of this approach, especially in older patients. Also, hepatotoxicity can rarely occur with HDMTX and is contraindicated in patients with effusions, because this can be a drug reservoir, thus enhancing toxicity. Further, given that HDMTX can also cause neutropenia, growth factor support should be considered if HDMTX is to be integrated with R-CHOP. Given the high frequency of leptomeningeal disease in high-risk CNS-IPI patients, intrathecal (IT) chemotherapy (MTX and/or cytarabine 4–8 doses, at least once per cycle of systemic chemotherapy) may be an alternative if HDMTX is contraindicated or integrated in more intense chemotherapy regimens such as EPOCH-R and R-Hyper-CVAD/MA (cyclophosphamide, vincristine sulfate, doxorubicin, dexamethasone/methotrexate and cytarabine) or as a result of patient preference.[76] There is an unmet need for prospective studies validating prognostic models integrating the diverse clinical, biochemical, molecular, and histologic features of aggressive B-cell lymphomas and new less toxic CNS prophylaxis therapies.

Tumor Lysis Syndrome Prophylaxis

Tumor lysis syndrome (TLS) is a potentially life-threatening oncologic emergency characterized by metabolic abnormalities, which may lead to renal insufficiency and cardiac arrhythmias. Cairo-Bishop

risk classification includes biological evidence of laboratory TLS (≥2 of the following changes within 3 days before or 7 days after cytotoxic therapy: uric acid ≥476 μmol/L or ≥25% increase from baseline, potassium ≥6.0 mmol/L or ≥25% increase from baseline and phosphate ≥2.1 mmol/L or ≥25% increase from baseline, calcium ≤1.75 mmol/L or 25% decrease of baseline); proliferation (particularly BL), bulk, and stage of aggressive B-cell NHL; and renal impairment and/or involvement at the time of TLS diagnosis.[108] The best treatment is prevention, based on disease-specific estimated risk of TLS. Low-risk disease is defined as an approximate risk of less than 1% of developing TLS, and requires intravenous fluids, allopurinol, and daily laboratory tests. Intermediate-risk disease is defined as a risk of approximately 1% to 5% of developing TLS, and requires intravenous fluids, allopurinol or rasburicase, and laboratory tests every 8 to 12 hours. Finally, high-risk disease is defined as a risk of greater than 5% of developing TLS, and requires intravenous fluids, rasburicase, cardiac monitoring, and laboratory tests every 6 to 8 hours.[108,109]

For further information about the prevention and management of TLS, please see Chapter 61, Oncologic Emergencies.

SPECIAL TYPES AND SITUATIONS OF LARGE B-CELL LYMPHOMAS

Diffuse Large B-Cell Lymphoma, Not Otherwise Specified

Double-Expressor DLBCL

Despite the inferior outcomes seen with R-CHOP therapy, there are limited data evaluating alternative treatment strategies for DEL. Indeed, several retrospective studies showed potentially improved outcome for patients treated with DA-EPOCH-R.[110,111] However, unplanned subset analyses from several trials, including the CALGB 50303 trial, have not found a difference with more intensive treatment for patients with DEL, although they were not powered to look for differences specifically in this subset.[92]

Interestingly, in a retrospective study, patients with DEL stage I/II treated with R-CHOP–like therapy, with or without radiation, did not show significantly inferior PFS or OS compared with patients with non-DEL.[112]

Further prospective clinical trials are needed to better delineate the optimum treatment approach in this patient population. In the absence of definitive data to guide decision making, both R-CHOP and more intensive induction regimens such as DA-EPOCH-R are reasonable approaches for DEL.[113] Because of the increased risk of CNS disease, evaluation for prophylaxis is recommended.

Testicular Involvement

Patients with testicular involvement in DLBCL have increased risk of CNS and extranodal disease and failure in contralateral testis. To prevent these events, it is standard practice to treat them similarly to that in the study IELSG-10, with six cycles of R-CHOP, CNS prophylaxis, preferably with systemic MTX (alternatively with 4 cycles of IT MTX), and RT to the contralateral testis (30 Gy) for all patients and RT to regional lymph nodes (30 to 36 Gy) for stage II disease.[114] Unilateral orchiectomy is usually performed for diagnostic purposes, but orchiectomy alone or RT alone is not a sufficient treatment, even for stage I disease.

T-Cell/Histiocyte-Rich Large B-Cell Lymphoma

Outside a clinical trial, THRLBCL should be treated similarly to other stage-matched DLBCLs. There is conflicting evidence regarding prognosis. However, some studies report that THRLBCL follows a natural history similar to those of other DLBCLs and responds similarly to therapy.[115] Nevertheless future therapies may target the relationship of the tumor cells with their inflammatory microenvironment.[116]

Primary Diffuse Large B-Cell Lymphoma of the Central Nervous System

The treatment of HIV-negative patients with primary diffuse large B-cell lymphoma of the central nervous system (PCNSL) is limited to drugs that can cross the blood-brain barrier, unlike R-CHOP. The most important drug is HDMTX, in general at doses ≥3.0 g/m^2. However, there is no uniform consensus regarding the optimal components of induction and consolidative therapy. Outside a clinical trial, the choice of a regimen is based on a patient's organ function, age, and comorbidities, as well as local institutional preferences.

The combination of chemoimmunotherapy using 5 to 7 cycles of rituximab, HDMTX, procarbazine, and vincristine (R-MPV) is considered one of the standards of care.[117] In this approach, patients have historically received consolidation with reduced-dose whole-brain radiation therapy (rdWBRT) of 23.40 Gy if they are in complete remission, although there is controversy regarding the role of RT. Lower doses of radiation have decreased the long-term neurotoxicity seen in prior studies.[118] In the previously mentioned approach with R-MPV and rdWBRT, patients receive consolidation with two cycles of high-dose cytarabine after completion of RT. Patients who could complete this whole therapy presented a 2-year PFS of 77% and 3-year OS of 87%.[117]

Based on different trials, efficacy of consolidative high-dose chemotherapy (HDCT)/autologous stem cell transplant (ASCT) is similar to WBRT, but the latter

approach carries a higher incidence of neurotoxicity. For instance, in the second phase of the IELSG32 trial, patients who had responsive or stable disease after induction with HDMTX/cytarabine-based therapy assigned to the HDCT/ASCT arm presented a 2-year PFS of 80% and a 2-year OS of 85%; patients assigned to the WBRT arm with 36 Gy presented a 2-year PFS of 69% ($P = .17$) and a 2-year OS of 71% ($P = .12$). As expected, hematologic toxicity was more common in patients treated with HDCT/ASCT, and neurotoxicity was more common in patients who received WBRT.[119]

PCNSL with leptomeningeal lymphoma can be treated with additional IT MTX.

Patients may present with intraocular lymphoma (IOL) either as part of primary IOL (without CNS involvement) or as part of PCNSL with ocular dissemination, which happens in 15% to 25% of cases.[120] Standard treatment of such cases remains unclear but includes MTX-based systemic chemotherapy with ocular external beam radiotherapy and intravitreal chemotherapy with MTX. Intravitreal rituximab is often used to decrease the frequency of methotrexate injections or for MTX-resistant IOL.[121]

For further information about AIDS-related B-cell lymphomas, please see Chapter 52, The Acquired Immunodeficiency Syndrome–Related Cancers.

Primary Cutaneous DLBCL, Leg Type

R-CHOP with or without IFRT 36–40 Gy for solitary or localized disease is considered the first line of treatment in these lymphomas.[122,123] According to some series, PCDLBCL-LT have increased risk for CNS involvement at the time of diagnosis or at relapse, and CNS prophylaxis may be warranted.[124]

EBV-Positive DLBCL, Not Otherwise Specified

Patients with EBV+ DLBCL–NOS should be managed following comparable guidelines as patients with EBV-negative DLBCL. EBV+ DLBCL–NOS, though, has a worse prognosis than EBV-negative DLBCL in the era of chemoimmunotherapy. There is an opportunity to study and develop targeted therapy such as CD30 antibody therapy in the treatment of patients with EBV+ DLBCL–NOS.[52,125]

DLBCL Associated With Chronic Inflammation

DLBCL-CI is very rare and can exhibit variable presentation and clinical course, including an indolent behavior for some cases. Moreover, there is a paucity of data regarding optimal management, which can include excisional surgery (such as pleuropneumonectomy with or without resection of adjacent involved tissues), systemic therapy such as R-CHOP, RT, or a combination of these. In a Japanese series, clinical stage was an important variable in the choice of therapy. Indeed, for limited stage, surgery resection alone was curative in two of four patients. However, advanced DLBCL-CI had a poor prognosis.[126] Because of the rarity of the disease and the multiple types of presentation, referral to a center with experience with DLBCL-CI multidisciplinary management is recommended.

EBV-Positive Mucocutaneous Ulcer

EBVMCU presents an often-benign course, including frequent spontaneous regressions and excellent responses to conservative treatments such as reduction of immunosuppression. If these measures are unsuccessful, some series reported patients responding to systemic therapy such as bendamustine rituximab, R-CHOP, or RT.[127,128]

Lymphomatoid Granulomatosis

Given the rarity of LYG, no standard treatment consensus exists, and treatment has varied widely from observation to systemic corticosteroids, interferon--2b, intravenous gamma globulin, anti-CD20 monoclonal antibody therapy such as rituximab, and/or chemotherapy such as DA-EPOCH-R.[58]

Large B-Cell Lymphoma With IRF4 Rearrangement

Patients with follicular neoplasms often have indolent disease and an excellent prognosis after tumor excision; chemotherapy may not be needed. Patients with purely diffuse neoplasms also have a good prognosis but require chemotherapy. Further studies are needed to determine whether chemotherapy can be reduced or whether a watch-and-wait strategy can be used for patients with localized disease after excision.[26,129]

Primary Mediastinal (Thymic) B-Cell Lymphoma

Because PMBL is uncommon and has been only recently described, there is a paucity of prospective treatment data and a lack of randomized studies.[64] A rituximab and anthracycline–containing frontline regimen is commonly used at most centers in the United States. Notably, DA-EPOCH-R without RT, as described in the phase 2 study of Dunleavy et al showed an excellent outcome with a 5-year EFS of 93% and a 5-year OS of 97%.[130] Alternatively, R-CHOP with RT can be considered equivalent in terms of lymphoma-related outcome, but it carries the risks associated with RT.[131] Nevertheless, a retrospective study of the BC Cancer Lymphoid Cancer Database showed that a PET-guided approach could reduce the use of RT by over 60% without compromising cure rates.[132] Randomized studies are required to validate the optimal approach.

Intravascular Large B-Cell Lymphomas

These lymphomas have a high incidence of CNS relapse. In the phase 2 PRIMEUR-IVL, IVDLBCL patients without apparent CNS involvement at diagnosis received three cycles of R-CHOP, followed by two cycles of rituximab with HDMTX, then three additional cycles of R-CHOP, with IT (methotrexate 15 mg, cytarabine 40 mg, and prednisolone 10 mg) administered four times during the R-CHOP phase. Overall, the 2-year PFS was 76% and the cumulative incidence of secondary CNS involvement was 3%.[133] This regimen warrants further investigation but presents promising clinical outcome.

ALK-Positive Large B-Cell Lymphoma

Because of the rarity of this malignancy, the data are limited to retrospective studies. In the case series of Pan et al, most patients received CHOP, CHOEP, EPOCH, or Hyper-CVAD, and some also underwent RT and HDCT/ASCT. However, patients with ALK+ LBCL showed a dismal outcome, with a 5-year OS of 34% and a median survival of 1.83 years. However, patients with stage I–II disease and/or patients younger than 35 years of age had a significantly better OS.[62] Whenever possible, these patients should be included in a clinical trial.

Plasmablastic Lymphoma

Overall, EPOCH is widely used to treat PBL, with complete response rate (CRR) of 71%.[134] Alternatively, a retrospective study with 16 patients showed that adding bortezomib to EPOCH could lead to a CRR of 94% and a 5-year OS of 63%.[135] However, added toxicity was an issue. Alternative regimens include CODOX-M/IVAC and Hyper-CVAD. Patients may benefit from HDT/ASCT in their first remission.[136] Nevertheless, further studies are required, and patients should be enrolled in a trial whenever possible.

For further information about AIDS-related B-cell lymphomas, please see Chapter 52, The Acquired Immunodeficiency Syndrome–Related Cancers.

HHV8-Positive Diffuse Large B-Cell Lymphoma

Patients with HHV8-positive DLBCL may be treated with similar regimens as patients with HIV-positive large B-cell lymphoma, such as EPOCH or CHOP, with rituximab in case of CD20 positivity.[137] There is a lack of data regarding optimal management of this uncommon malignancy. For further information about AIDS-related B-cell lymphomas, please see Chapter 52, The Acquired Immunodeficiency Syndrome–Related Cancers.

Primary Effusion Lymphoma

There are no prospective studies of PEL. However, in a retrospective study, modified EPOCH resulted in 3-year cancer-specific survival of 47%.[138] Nevertheless, such outcomes of EPOCH or CHOP-like are still unsatisfactory, and an effort to further improve outcomes is needed.[139]

For further information about AIDS-related B-cell lymphomas, please see Chapter 52, The Acquired Immunodeficiency Syndrome–Related Cancers.

High-Grade B-Cell Lymphoma

High-Grade B-Cell Lymphoma, With MYC and BCL2 and/or BCL6 Rearrangements

There is a lack of prospective data to help establish an optimal induction regimen. Multiple retrospective studies have suggested that intensification of upfront therapy such as DA-EPOCH-R, R-CODOX-M/IVAC (cyclophosphamide, doxorubicin, vincristine, methotrexate/ifosfamide, etoposide, high-dose cytarabine, also called "Magrath regimen"), and R-Hyper-CVAD may be superior to R-CHOP, notably with longer PFS.[31,140] At MDACC, our approach to double-hit DLBCL currently includes DA R-EPOCH outside of a clinical trial. CNS prophylaxis is warranted. Retrospective data suggest that there is no improvement of OS with consolidative ASCT in the first remission in patients who were treated with intensive induction regimens.[141] Because of the inferior prognosis of DHL, participation in a clinical trial is highly recommended.

Interestingly, in a retrospective study with DHL stage I/II patients treated with R-CHOP–like therapy, with or without radiation, double-hit status was not significantly associated with inferior PFS or OS. It is possible that early-stage DHLs have a different biology and a more favorable outcome not requiring more intensive therapies.[112]

High-Grade B-Cell Lymphoma, Not Otherwise Specified

HGBL–NOS is associated with a short survival period and substantial extranodal involvement. High-intensity chemotherapy such as DA-EPOCH-R, R-CODOX-M/IVAC, or R-Hyper-CVAD may improve outcome compared with R-CHOP, as shown in the retrospective study of Li et al. CNS prophylaxis is recommended. Consolidative RT for localized disease can be considered. Participation in a clinical trial is suggested.[142]

B-Cell Lymphoma, Unclassifiable

B-Cell Lymphoma, Unclassifiable, With Features Intermediate Between DLBCL and Classical Hodgkin Lymphoma

There is no standard of care regarding the management of patients with GZL. The prospective study of Wilson

et al, with 24 untreated MGZL patients treated with 6 to 8 cycles of DA-EPOCH-R, showed a 59-month EFS of 62% and a 59-month OS of 74%.[143] However, there is no study proving the superiority of R-CHOP to R-EPOCH, and R-CHOP is a valid therapy.[63] Consolidative RT can be considered for bulky or localized disease.[63,144]

Burkitt Lymphoma

The optimal therapy of BL has yet to be defined in a prospective, randomized trial, but R-CHOP is not an adequate therapy. However, if a patient cannot be enrolled in a clinical trial, we use aggressive combination chemotherapy such as DA-EPOCH-R, R-CODOX-M/IVAC, or R-Hyper-CVAD with CNS prophylaxis (Table 9-9). However, in a multi-institutional retrospective study, the risk of CNS recurrence differed according to chemotherapy regimen and was significantly higher for patients treated with DA-EPOCH with intrathecal chemotherapy (12% at 3 years vs CODOX-M/IVAC [4%] or Hyper-CVAD/MA [3%]).[145] Nevertheless, R-EPOCH is less toxic than R-CODOX-M/IVAC or R-Hyper-CVAD and might be an acceptable alternative for patients without evidence of CNS disease, who are unable to tolerate more intensive regimens. However, adequate CNS prophylaxis, notably with HDMTX, should be evaluated.

Patient with low-risk disease (ECOG 0–1, normal LDH, stage I–II, and mass <10 cm) may be treated with a shorter course of chemotherapy.[146–148]

AIDS-related BL should be treated with similar regimens as for HIV-negative patients with BL. Antiretroviral therapy can be safely administered with chemotherapy.[149] For further information about AIDS-related B-cell lymphomas, please see Chapter 52, The Acquired Immunodeficiency Syndrome–Related Cancers.

Burkitt-Like Lymphoma With 11q Aberration

BLL-11q is rare and its optimal management is undefined, although it is most often treated like typical BL.[68,150] Further studies are needed.

Table 9–9 R-Hyper-CVAD Regimen Used in Mantle Cell Lymphoma and Highly Aggressive Lymphomas[a]

Regimen	Dose/Route	Days	Interval
Hyper-CVAD/Methotrexate/ Ara-C			21–28 days
Cycles 1, 3, 5, 7			
Rituxan	375 mg/m^2 IV by slow infusion	1	
Cyclophosphamide	300 mg/m^2/dose over 3 h q 12 h × 6 doses	1–3	
Mesna	600 mg/m^2/day CIV over 24 h daily (Start 1 h prior to cyclophosphamide and complete by 12 h after last dose of cyclophosphamide)	1–3	
Doxorubicin	25 mg/m^2/day CIV over 24 h daily (Begin at 12 h after last dose of cyclophosphamide)	4–5	
Vincristine	1.4 mg/m^2 IV (max 2 mg) (Give 12 h after last dose of cyclophosphamide and on day 11)	4 and 11	
Dexamethasone	40 mg PO daily	1–4 and 11–14	
Cycles 2, 4, 6, 8			
Methotrexate	200 mg/m^2 IV over 2 h then 800 mg/m^2 IV over 22 h	1	
Solumedrol	50 mg IV q 12 h × 6 doses	1–3	
Ara-C	3 g/m^2 IV over 2 h every 12 h × 4 doses	2–3	
Leucovorin	50 mg IV followed by 15 mg IV q 6 h × 8 doses (start 12 h after completion of methotrexate)		
Intrathecal therapy[b]			
Ara-C	100 mg	2	
Methotrexate	12 mg (6 mg if Ommaya reservoir)	7	

[a]Dose reductions for renal insufficiency, age, and previous toxicity are required. Intrathecal chemotherapy is more frequent for proven CNS disease.
[b]Mantle cell lymphoma is not typically treated with intrathecal therapy.

Therapy in Older Adult Patients

As has been repeatedly shown, patients with aggressive NHL over the age of 60 years have a worse prognosis, notably because of comorbid conditions, lower treatment tolerance, and administration of inadequate therapy. We suggest screening for clinical trials with novel therapies. Outside a clinical trial, we recommend full-dose R-CHOP with growth factor support for patients older than 60 years. In the REMARC study, lenalidomide maintenance versus placebo given to 60- to 80-year-old patients with DLBCL after completion of R-CHOP therapy increased the PFS but not the OS, and at the cost of increased toxicity.[151] Alternatively, attenuated immunochemotherapy regimen (R-miniCHOP) can be considered in adult patients older than 80 years.[152]

Patients With Cardiac Disease

Patients with cardiac disease showing a contraindication to doxorubicin can be treated with an alternative regimen. There is a paucity of data to guide the choice of therapy. In a retrospective study with R-CEOP (etoposide substituted for doxorubicin), patients treated with R-CEOP presented a 5-year OS of 49% versus 64% for patients treated with R-CHOP.[153]

Therapy of Refractory or Relapsed Aggressive Non-Hodgkin B-Cell Lymphoma

General Management of Large B-Cell Lymphomas and High-Grade B-Cell Lymphomas

First Relapse

Approximately 10% of patients treated for aggressive NHL fail to achieve a complete remission after induction therapy; their disease is termed *primary refractory* (see Fig. 8–20). A larger portion of patients with aggressive NHL, up to one-third of all patients, will relapse after initially responding to chemotherapy, usually within the first two years.

In the SCHOLAR-1 study, which was done before chimeric antigen receptor (CAR)-T cell therapy, patients with refractory DLBCL had an ORR of 26% (CRR of 7%) to the next line of therapy, and the median OS was 6.3 months. Overall, 20% of patients were alive at 2 years.[89]

Before proceeding to further therapy, the relapse needs to be histologically proven and restaging completed. Participation in a clinical trial is highly recommended.

Intention to Proceed to Transplant

Outside a clinical trial, the standard of care is salvage therapy and HDCT followed by ASCT in chemosensitive patients. Notably, the PARMA trial examined autologous bone marrow transplantation versus salvage chemotherapy in patients with relapsed, chemotherapy-sensitive NHL. Patients were randomly assigned to receive four more cycles of DHAP (rituximab, cisplatin, dexamethasone, high-dose cytarabine) versus high-dose therapy with stem-cell support, showing an EFS rate of 46% in the high-dose arm but only 12% in the DHAP-alone arm.[154]

Conventional salvage therapies include rituximab combined with standard chemotherapeutics such as ifosfamide, etoposide, taxanes, and platinum compounds. Among the most commonly used are R-DHAP, R-ICE (ifosfamide, carboplatin, and etoposide) (Table 9-8), R-GDP (gemcitabine, dexamethasone, and cisplatin), TTR (paclitaxel, topotecan, and rituximab), and R-ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin). The best chemotherapy regimen would provide the highest response rates with the most tolerable toxicity. There remains no clear evidence regarding the superiority of one regimen over another in randomized studies. Moreover, failure to collect peripheral stem cells is around 10% and does not seem, in the first relapse, to be different from one regimen to another. In particular, the CORAL trial found no difference between R-DHAP and R-ICE. Overall, only 50% of the patients could proceed to HDCT/ASCT, mainly because of an insufficient response to second-line treatment. The rate of collection failure of stem cells was 10% in both arms.[155]

In relapsed disease, the prognostic impact of COO remains less clear. Although the Bio-CORAL study suggested that GCB DLBCL treated with R-DHAP had an improved 3-year PFS compared with those treated with R-ICE, multiple other studies have failed to reproduce these results, including in patients who went on to receive consolidative ASCT.[156] The topic of ASCT if discussed in further detail in Chapter 18, Autologous Hematopoietic Progenitor Cell Transplantation.

Patients who respond to second-line treatment, but who are unable to mobilize stem-cell treatment, should be considered for alternative options such as chimeric antigen receptor T-cell therapy (see Chapter 17, Cellular Therapy for Lymphomas) or donor transplant (see Chapter 19, Allogeneic Transplantation).

Noncandidates for Transplant

Overall, most such patients cannot tolerate the platinum-containing salvage regimens described above, and other salvage regimens are unlikely to achieve a complete and/or sustained remission. The choice of therapy depends on different factors, including performance status, organ function, pathologic features of the disease, and the patient's preferences. We favor participation in a clinical trial, or when a clinical trial is not available, we suggest either ibrutinib (ORR 40%[157]) or lenalidomide with or without rituximab (ORR 28.6%–33%[158,159]) for ABC-subtype lymphomas.

Other acceptable options for second-line salvage therapy include bendamustine rituximab (ORR 62.7%, CRR 37.3%, median PFS 6.7 months),[160] lenalidomide with or without rituximab or rituximab-gemcitabine-oxaliplatin (ORR 61%, CRR 44%).[161]

Second Relapse and More

Optimal treatment for patients who experience failure of at least two different systemic therapies is unknown, and selection of treatment depends on prior therapies, performance status, available resources, institutional preferences, and patient wishes. We recommend participation in a clinical trial. Some patients will choose palliation of symptoms, which may include chemotherapy or immunotherapy as described above.

Outside of a clinical trial, we recommend CAR–T cell therapy, if good performance status and acceptable organ function.

Currently, CAR–T cell therapy is FDA approved after failure of two lines of systemic therapy; however, several trials enroll patients after failure of one systemic therapy. CAR–T cell therapy is explained in further details in Chapter 17, Cellular Therapy for Lymphomas.

When CAR–T cell therapy is not available, we offer allogenic HCT for patients who are medically eligible (see Chapter 19, Allogeneic Transplantation).

For patients ineligible for trials, CAR–T cell therapy, or transplant, who have failed two lines of systemic therapy, polatuzumab-vedotin-BR is FDA approved and presents significant activity (ORR 45%, CRR 40%, median OS 12.4 months).[162]

In addition, the combination of tafasitamab (MOR208), an Fc-enhanced humanized anti-CD19 monoclonal antibody, with lenalidomide showed an ORR of 60% and CRR of 43% in the L-MIND trial.[163]

Alternatively, brentuximab vedotin can be considered for CD30-positive DLBCL (ORR 44%, CRR 15%, median PFS 4 months).[164]

Special Types of Aggressive B-Cell Lymphomas

Transformed Follicular Lymphoma

Patients with a history of follicular lymphoma with subsequent transformation to DLBCL, who had prior doxorubicin-based treatment, should be treated with salvage therapy for recurrent DLBCL.

Recurrent Primary Central Nervous System and Ocular Lymphoma

The treatment of recurrent primary CNS lymphoma is limited because of the inability of many drugs to penetrate the CNS. Moreover, the choice of therapy will depend on the performance status, organ reserve, and patient preferences. Outside a clinical trial, retreatment with high-dose methotrexate (ORR 91%, median PFS after first relapse 61.9 months) with or without rituximab can be attempted if there was a long duration of the first remission.[165] Patients with recent prior whole-brain RT may be at high risk for methotrexate-induced encephalopathy.

In case of refractory disease or short duration of remission after HDMTX, alternative therapies including lenalidomide and rituximab (ORR 32.0%, median PFS 7.8 months[166]), ibrutinib (ORR 52%, CRR 19%, median PFS 4.8 months[167]), HD cytarabine and etoposide (ORR 47%[168]), and rituximab and temozolomide (ORR 53%, median OS 14 months[169]) should be considered.

Responding patients may benefit from consolidation with high-dose chemotherapy (especially with preparative regimens including thiotepa), followed by ASCT.

Primary Mediastinal B-Cell Lymphoma

Relapsed/refractory PMBL should be managed like aggressive B-cell lymphoma. However, some cases with localized disease can be salvaged with RT only. Moreover, in the CHECKMATE-436 trial, patients with relapsed refractory (rr) PMBL that failed at least two lines of therapy presented an ORR of 70% and CRR 43% with brentuximab vedotin, and nivolumab.[170] Alternatively, in the trial KEYNOTE-170, a similar population presented an ORR of 45% when treated with pembrolizumab.[171]

ALK-Positive Large B-Cell Lymphoma

There is a paucity of data regarding optimal management of rr-ALK+LBCL, and participation in a clinical trial is recommended. Outside a clinical trial, there have been reports of short response with ALK inhibitors such as crizotinib[172] or nivolumab.[173] Outcome is generally poor.

B-Cell Lymphoma, Unclassifiable, With Features Intermediate Between DLBCL and Classic Hodgkin Lymphoma

Optimal therapy of rr-GZL is unknown and participation in a clinical trial is recommended. Because of some common biological features with PMBL, there are reports of activity of checkpoint inhibitors[174] and brentuximab vedotin.[163]

Burkitt Lymphoma

Prognosis is poor for patients with rr-BL,[175] and participation in a clinical trial is highly recommended. Outside a clinical trial, for patients with relapse longer than 6 months after completion of appropriate first-line therapy, a second-line therapy such as R-ICE should be considered. If a complete response is achieved, consider HDT/ASCT or allo-SCT. However, patients who do not receive appropriate frontline therapy may respond to a dose-intensive regimen such as R-CODOX-M/IVAC, or R-Hyper-CVAD.

RESPONSE AND FOLLOW-UP

Definitions of Response

Response to therapy is assessed according to criteria based on the anatomic and metabolic changes that occur in disease-involved nodal and extranodal sites.[69] A recent consensus statement was issued by leading clinical investigators to attempt standardization of response criteria to be used in clinical trials. There remains controversy about what constitutes an abnormal PET scan, and it is generally recommended that uptake be compared with the mediastinal blood pool and liver as internal controls and that the results be scored based on these results (Table 9–10).

The use of interim PET/CT is controversial, notably because of false-positive and inter-reader variability, and is not recommended for treatment decisions as part of routine clinical practice.[176]

Restaging

Fluorodeoxyglucose-PET has proven very useful in assessing responses to therapy and is now considered standard of care for initial post-therapy restaging in FDG-avid lymphomas.[69] Despite this recommendation, FDG-PET/CT should not be used for long-term follow-up imaging after initial response is confirmed (Fig. 9–13).

Surveillance

Follow-up of patients with aggressive NHL after complete remission and cessation of therapy is

Table 9–10 Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive before therapy; mass of any size permitted if PET is negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive before therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥50% of previously involved sites from nadir	Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase in longest diameter of a previously identified node >1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	>50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

CR, complete remission; CT, computed tomography; FDG, [^{18}F] fluorodeoxyglucose; PD, progressive disease; PET, positron emission tomography; PR, partial remission; SD, stable disease; SPD, sum of the product of the diameters.
Reproduced with permission from Cheson BD, Pfistner B, Juweid ME, et al: Revised response criteria for malignant lymphoma, *J Clin Oncol*. 2007 Feb 10;25(5):579-586.

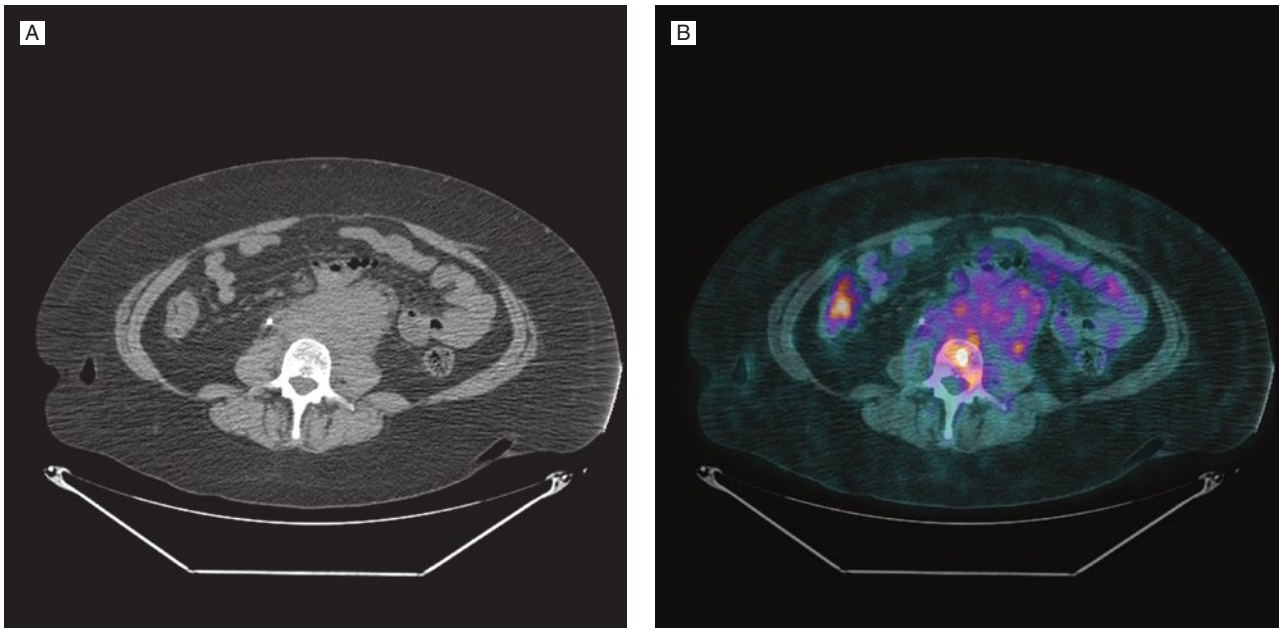


FIGURE 9–13 **Residual mass, not residual lymphoma. After completing chemotherapy, this patient had a residual soft tissue abnormality in the retroperitoneum. A. This was previously positive on FDG-PET, but now does not have activity above background levels and is considered negative. B. Biopsy of this mass was negative, and it was stable on follow-up studies. Previously, this would be considered a partial response (PR) or unconfirmed complete response (CRu). Under the revised criteria, considering the FDG-PET findings, this is considered a complete response (CR).**

typically done every 3 to 6 months for 2 years, then annually until year 5, although there is significant controversy about optimal use of surveillance imaging. A large retrospective evaluation of the utility of surveillance imaging to detect recurrence, compared with patient-reported complaints, found that most DLBCL recurrences were identified based on symptoms and not imaging alone and that outcomes were not different between imaging and symptom-identified recurrences.[177] The emergence of blood-based minimal residual disease detection techniques may ultimately make the debate about the utility of imaging moot.

Relapse or Recurrence

The presence of a new lesion, either by anatomic criteria or on FDG-PET scan, is highly suspicious for relapsed or progressive disease. However, a biopsy to confirm imaging findings is essential. FDG-PET is nonspecific, and uptake may occur in both benign and malignant tumors, in inflammatory or infectious lesions, and with normal physiologic processes. Sarcoidosis and fungal infections may mimic lymphoma, and biopsy is often necessary to exclude recurrence (Fig. 9–14). A single persistent or new focus of activity, with paradoxical response at other sites of disease, requires further evaluation with a biopsy, because findings may represent a premalignant lesion, such as a thyroid or colonic adenoma, or an incidental second malignant tumor (Fig. 9–15).

NEW DIRECTIONS

Over the last 30 years, remarkable advances have been made in the diagnosis, characterization, and treatment of patients with aggressive NHL. It is our strong recommendation that all patients be considered for clinical trials to move the field forward.

The multitude of the dysregulated circuits, the overall complexity and heterogeneity of aggressive B-cell lymphomas (which may also involve nongenetic mechanisms), and the interplay with the microenvironment underscore the need for more precise patient stratification to improve personalized medicine. Moreover, advancements in bioinformatics and gene-editing technologies in translational medicine will lead to significant progress in this area in the near future.

In addition, significant advances may come from the use of circulating tumor DNA (ctDNA), which proved to be a reliable surrogate for simultaneously tracking multiple somatic mutations in aggressive B-cell lymphomas, with high specificity and sensitivity.[178] This approach was superior to radiographic

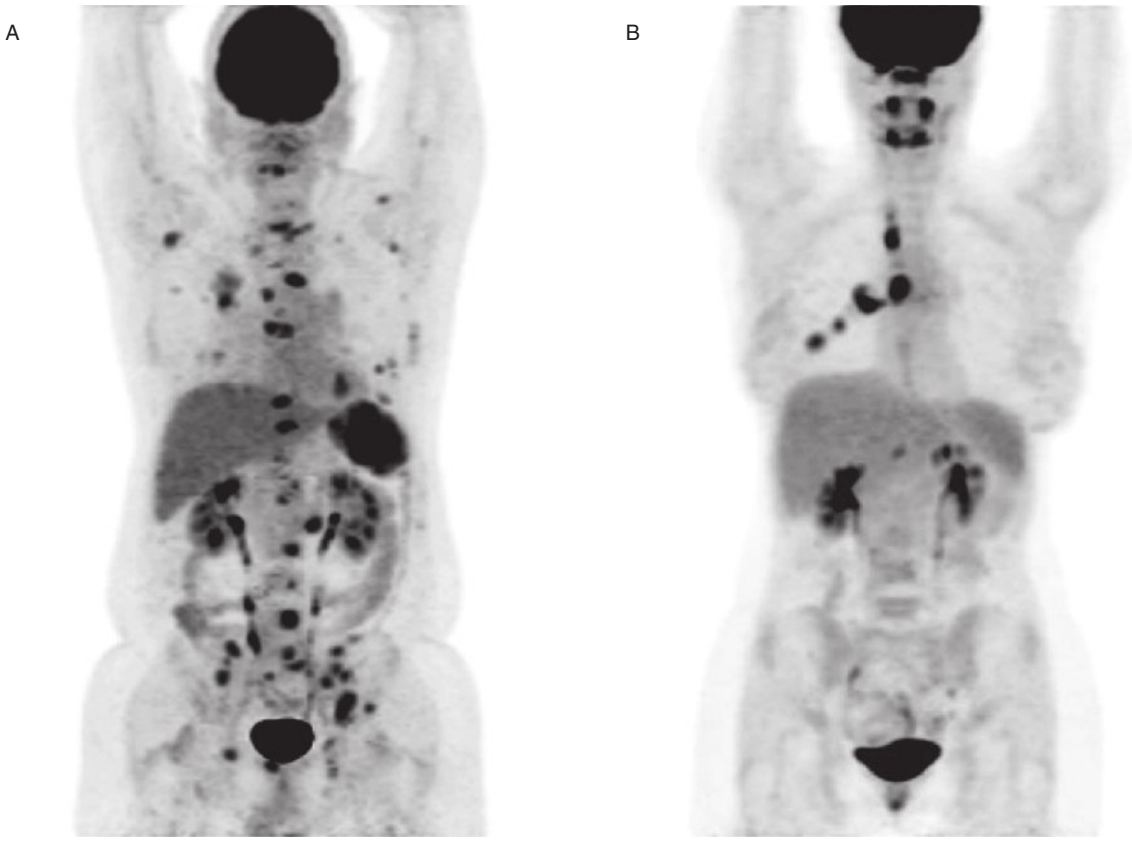


FIGURE 9–14 **Examples of false-positive FDG-PET. Restaging study is suspicious for recurrent lymphoma. A. With predominantly osseous involvement; however, biopsy revealed non-necrotizing granulomas thought to be caused by sarcoidosis. Two months later, nearly all of the FDG-avid sites resolved without any therapy. B. A second patient presented over 10 years after successful treatment for lymphoma with new lymphadenopathy and lung opacities that were positive on FDG-PET. Biopsy revealed fungal lymphadenitis.**

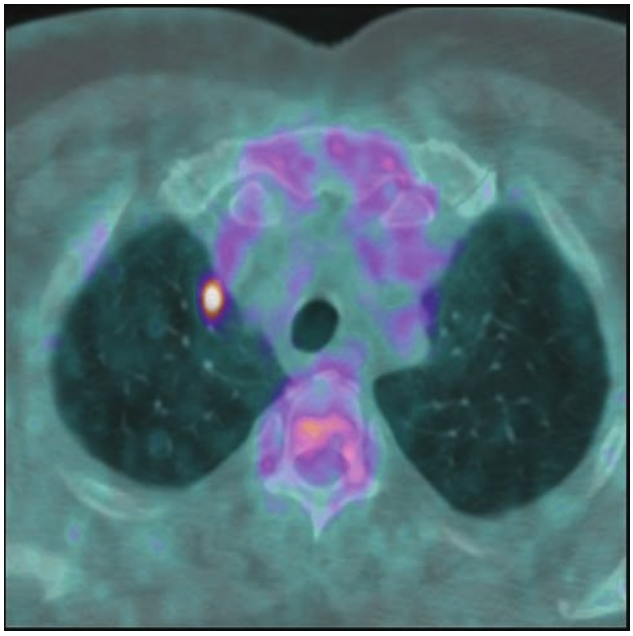


FIGURE 9–15 **Incidental significant finding on FDG-PET/CT. An enlarging metabolically active lung nodule is seen. Biopsy revealed non–small-cell lung cancer, and the patient went on to have lobectomy for stage I lung cancer.**

imaging for the detection of minimal residual disease and was independently predictive of clinical outcome in a study. Moreover, ctDNA genotyping allows the identification of distinct patterns of clonal evolution, which makes it a valuable tool in the setting of transformation or relapse, by informing individualized therapy.[179] Furthermore, the discovery of genes and pathways that are recurrently disrupted in DLBCL reveals vulnerabilities in the lymphoma cells that are often uniquely associated with distinct lymphoma subtypes and could thus be exploited for the design of more effective, targeted therapeutic approaches. It is expected that additional novel therapeutic targets will be identified as more mutational events become functionally dissected.[180]

There is an unmet need to improve the prognosis of relapsed/refractory disease, to decrease the relapse rate of frontline therapy, decrease toxicity, and to tailor treatments for rarer malignancies. Improved novel, immune, and cellular therapies such as CAR–T cell therapies will likely be moved from the last line of therapy to the second line and frontline, and use of standard cytotoxic therapy might become progressively obsolete.

MD ANDERSON PRACTICE TIPS

- Our preference is that all patients with aggressive B-cell lymphoma be evaluated for a clinical trial at each treatment stage at MDACC.
- Therapy of early-stage, favorable prognosis, nonbulky (maximal tumor diameter <7.5 cm) DLBCL can include a shorter course of R-CHOP without consolidative RT, if complete response is achieved at completion of systemic therapy.
- There is a lack of prospective data to help establish an optimal induction regimen of HGBL, with MYC and BCL2 and/or BCL6 rearrangements (double-hit lymphoma [DHL]). Our approach currently includes DA R-EPOCH with CNS prophylaxis, outside a clinical trial. However, in a retrospective study with DHL, stage I/II patients treated with R-CHOP–like therapy with or without radiation, double-hit status was not significantly associated with inferior PFS or OS. Early-stage DHL may have different biology and a more favorable outcome, not requiring more intensive therapies.[1] More studies are required.
- In the CHECKMATE-436 trial, patients with relapsed refractory PMBL who failed at least two lines of therapy presented an ORR of 70% and CRR of 43% with brentuximab vedotin and nivolumab.[2] Considering the biology of PMBL, these immune therapies present an appropriate option.
- For patients ineligible for trials, CAR–T cell therapy, or stem-cell transplant, who have failed two lines of systemic therapy, polatuzumab-vedotin-BR is FDA approved and presents significant activity (ORR 45%, CRR 40%, median OS 12.4 months). In addition, the combination of tafasitamab (MOR208), an Fc-enhanced humanized anti-CD19 monoclonal antibody, with lenalidomide showed an ORR of 60% and CRR of 43% in the L-MIND trial for a similar population.[3]
- Novel, immune, and cellular therapies such as CAR–T cell therapies will likely be moved from latter lines of therapy of aggressive B-cell lymphomas to second line, and possibly frontline, and use of standard cytotoxic therapy might become progressively obsolete.

REFERENCES

1. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood.* 2016;127(20):2375-2390.
2. Teras LR, DeSantis CE, Cerhan JR, et al. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. *CA Cancer J Clin.* 2016;66(6):443-459.
3. National Cancer Institute. Cancer Stat Facts: Non-Hodgkin Lymphoma. Accessed March 25, 2020. https://seer.cancer.gov/statfacts/html/nhl.html, access date 03/25/2020
4. Li Y, Wang Y, Wang Z, et al. Racial differences in three major NHL subtypes: descriptive epidemiology. *Cancer Epidemiol.* 2015;39(1):8-13.
5. Tomasetti C, Vogelstein B. Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. *Science.* 2015;347(6217):78-81.
6. Godfrey J, Leukam MJ, Smith SM. An update in treating transformed lymphoma. *Best Pract Res Clin Haematol.* 2018;31(3):251-261.
7. Filipovich AH, Mathur A, Kamat D, et al. Primary immunodeficiencies: genetic risk factors for lymphoma. *Cancer Res.* 1992;52(suppl 19):5465s-5467s.
8. Mueller N. Overview of the epidemiology of malignancy in immune deficiency. *J Acquir Immune Defic Syndr.* 1999;21(suppl 1):S5-10.
9. Opelz G, Dohler B. Lymphomas after solid organ transplantation: a collaborative transplant study report. *Am J Transplant.* 2004;4(2):222-230.
10. Brown SL, Greene MH, Gershon SK, et al. Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration. *Arthritis Rheum.* 2002;46(12):3151-3158.
11. Salloum E, Cooper DL, Howe G, et al. Spontaneous regression of lymphoproliferative disorders in patients treated with methotrexate for rheumatoid arthritis and other rheumatic diseases. *J Clin Oncol.* 1996;14(6):1943-1949.
12. Lyons SF, Liebowitz DN. The roles of human viruses in the pathogenesis of lymphoma. *Semin Oncol.* 1998;25(4):461-75.
13. Centers for Disease Control and Prevention (CDC). Revised surveillance case definition for HIV infection—United States. *MMWR Recomm Rep.* 2014;63(Rr-03):1-10.
14. Shiels MS, Pfeiffer RM, Hall HI, et al. Proportions of Kaposi sarcoma, selected non-Hodgkin lymphomas, and cervical cancer in the United States occurring in persons with AIDS, 1980-2007. *JAMA.* 2011;305(14):1450-1459.
15. Coté TR, Biggar RJ, Rosenberg PS, et al. Non-Hodgkin's lymphoma among people with AIDS: incidence, presentation and public health burden. AIDS/Cancer Study Group. *Int J Cancer.* 1997;73(5):645-650.
16. Young LS, Murray PG. Epstein-Barr virus and oncogenesis: from latent genes to tumours. *Oncogene.* 2003;22(33):5108-5121.
17. Goedert JJ. The epidemiology of acquired immunodeficiency syndrome malignancies. *Semin Oncol.* 2000;27(4):390-401.
18. Pozzato G, Mazzaro C, Dal Maso L, et al. Hepatitis C virus and non-Hodgkin's lymphomas: meta-analysis of epidemiology data and therapy options. *World J Hepatol.* 2016;8(2):107-116.
19. Cerhan JR, Kricker A, Paltiel O, et al. Medical history, lifestyle, family history, and occupational risk factors for diffuse large B-cell lymphoma: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. *J Natl Cancer Inst Monogr.* 2014;2014(48):15-25.
20. Guyton KZ, Loomis D, Grosse Y, et al. Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate. *Lancet Oncol.* 2015;16(5):490-491.
21. McDuffie HH, Pahwa P, McLaughlin JR, et al. Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. *Cancer Epidemiol Biomarkers Prev.* 2001;10(11):1155-1163.
22. Chatterjee N, Hartge P, Cerhan JR, et al. Risk of non-Hodgkin's lymphoma and family history of lymphatic, hematologic, and other cancers. *Cancer Epidemiol Biomarkers Prev.* 2004;13(9):1415-1421.
23. Anderson T, Chabner BA, Young RC, et al. Malignant lymphoma. 1. The histology and staging of 473 patients at the National Cancer Institute. *Cancer.* 1982;50(12):2699-2707.
24. Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. *J Clin Oncol.* 1998;16(8):2780-2795.
25. Swerdlow SH, Campo E, Harris NL, et al. *WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues*. Revised 4th ed. IARC; 2017.
26. Sukswai N, Lyapichev K, Khoury JD, et al. Diffuse large B-cell lymphoma variants: an update. *Pathology.* 2020;52(1):53-67.
27. Moller MB, Pedersen NT, Christensen BE. Diffuse large B-cell lymphoma: clinical implications of extranodal versus nodal presentation--a population-based study of 1575 cases. *Br J Haematol.* 2004;124(2):151-159.
28. Persky DO, Unger JM, Spier CM, et al. Phase II study of rituximab plus three cycles of CHOP and involved-field radiotherapy for patients with limited-stage aggressive B-Cell lymphoma: Southwest Oncology Group Study 0014. *J Clin Oncol.* 2008;26(14):2258-2263.
29. Horn H, Staiger AM, Vöhringer M, et al. Diffuse large B-cell lymphomas of immunoblastic type are a major reservoir for MYC-IGH translocations. *Am J Surg Pathol.* 2015;39(1):61-66.
30. Rosenthal A, Younes A. High grade B-cell lymphoma with rearrangements of MYC and BCL2 and/or BCL6: double hit and triple hit lymphomas and double expressing lymphoma. *Blood Rev.* 2017;31(2):37-42.
31. Oki Y, Noorani M, Lin P, et al. Double hit lymphoma: the MD Anderson Cancer Center clinical experience. *Br J Haematol.* 2014;166(6):891-901.
32. Johnson NA, Slack GW, Savage KJ, et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J Clin Oncol.* 2012;30(28):3452-3429.
33. Green TM, Young KH, Visco C, et al. Immunohistochemical double-hit score is a strong predictor of outcome in patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J Clin Oncol.* 2012;30(28):3460-3467.
34. Cheah CY, Oki Y, Westin JR, et al. A clinician's guide to double hit lymphomas. *Br J Haematol.* 2015;168(6):784-795.
35. Thieblemont C, Brière J. MYC, BCL2, BCL6 in DLBCL: impact for clinics in the future? *Blood.* 2013;121(12):2165-2166.
36. Horn H, Ziepert M, Becher C, et al. MYC status in concert with BCL2 and BCL6 expression predicts outcome in diffuse large B-cell lymphoma. *Blood.* 2013. 121(12):2253-63.
37. Lenz G, Staudt LM. Aggressive lymphomas. *N Engl J Med.* 2010. 362(15):1417-29.
38. Scott DW, et al. Prognostic significance of diffuse large B-cell lymphoma cell of origin determined by digital gene expression in formalin-fixed paraffin-embedded tissue biopsies. *J Clin Oncol.* 2015;33(26):2848-2856.
39. Schmitz R, Wright GW, Huang DW, et al. Genetics and pathogenesis of diffuse large B-cell lymphoma. *N Engl J Med.* 2018;378(15):1396-1407.
40. Wright GW, Huang DW, Phelan JD, et al. A probabilistic classification tool for genetic subtypes of diffuse large B cell lymphoma with therapeutic implications. *Cancer Cell.* 2020;37(4):551-568. e14.

41. Scott DW, Wright GW, Williams PM, et al. Determining cell-of-origin subtypes of diffuse large B-cell lymphoma using gene expression in formalin-fixed paraffin-embedded tissue. *Blood.* 2014;123(8):1214-1217.
42. Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood.* 2004;103(1):275-282.
43. Visco C, Li Y, Xu-Monette ZY, et al. Comprehensive gene expression profiling and immunohistochemical studies support application of immunophenotypic algorithm for molecular subtype classification in diffuse large B-cell lymphoma: a report from the International DLBCL Rituximab-CHOP Consortium Program Study. *Leukemia.* 2012;26(9):2103-2113.
44. Achten R, Verhoef G, Vanuytsel L, et al. T-cell/histiocyte-rich large B-cell lymphoma: a distinct clinicopathologic entity. *J Clin Oncol.* 2002;20(5):1269-1277.
45. Braggio E, Van Wier S, Ojha J, et al. Genome-wide analysis uncovers novel recurrent alterations in primary central nervous system lymphomas. *Clin Cancer Res.* 2015;21(17):3986-3994.
46. Montesinos-Rongen M, Brunn A, Bentink S, et al. Gene expression profiling suggests primary central nervous system lymphomas to be derived from a late germinal center B cell. *Leukemia.* 2008;22(2):400-405.
47. Moulignier A, Lamirel C, Picard H, et al. Long-term AIDS-related PCNSL outcomes with HD-MTX and combined antiretroviral therapy. *Neurology.* 2017;89(8):796-804.
48. Uldrick TS, Pipkin S, Scheer S, et al. Factors associated with survival among patients with AIDS-related primary central nervous system lymphoma. *AIDS.* 2014;28(3):397-405.
49. Willemze R, Cerroni L, Kempf W, et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. *Blood.* 2019;133(16):1703-1714.
50. Grange F, Bekkenk MW, Wechsler J, et al. Prognostic factors in primary cutaneous large B-cell lymphomas: a European multicenter study. *J Clin Oncol.* 2001;19(16):3602-3610.
51. Dijkman R, Tensen CP, Jordanova ES, et al. Array-based comparative genomic hybridization analysis reveals recurrent chromosomal alterations and prognostic parameters in primary cutaneous large B-cell lymphoma. *J Clin Oncol.* 2006;24(2):296-305.
52. Castillo JJ, Beltran BE, Miranda RN, et al. EBV-positive diffuse large B-cell lymphoma, not otherwise specified: 2018 update on diagnosis, risk-stratification and management. *Am J Hematol.* 2018;93(7):953-962.
53. Hong JY, Yoon DH, Suh C, et al. EBV-positive diffuse large B-cell lymphoma in young adults: is this a distinct disease entity? *Ann Oncol.* 2015;26(3):548-555.
54. Nakatsuka S, Yao M, Hoshida Y, et al. Pyothorax-associated lymphoma: a review of 106 cases. *J Clin Oncol.* 2002;20(20):4255-4260.
55. Hart M, et al. EBV-positive mucocutaneous ulcer in organ transplant recipients: a localized indolent post-transplant lymphoproliferative disorder. *Am J Surg Pathol.* 2014;38(11):1522-1529.
56. Dojcinov SD, Venkataraman G, Raffeld M, et al. EBV positive mucocutaneous ulcer—a study of 26 cases associated with various sources of immunosuppression. *Am J Surg Pathol.* 2010;34(3):405-417.
57. Jain P, et al. Characteristics, treatments, and outcomes of patients with lymphomatoid granulomatosis—MD Anderson Cancer Center experience. *Blood.* 2017;130(suppl 1):2852.
58. Melani C, Jaffe ES, Wilson WH. Pathobiology and treatment of lymphomatoid granulomatosis, a rare EBV-driven disorder. *Blood.* 2020;135(16):1344-1352.
59. Colby TV. Current histological diagnosis of lymphomatoid granulomatosis. *Mod Pathol.* 2012;25(suppl 1):S39-42.
60. Savage KJ, Al Rajhi N, Voss N, et al. Favorable outcome of primary mediastinal large B-cell lymphoma in a single institution: the British Columbia experience. *Ann Oncol.* 2006;17(1):123-130.
61. Jiang X-N, Yu B-H, Wang W-G, et al. Anaplastic lymphoma kinase-positive large B-cell lymphoma: clinico-pathological study of 17 cases with review of literature. *PLoS One.* 2017;12(6):e0178416.
62. Pan Z, Hu S, Li M, et al. ALK-positive large B-cell lymphoma: a clinicopathologic study of 26 cases with review of additional 108 cases in the literature. *Am J Surg Pathol.* 2017;41(1):25-38.
63. Evens AM, Kanakry JA, Sehn LH, et al. Gray zone lymphoma with features intermediate between classical Hodgkin lymphoma and diffuse large B-cell lymphoma: characteristics, outcomes, and prognostication among a large multicenter cohort. *Am J Hematol.* 2015;90(9):778-783.
64. Dunleavy K, Wilson WH. Primary mediastinal B-cell lymphoma and mediastinal gray zone lymphoma: do they require a unique therapeutic approach? *Blood.* 2015;125(1):33-39.
65. Tanaka Y, Maeshima AM, Nomoto J, et al. Expression pattern of PD-L1 and PD-L2 in classical Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, and gray zone lymphoma. *Eur J Haematol.* 2018;100(5):511-517.
66. Chihara D, Westin JR, Miranda RN, et al. Dose adjusted-EPOCH-R and mediastinal disease may improve outcomes for patients with gray-zone lymphoma. *Br J Haematol.* 2017;179(3):503-506.
67. Dunleavy K. Approach to the diagnosis and treatment of adult Burkitt's lymphoma. *J Oncol Pract*. 2018;14(11):665-671.
68. Gonzalez-Farre B, Ramis-Zaldivar JE, Salmeron-Villalobos J, et al. Burkitt-like lymphoma with 11q aberration: a germinal center-derived lymphoma genetically unrelated to Burkitt lymphoma. *Haematologica.* 2019;104(9):1822-1829.
69. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol.* 2014;32(27):3059-3068.
70. Chaganti S, Illidge T, Barrington S, et al. Guidelines for the management of diffuse large B-cell lymphoma. *Br J Haematol.* 2016;174(1):43-56.
71. Vercellino L, Cottereau AS, Casasnovas O, et al. High total metabolic tumor volume at baseline predicts survival independent of response to therapy. *Blood.* 2020;135(16):1396-1405.
72. Tilly H, Gomes da Silva M, Vitolo U, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2015;26(suppl 5):v116-v125.
73. Coller BS, Chabner BA, Gralnick HR. Frequencies and patterns of bone marrow involvement in non-Hodgkin lymphomas: observations on the value of bilateral biopsies. *Am J Hematol.* 1977;3:105-119.
74. Schmitz N, Zeynalova S, Nickelsen M, et al. CNS International Prognostic Index: a risk model for CNS relapse in patients with diffuse large B-cell lymphoma treated with R-CHOP. *J Clin Oncol.* 2016;34(26):3150-3156.
75. Cox MC, Di Napoli A, Scarpino S, et al. Clinicopathologic characterization of diffuse-large-B-cell lymphoma with an associated serum monoclonal IgM component. *PLoS One.* 2014;9(4):e93903.
76. Savage KJ. Secondary CNS relapse in diffuse large B-cell lymphoma: defining high-risk patients and optimization of prophylaxis strategies. *Hematology Am Soc Hematol Educ Program.* 2017;2017(1):578-586.
77. Klanova M, Sehn LH, Bence-Bruckler I, et al. Integration of cell of origin into the clinical CNS International Prognostic Index improves CNS relapse prediction in DLBCL. *Blood.* 2019;133(9):919-926.

78. Vitolo U, Seymour JF, Martelli M, et al. Extranodal diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2016;27(suppl 5):v91-v102.
79. Shimada K, Kinoshita T, Naoe T, et al. Presentation and management of intravascular large B-cell lymphoma. *Lancet Oncol.* 2009;10(9):895-902.
80. Wang XJ, Medeiros LJ, Bueso-Ramos CE, et al. P53 expression correlates with poorer survival and augments the negative prognostic effect of MYC rearrangement, expression or concurrent MYC/BCL2 expression in diffuse large B-cell lymphoma. *Mod Pathol.* 2017;30(2):194-203.
81. Cai Q, Westin J, Fu K, et al. Accelerated therapeutic progress in diffuse large B cell lymphoma. *Ann Hematol.* 2014;93(4):541-556.
82. Vose JM, Armitage JO, Weisenburger DD, et al. The importance of age in survival of patients treated with chemotherapy for aggressive non-Hodgkin's lymphoma. *J Clin Oncol.* 1988;6(12):1838-1844.
83. Sehn LH, Berry B, Chhanabhai M, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood.* 2007;109(5):1857-1861.
84. Zhou Z, Sehn LH, Rademaker AW, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. *Blood.* 2014;123(6):837-842.
85. Ruppert AS, Dixon JG, Salles G, et al. International prognostic indices in diffuse large B-cell lymphoma: a comparison of IPI, R-IPI, and NCCN-IPI. *Blood.* 2020;135(23):2041-2048.
86. Ferreri AJ. How I treat primary CNS lymphoma. *Blood.* 2011;118(3):510-522.
87. Schöder H, Polley M-Y C, Knopp MV, et al. Prognostic value of interim FDG-PET in diffuse large cell lymphoma: results from the CALGB 50303 clinical trial. *Blood.* 2020;135(25):2224-2234.
88. Moskowitz CH, Schöder H, Teruya-Feldstein J, et al. Risk-adapted dose-dense immunochemotherapy determined by interim FDG-PET in Advanced-stage diffuse large B-Cell lymphoma. *J Clin Oncol.* 2010;28(11):1896-1903.
89. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood.* 2017;130(16):1800-1808.
90. Cunningham D, Hawkes EA, Jack A, et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. *Lancet.* 2013;381(9880):1817-1826.
91. Vitolo U, et al. Obinutuzumab or rituximab plus CHOP in patients with previously untreated diffuse large B-cell lymphoma: final results from an open-label, randomized phase 3 study (GOYA). *Blood.* 2016;128(22):470.
92. Bartlett NL, Wilson WH, Jung S-H, et al. Dose-adjusted EPOCH-R compared with R-CHOP as frontline therapy for diffuse large B-cell lymphoma: clinical outcomes of the phase III Intergroup Trial Alliance/CALGB 50303. *J Clin Oncol.* 2019;37(21):1790-1799.
93. Poeschel V, Held G, Ziepert M, et al. Four versus six cycles of CHOP chemotherapy in combination with six applications of rituximab in patients with aggressive B-cell lymphoma with favourable prognosis (FLYER): a randomised, phase 3, non-inferiority trial. *Lancet.* 2020;394(10216):2271-2281.
94. Stephens DM, Li H, LeBlanc ML, et al. Continued risk of relapse independent of treatment modality in limited-stage diffuse large B-cell lymphoma: final and long-term analysis of Southwest Oncology Group Study S8736. *J Clin Oncol.* 2016;34(25):2997-3004.
95. Held G, Murawski N, Ziepert M, et al. Role of radiotherapy to bulky disease in elderly patients with aggressive B-cell lymphoma. *J Clin Oncol.* 2014;32(11):1112-1118.
96. Persky DO, Li H, Stephens DM, et al. PET-directed therapy for patients with limited-stage diffuse large B-cell lymphoma—results of Intergroup National Clinical Trials Network Study S1001. *Blood.* 2019;134(supplement 1):349.
97. Pfreundschuh M, Trümper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol.* 2006;7(5):379-391.
98. Liu Y, Barta SK. Diffuse large B-cell lymphoma: 2019 update on diagnosis, risk stratification, and treatment. *Am J Hematol.* 2019;94(5):604-616.
99. Younes A, Sehn LH, Johnson P, et al. Randomized phase III trial of ibrutinib and rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in non-germinal center B-cell diffuse large B-cell lymphoma. *J Clin Oncol.* 2019;37(15):1285-1295.
100. Leonard JP, Kolibaba KS, Reeves JA, et al. Randomized phase II study of R-CHOP with or without bortezomib in previously untreated patients with non-germinal center B-cell-like diffuse large B-cell lymphoma. *J Clin Oncol.* 2017;35(31):3538-3546.
101. Vitolo U, et al. ROBUST: first report of phase III randomized study of lenalidomide/R-CHOP (R2-CHOP) vs placebo/R-CHOP in previously untreated ABC-type diffuse large B-cell lymphoma. *Hematol Oncol.* 2019;37(suppl 2):36-37.
102. Molina TJ, Canioni D, Copie-Bergman C, et al. Young patients with non-germinal center B-cell-like diffuse large B-cell lymphoma benefit from intensified chemotherapy with ACVBP plus rituximab compared with CHOP plus rituximab: analysis of data from the Groupe d'Etudes des Lymphomes de l'Adulte/lymphoma study association phase III trial LNH 03-2B. *J Clin Oncol.* 2014;32(35):3996-4003.
103. Ghose A, Elias HK, Guha G, et al. Influence of rituximab on central nervous system relapse in diffuse large B-cell lymphoma and role of prophylaxis—a systematic review of prospective studies. *Clin Lymphoma Myeloma Leuk.* 2015;15(8):451-457.
104. Villa D, Connors JM, Sehn LH, et al. Diffuse large B-cell lymphoma with involvement of the kidney: outcome and risk of central nervous system relapse. *Haematologica.* 2011;96(7):1002-1007.
105. Hall KH, Panjic EH, Valla K, et al. How to decide which DLBCL patients should receive CNS prophylaxis. *Oncology (Williston Park).* 2018;32(6):303-309.
106. Abramson JS, Hellmann M, Barnes JA, et al. Intravenous methotrexate as central nervous system (CNS) prophylaxis is associated with a low risk of CNS recurrence in high-risk patients with diffuse large B-cell lymphoma. *Cancer.* 2010;116(18):4283-4290.
107. Ferreri AJ, Bruno-Ventre M, Donadoni G, et al. Risk-tailored CNS prophylaxis in a mono-institutional series of 200 patients with diffuse large B-cell lymphoma treated in the rituximab era. *Br J Haematol.* 2015;168(5):654-662.
108. Cairo MS, Coiffier B, Reiter A, et al. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. *Br J Haematol.* 2010;149(4):578-586.
109. Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. *N Engl J Med.* 2011;364(19):1844-1854.
110. Dodero A, Guidetti A, Tucci A, et al. Dose-adjusted EPOCH plus rituximab improves the clinical outcome of young patients affected by double expressor diffuse large B-cell lymphoma. *Leukemia.* 2019;33(4):1047-1051.

111. Aggarwal A, et al. Outcome of patients with double-expressor lymphomas (DELs) treated with R-CHOP or R-EPOCH. *Blood.* 2016;128(22):5396.
112. Barraclough A, Alzahrani M, Ettrup MS, et al. COO and MYC/BCL2 status do not predict outcome among patients with stage I/II DLBCL: a retrospective multicenter study. *Blood Adv.* 2019;3(13):2013-2021.
113. Riedell PA, Smith SM. Double hit and double expressors in lymphoma: definition and treatment. *Cancer.* 2018;124(24):4622-4632.
114. Vitolo U, Chiappella A, Ferreri AJM, et al. First-line treatment for primary testicular diffuse large B-cell lymphoma with rituximab-CHOP, CNS prophylaxis, and contralateral testis irradiation: final results of an international phase II trial. *J Clin Oncol.* 2011;29(20):2766-2772.
115. Bouabdallah R, Mounier N, Guettier C, et al. T-cell/histiocyte-rich large B-cell lymphomas and classical diffuse large B-cell lymphomas have similar outcome after chemotherapy: a matched-control analysis. *J Clin Oncol.* 2003;21(7):1271-1277.
116. Abramson JS. T-cell/histiocyte-rich B-cell lymphoma: biology, diagnosis, and management. *Oncologist.* 2006;11(4):384-392.
117. Morris PG, Correa DD, Yahalom J, et al. Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: final results and long-term outcome. *J Clin Oncol.* 2013;31(31):3971-3979.
118. Correa DD, Rocco-Donovan M, DeAngelis LM, et al. Prospective cognitive follow-up in primary CNS lymphoma patients treated with chemotherapy and reduced-dose radiotherapy. *J Neurooncol.* 2009;91(3):315-321.
119. Ferreri AJM, Cwynarski K, Pulczynski E, et al. Whole-brain radiotherapy or autologous stem-cell transplantation as consolidation strategies after high-dose methotrexate-based chemoimmunotherapy in patients with primary CNS lymphoma: results of the second randomisation of the International Extranodal Lymphoma Study Group-32 phase 2 trial. *Lancet Haematol.* 2017;4(11):e510-e523.
120. Grimm SA, McCannel CA, Omuro AMP, et al. Primary CNS lymphoma with intraocular involvement: International PCNSL Collaborative Group Report. *Neurology.* 2008;71(17):1355-1360.
121. Tang LJ, Gu CL, Zhang P. Intraocular lymphoma. *Int J Ophthalmol.* 2017;10(8):1301-1307.
122. Specht L, Dabaja B, Illidge T, et al. Modern radiation therapy for primary cutaneous lymphomas: field and dose guidelines from the International Lymphoma Radiation Oncology Group. *Int J Radiat Oncol Biol Phys.* 2015;92(1):32-39.
123. Senff NJ, Noordijk EM, Kim YH, et al. European Organization for Research and Treatment of Cancer and International Society for Cutaneous Lymphoma consensus recommendations for the management of cutaneous B-cell lymphomas. *Blood.* 2008;112(5):1600-1609.
124. Gardette E, Maraval A, Brunet-Possenti F, et al. Central nervous system involvement of primary cutaneous diffuse large B-cell lymphoma, leg type: 13 cases. *J Eur Acad Dermatol Venereol.* 2017;31(11):e498-e501.
125. Oyama T, Yamamoto K, Asano N, et al. Age-related EBV-associated B-cell lymphoproliferative disorders constitute a distinct clinicopathologic group: a study of 96 patients. *Clin Cancer Res.* 2007;13(17):5124-5132.
126. Narimatsu H, Ota Y, Kami M, et al. Clinicopathological features of pyothorax-associated lymphoma; a retrospective survey involving 98 patients. *Ann Oncol.* 2007;18(1):122-128.
127. Prieto-Torres L, Eraña I, Gil-Redondo R, et al. The spectrum of EBV-positive mucocutaneous ulcer: a study of 9 cases. *Am J Surg Pathol.* 2019;43(2):201-210.
128. Satou A, Banno S, Hanamura I, et al. EBV-positive mucocutaneous ulcer arising in rheumatoid arthritis patients treated with methotrexate: single center series of nine cases. *Pathol Int.* 2019;69(1):21-28.
129. Chisholm KM, Mohlman J, Liew M, et al. IRF4 translocation status in pediatric follicular and diffuse large B-cell lymphoma patients enrolled in Children's Oncology Group trials. *Pediatr Blood Cancer.* 2019;66(8):e27770.
130. Dunleavy K, Pittaluga S, Maeda LS, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. *N Engl J Med.* 2013;368(15):1408-1416.
131. Chan EHL, Koh LP, Lee J, et al. Real world experience of R-CHOP with or without consolidative radiotherapy vs DA-EPOCH-R in the first-line treatment of primary mediastinal B-cell lymphoma. *Cancer Med.* 2019;8(10):4626-4632.
132. Hayden A, et al. Outcome of primary mediastinal large B-cell lymphoma in the rituximab era: impact of a PET-guided approach. *Hematol Oncol.* 2019;37(suppl 2):156-157.
133. Shimada K, Yamaguchi M, Atsuta Y, et al. Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone combined with high-dose methotrexate plus intrathecal chemotherapy for newly diagnosed intravascular large B-cell lymphoma (PRIMEUR-IVL): a multicentre, single-arm, phase 2 trial. *Lancet Oncol.* 2020;21(4):593-602.
134. Ramos JC, et al. A randomized trial of EPOCH-based chemotherapy with vorinostat for highly aggressive HIV-associated lymphomas: updated results evaluating impact of diagnosis-to-treatment interval (DTI) and pre-protocol systemic therapy on outcomes. *Blood.* 2019;134(suppl 1):1588.
135. Castillo JJ, Guerrero-Garcia T, Baldini F, et al. Bortezomib plus EPOCH is effective as frontline treatment in patients with plasmablastic lymphoma. *Br J Haematol.* 2019;184(4):679-682.
136. Liu JJ, Zhang L, Ayala E, et al. Human immunodeficiency virus (HIV)-negative plasmablastic lymphoma: a single institutional experience and literature review. *Leuk Res.* 2011;35(12):1571-1577.
137. Ramos JC, et al. Response-adapted therapy with infusional EPOCH chemotherapy plus rituximab in HIV-associated, B-cell non-Hodgkin's lymphoma. *Blood.* 2019;134(suppl 1):2872.
138. Lurain K, Polizzotto MN, Aleman K, et al. Viral, immunologic, and clinical features of primary effusion lymphoma. *Blood.* 2019;133(16):1753-1761.
139. Shimada K, Hayakawa F, Kiyoi H. Biology and management of primary effusion lymphoma. *Blood.* 2018;132(18):1879-1888.
140. Howlett C, Snedecor SJ, Landsburg DJ, et al. Front-line, dose-escalated immunochemotherapy is associated with a significant progression-free survival advantage in patients with double-hit lymphomas: a systematic review and meta-analysis. *Br J Haematol.* 2015;170(4):504-514.
141. Petrich AM, et al. Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. *Blood.* 2014. 124(15):2354-61.
142. Li J, Liu X, Yao Z, et al. High-grade B-cell lymphomas, not otherwise specified: a study of 41 cases. *Cancer Manag Res.* 2020;12:1903-1912.
143. Wilson WH, Pittaluga S, Nicolae A, et al. A prospective study of mediastinal gray-zone lymphoma. *Blood.* 2014;124(10):1563-1569.
144. Kritharis A, Pilichowska M, Evens AM. How I manage patients with grey zone lymphoma. *Br J Haematol.* 2016;174(3):345-350.
145. Zayac A, et al. Outcomes of patients with newly-diagnosed Burkitt lymphoma (BL) and central nervous system (CNS) involvement treated in the modern era: a multi-institutional real-world analysis. *Blood.* 2019;134(suppl 1):402.
146. Dunleavy K, et al. Risk-adapted therapy in adults with Burkitt lymphoma: updated results of a multicenter prospective phase II study of DA-EPOCH-R. *Hematol Oncol.* 2017;35(S2):133-134.
147. Mead GM, Sydes MR, Walewski J, et al. An international evaluation of CODOX-M and CODOX-M alternating with IVAC in adult Burkitt's lymphoma: results of United Kingdom Lymphoma Group LY06 study. *Ann Oncol.* 2002;13(8):1264-1274.

148. Roschewski M, Dunleavy K, Abramson JS, et al. Multicenter study of risk-adapted therapy with dose-adjusted EPOCH-R in adults with untreated Burkitt lymphoma. *J Clin Oncol.* 2020;38(22):2519-2529.
149. Cortes J, Thomas D, Rios A, et al. Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone and highly active antiretroviral therapy for patients with acquired immunodeficiency syndrome-related Burkitt lymphoma/leukemia. *Cancer.* 2002;94(5):1492-1499.
150. Barrans S, et al. Defining Burkitt-like lymphoma with 11q aberration in a specialised UK haematopathology diagnostic service. *Hematol Oncol.* 2019;37(S2):143-144.
151. Thieblemont C, Tilly H, Gomes da Silva M, et al. Lenalidomide maintenance compared with placebo in responding elderly patients with diffuse large B-cell lymphoma treated with first-line rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J Clin Oncol.* 2017;35(22):2473-2481.
152. Peyrade F, Jardin F, Thieblemont C, et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. *Lancet Oncol.* 2011;12(5):460-468.
153. Moccia AA, et al. R-CHOP with etoposide substituted for doxorubicin (R-CEOP): excellent outcome in diffuse large B cell lymphoma for patients with a contraindication to anthracyclines. *Blood.* 2009;114(22):408.
154. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med.* 1995;333(23):1540-1545.
155. Gisselbrecht C, Schmitz N, Mounier N, et al. Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD20(+) diffuse large B-cell lymphoma: final analysis of the collaborative trial in relapsed aggressive lymphoma. *J Clin Oncol.* 2012;30(36):4462-4469.
156. Thieblemont C, Brière J, Mounier N, et al. The germinal center/activated B-cell subclassification has a prognostic impact for response to salvage therapy in relapsed/refractory diffuse large B-cell lymphoma: a bio-CORAL study. *J Clin Oncol.* 2011;29(31):4079-4087.
157. Wilson WH, Young RM, Schmitz R, et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. *Nat Med.* 2015;21(8):922-926.
158. Wang M, Fowler N, Wagner-Bartak N, et al. Oral lenalidomide with rituximab in relapsed or refractory diffuse large cell, follicular and transformed lymphoma: a phase II clinical trial. *Leukemia.* 2013;27(9):1902-1909.
159. Czuczman MS, Trněný M, Davies A, et al. A phase 2/3 multicenter, randomized, open-label study to compare the efficacy and safety of lenalidomide versus investigator's choice in patients with relapsed or refractory diffuse large B-cell lymphoma. *Clin Cancer Res.* 2017;23(15):4127-4137.
160. Ohmachi K, Niitsu N, Uchida T, et al. Multicenter phase II study of bendamustine plus rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma. *J Clin Oncol.* 2013;31(17):2103-2109.
161. Mounier N, Gnaoui TE, Tilly H, et al. Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II Lymphoma Study Association trial. *Haematologica.* 2013;98(11):1726-1731.
162. Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. *J Clin Oncol.* 2020;38(2):155-165.
163. Salles G, Duell J, González Barca E, et al. Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. *Lancet Oncol.* 2020;21(7):978-988.
164. Jacobsen ED, Sharman JP, Oki Y, et al. Brentuximab vedotin demonstrates objective responses in a phase 2 study of relapsed/refractory DLBCL with variable CD30 expression. *Blood.* 2015;125(9):1394-1402.
165. Plotkin SR, Betensky RA, Hochberg FH, et al. Treatment of relapsed central nervous system lymphoma with high-dose methotrexate. *Clin Cancer Res.* 2004;10(17):5643-5646.
166. Ghesquieres H, Chevrier M, Laadhari M, et al. Lenalidomide in combination with intravenous rituximab (REVRI) in relapsed/refractory primary CNS lymphoma or primary intraocular lymphoma: a multicenter prospective 'proof of concept' phase II study of the French Oculo-Cerebral lymphoma (LOC) Network and the Lymphoma Study Association (LYSA)†. *Ann Oncol.* 2019;30(4):621-628.
167. Soussain C, Choquet S, Blonski M, et al. Ibrutinib monotherapy for relapse or refractory primary CNS lymphoma and primary vitreoretinal lymphoma: Final analysis of the phase II 'proof-of-concept' iLOC study by the Lymphoma study association (LYSA) and the French oculo-cerebral lymphoma (LOC) network. *Eur J Cancer.* 2019;117:121-130.
168. Soussain C, Hoang-Xuan K, Taillandier L, et al. Intensive chemotherapy followed by hematopoietic stem-cell rescue for refractory and recurrent primary CNS and intraocular lymphoma: Societe Francaise de Greffe de Moelle Osseuse-Therapie Cellulaire. *J Clin Oncol.* 2008;26(15):2512-2518.
169. Enting RH, Demopoulos A, DeAngelis LM, et al. Salvage therapy for primary CNS lymphoma with a combination of rituximab and temozolomide. *Neurology.* 2004;63(5):901-903.
170. Zinzani PL, Santoro A, Gritti G, et al. Nivolumab combined with brentuximab vedotin for relapsed/refractory primary mediastinal large B-cell lymphoma: efficacy and safety from the phase II CheckMate 436 study. *J Clin Oncol.* 2019;37(33):3081-3089.
171. Armand P, Rodig S, Melnichenko V, et al. Pembrolizumab in relapsed or refractory primary mediastinal large B-cell lymphoma. *J Clin Oncol.* 2019;37(34):3291-3299.
172. Wass M, Behlendorf T, Shädlich B, et al. Crizotinib in refractory ALK-positive diffuse large B-cell lymphoma: a case report with a short-term response. *Eur J Haematol.* 2014;92(3):268-270.
173. Sandoval-Sus JD, Brahim A, Khan A, et al. Complete response of primary refractory ALK-positive large B-cell lymphoma treated with single-agent nivolumab. *Clin Lymphoma Myeloma Leuk.* 2020;20(3):e113-e117.
174. Melani C, Major A, Schowinsky J, et al. PD-1 blockade in mediastinal gray-zone lymphoma. *N Engl J Med.* 2017;377(1):89-91.
175. Short NJ, Kantarjian HM, Ko H, et al. Outcomes of adults with relapsed or refractory Burkitt and high-grade B-cell leukemia/lymphoma. *Am J Hematol.* 2017;92(6):e114-e117.
176. Kitajima K, Okada M, Yoshihara K, et al. Predictive value of interim FDG-PET/CT findings in patients with diffuse large B-cell lymphoma treated with R-CHOP. *Oncotarget.* 2019;10(52):5403-5411.
177. Thompson CA, Ghesquieres H, Maurer MJ, et al. Utility of routine post-therapy surveillance imaging in diffuse large B-cell lymphoma. *J Clin Oncol.* 2014;32(31):3506-3512.
178. Kurtz DM, Scherer F, Jin MC, et al. Circulating tumor DNA measurements as early outcome predictors in diffuse large B-cell lymphoma. *J Clin Oncol.* 2018;36(28):2845-2853.
179. Rossi D, Diop F, Spaccarotella E, et al. Diffuse large B-cell lymphoma genotyping on the liquid biopsy. *Blood.* 2017;129(14):1947-1957.
180. Pasqualucci L, Dalla-Favera R. Genetics of diffuse large B-cell lymphoma. *Blood.* 2018;131(21):2307-2319.

This page intentionally left blank

10 Mantle Cell Lymphoma

Preetesh Jain
Michael Wang

KEY CONCEPTS

- Advances in the field of mantle cell lymphoma (MCL) have significantly changed our understanding of its pathobiology. With the treatment modalities currently available, the response rates and survival have improved but this lymphoma still remains incurable. Heterogeneity in clinical presentation of patients poses a therapeutic dilemma among the clinicians. Broadly, two distinct clinical variants are recognized—an indolent non-nodal leukemic phase, which is generally SOX-11–negative, and another nodal or extranodal SOX-11–positive conventional MCL.
- Pathogenic relevance of factors such as overexpression of SOX-11 in lymphoma cells, proliferative lymph node microenvironment, clonal and subclonal evolution, presence of mutations in epigenetic modifiers, and presence of CCND1 genes in addition to other cell cycle–associated genetic aberrancies are closely associated with survival, growth, proliferation and maintenance of MCL clones in tumor microenvironment and maintain minimal residual disease.
- An improved understanding of B-cell receptor kinase signaling pathways, such as Bruton tyrosine kinase (BTK) pathway is identified as a critical pathway for therapeutic targeting of MCL B-cells.
- Patients with MCL who exhibit high-risk features at initial diagnosis such as high-risk MCL international prognostic index (MIPI) score, blastoid and/or pleomorphic histology, high Ki-67% (≥50%), *TP53* aberrations, MYC gene rearrangement, complex genomics (*CCND1, CDKN2A, NSD2, KMT2D, SMARCA4*, and *NOTCH1* or *NOTCH2* mutations) and complex karyotype generally portend a poor prognosis and frequent relapses.
- Long-term follow-up of intensive chemoimmunotherapy studies demonstrated durable responses and remissions in a subset of patients with MCL. However, the advent of newer agents for frontline therapy, such as ibrutinib, acalabrutinib, and their combinations with rituximab and venetoclax, are very promising and under active investigation.
- The focus of treating MCL is rapidly changing toward investigation of "chemotherapy-free" agents such as BTK inhibitors, venetoclax, and rituximab. Most recently, the FDA approval of anti–CD19-chimeric antigen receptor therapy (CAR-T)—brexucabtagene autoleucel—has been a landmark advancement in treating patients with MCL.

Mantle cell lymphoma (MCL) is a distinct category of B-cell non-Hodgkin lymphoma (B-NHL). These patients generally exhibit an aggressive, albeit heterogeneous, clinical course but smoldering or indolent forms of MCL are also recognized. In this chapter, we will provide a comprehensive update on various aspects of MCL—factors associated with the etiopathogenesis, clinical and diagnostic features, advances in risk stratification, management of MCL, current challenges, and management approach at MDACC to treat MCL.

INCIDENCE AND POSSIBLE PREDISPOSING RISK FACTORS

MCL comprises about 3% to 10% of adult-onset NHL in Western countries, with an incidence of approximately four to eight cases per million persons per year, and its incidence is rising, with an estimated 3320 cases[1] diagnosed in 2016.[2–4] Its incidence appears to be rising in older adult patients (age ≥65 years) and in non-Hispanic whites.[5] The median age at initial

presentation in Western countries is 68 or 71 years old. Furthermore, the incidence of MCL in Asian countries is variable[6,7] (1%–6%) and appears to be lower than in Western countries, and MCL initially presents at a lower median age of 60 years in Asian countries.[8,9] Overall, the incidence of MCL is higher in whites.[10] A male predilection of MCL with a male/female ratio of more than 2:1 is common.[11] Precise reasons for male predisposition is unknown.

Few possible predisposing risk factors for MCL include[12] possible associations with European strains of the *Borrelia burgdorferi* when it involves skin as acrodermatitis chronica atrophicans,[13] living/working on farm houses,[14] polymorphisms in IL-10 to 1082A>G,[15] and twofold increase risk of hematologic malignancies in first-degree relatives of patients with MCL.[14,16] Autoimmune diseases (10% of MCL can be associated with autoimmune diseases),[17] and B-cell–mediated autoimmune diseases posed a negative impact on the survival of patients with MCL.[18] Similar to findings from studies in small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL), antigenic drive is hypothesized to have a role in the development of MCL. This is probably related to the finding of a biased and highly restricted immunoglobulin (IGHV) gene repertoire[19] with stereotyped variable heavy chain (VH) complementary determining region (CDR3s) and recognition of superantigens[20] by the B-cell receptor (BCR) of clonal MCL B-cells. The role of micro-RNA (miR-155, miR18b, and miR-17-92) and epigenetic perturbations[21] (aberrant methylation especially for NFkB and HDAC1 and methylation status) in MCL etiopathogenesis is also being explored. Further, patients with MCL are at higher risk of developing second primary cancers (melanoma, thyroid, nonepithelial skin cancers, SLL/CLL, and other hematologic malignancies).[22]

DECODING THE ETIOPATHOGENESIS OF MCL

In the last decade, our understanding on the development, origin, and growth of MCL cells has significantly improved. Various factors[23] such as SOX-11 (SRY [sex-determining regions-Y] box transcription factor 11) nuclear transcription factor, cell cycle dysregulation, genomic instability, microenvironment, resistance to apoptosis, and epigenetic perturbations are involved.[24] Most MCL cases are postulated to derive from naïve pre–germinal center B-cells of the mantle zone, which do not demonstrate somatic hypermutation of IGHV genes, whereas a subset of MCL may originate from marginal zone or peripheral blood memory B-cells. Of note, MCL is a distinct lymphoma but demonstrates a close resemblance to SLL/CLL.[25] The heterogeneity in the clinical course of MCL is likely caused by the extent to which these factors are involved in an individual patient.

Based on these developments, two forms of MCL are recognized in the World Health Organization classification of B-NHL in 2016.[26] Figure 10–1 depicts the development of the two forms of MCL.[23]

Nodal or Extranodal

This is a conventional form of MCL with unmutated IGHV, SOX-11–positive, aggressive MCL. Naïve B-cells do not undergo germinal center reaction.[27] SOX11 has been reported to block B-cell differentiation, suggesting that it has a direct role in MCL pathogenesis, a higher degree of genomic instability, and increased frequency of *ATM*, *TP53*, *CDKN2A*, and *KMT2D* mutations.

Non-Nodal, Leukemic and SOX-11–Negative, Mutated IGHV

This form develops with a generally, indolent or smoldering clinical course. The smoldering variant is thought to develop from an antigen-experienced, memory B-cells.[28,29] These patients have a generally stable genome. Compared with conventional MCL, the non-nodal variant has fewer copy number alterations and fewer structural variants.[30] With leukemic clinical presentation, it can masquerade as CLL and CD200 can be positive.[31] TLR2 and CCND1 mutations are overrepresented. A high number of DNA methylation changes[27] and/or presence of *TP53* mutations in these patients may negatively affect the prognosis.

In addition, biopsies from patients may reveal the presence of cyclin D1+ cells in the inner mantle zone of lymphoid follicles (this is termed in situ mantle cell neoplasia).[26,32] Instances of patients with this variant are rare, with an indolent course and low risk of progression to overt MCL. These patients must be recognized to avoid inadvertent systemic therapy.

MAJOR PATHOGENETIC FEATURES OF MCL

Cyclin D1 Overexpression

Constitutive overexpression of cyclin D1 with translocation t(11;14) (q13;q32) is considered the hallmark oncogenic step in almost all MCL. This translocation is not specific to MCL and can be seen in multiple myeloma. The juxtaposition of DNA coding sequence for cyclin D1 at 11q13 with the immunoglobulin heavy chain joining region at 14q32 promotes cell cycle transition from G1 to S phase and promotes cell proliferation. Overexpressed cyclin D1 activates cyclin-dependent

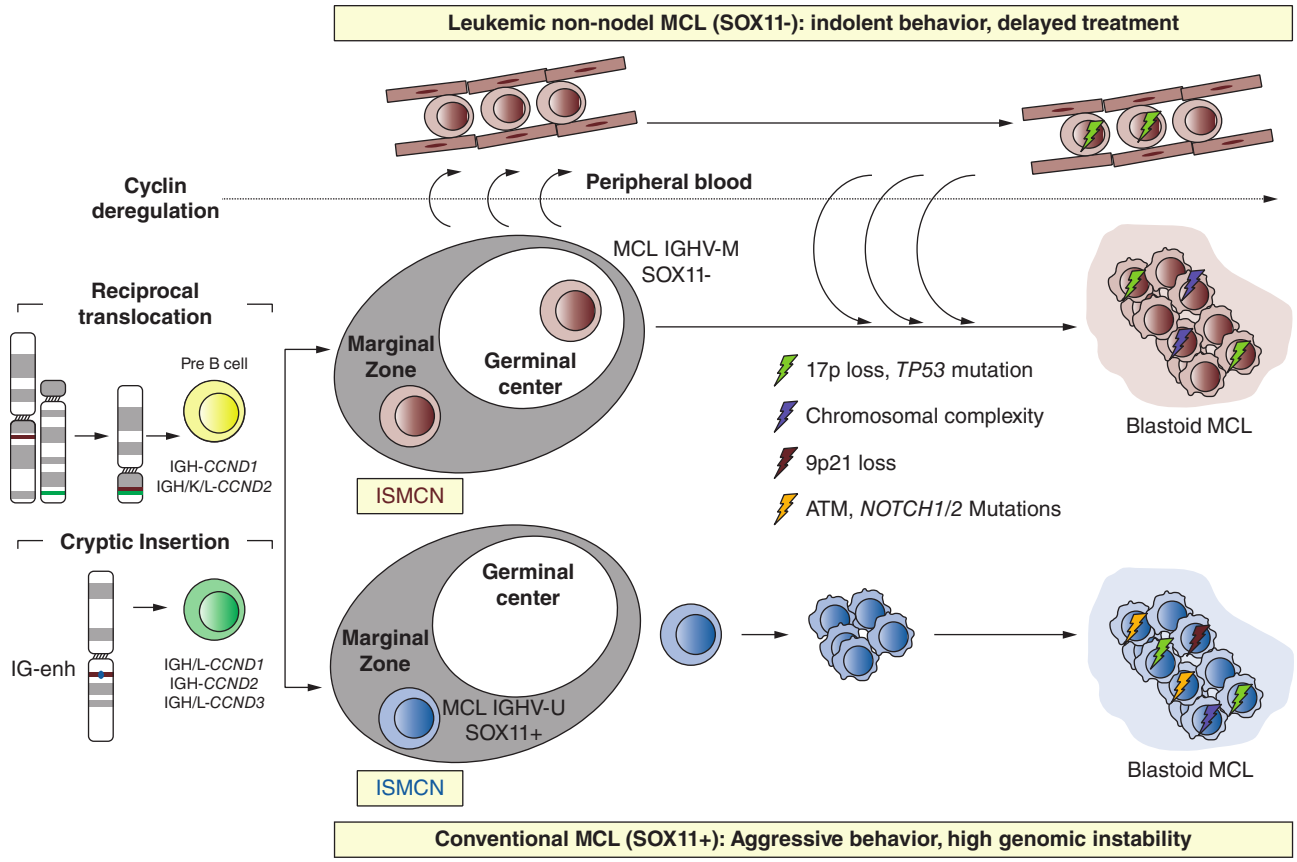


FIGURE 10–1 **Possible model for development of mantle cell lymphoma (MCL). Two major clinical forms: one is a common conventional form, which is aggressive in its clinical course and is characterized by SOX-11–positive and unmutated immunoglobulin heavy chain variable region (IGHV) and another is an indolent form of MCL, which is generally leukemic, non-nodal, SOX-11–negative, and exhibits germinal center reaction feature with somatic hypermutation of IGHV. In situ mantle cell neoplasia (ISMCN) is the presence of MCL clones in the inner mantle zone without disrupting the nodal architecture. The addition of other aberrant molecular changes such as TP53 and CDKN2A deletions are shown to alter the clinical course toward an aggressive blastoid or pleomorphic type of MCL. (Reproduced with permission from Navarro A, Beà S, Jares P, et al: Molecular Pathogenesis of Mantle Cell Lymphoma, *Hematol Oncol Clin North Am* 2020 Oct;34(5):795-807.)**

kinases 4 and 6, which in turn phosphorylate and inactivate Rb (tumor suppressor gene) and promote G1 to the S phase, leading to rapid cell proliferation. Cyclin D1 also interacts with chromatin remodeling, histone-modifying enzymes and transcription factors and modulates transcriptome. Perinucleolar localization of t(11;14)[33] or the CCND1 allele is important because these areas are rich in RNA polymerase II, leading to activation of cyclin D1 transcription.[34] Truncated form of cyclin D1 (deletion affecting the 3′ untranslated region of cyclin D1) stabilizes the cyclin D1 transcript,[35] and this results in increased cyclin D1 mRNA levels. Increase in the truncated form of cyclin D1 is associated with poor clinical outcome.[36]

Cryptic Pyclin D1-Positive MCL

Rarely, variant cyclin D1 translocations such as translocation t(2;11) (p11;q13)[37] and t(11;22) (q13;q11.2),[38] where the MCL cases show cyclin D1 rearrangement with IgK or IgL, are observed. Conventional karyotype or fusion or break-apart fluorescent in situ hybridization (FISH) probes fail to detect these variant translocations. Occasionally, cyclin D1 may not be detectable by immunohistochemistry but is detectable by FISH, and this is related to the presence of cyclin D1b isoform[39] or a mutation in C-terminal domain on cyclin D1.

Cyclin D1-Negative MCL

Rarely, cyclin D1 is negative by immunohistochemistry and t(11;14) is not detectable by FISH. Cyclin D2 or cyclin D3 gene rearrangements or an upregulation of cyclin E can be observed.[40,41] In a third of these rare cases, Ig light chain enhancer hijacking is observed as the initial oncogenic aberration. Generally, these cases are associated with SOX-11 positivity, exhibit a similar

gene expression profile, and clinical course to that of conventional MCL, but very rare cases with cyclin E dysregulation are associated with blastoid morphology and an aggressive clinical course.[41]

Other Cell Cycle Dysregulations

CDKN2A Deletions

CDKN2A gene encodes for p16 (INK4A; a cyclin-dependent kinase inhibitor that specifically inhibits CDK4 and CDK6 keeping RB1 active) and for p14 (ARF; a E3 ubiquitin-protein ligase that stabilizes *TP53* by interacting with MDM2 preventing its degradation).[42] Deletion of INK4a/ARF locus on 9p21 occurs in about 20% to 25% MCL and is associated with aggressive histology MCL.[43]

CDK4 Amplification

Gains in 12q or copy number gains in 12q are associated with promotion of cell cycle dysregulation and an aggressive (blastoid) histology MCL.[44] Inhibition of CDK4 can possibly overcome ibrutinib resistance.[45]

SOX-11 Overexpression

SOX-11 is a neural transcription factor that plays a critical role in the pathogenesis of MCL. Overexpression of SOX-11 is observed in conventional MCL and in 25% to 50% of Burkitt lymphoma.[46] SOX-11 overexpression in MCL is shown to influence MCL cells via various mechanisms—constitutive activation of PAX-5, thereby blocking the differentiation of B-cells to plasma cells by impairing BLIMP1[47]; augmented BCR signaling[48]; suppression of Bcl-6 to avoid germinal center transit of MCL cells, which exhibit unmutated IGHV[49]; promotion of angiogenesis via platelet-derived growth factor α[50]; and migration and adhesion of MCL cells to stromal cells via upregulation of CXCR4 and focal adhesion kinases, leading to enhanced PI3K/AKT signaling and promoting cell adhesion–mediated drug resistance.[51]

TP53 Mutations

TP53 gene (tumor protein 53) is a tumor suppresser gene located at 17p13.1, which, when inactivated, deleted, or mutated, can unleash genomic instability, cell cycle upregulation, inhibition of apoptosis, and promotion of cell growth. *TP53* mutations predict an aggressive disease course and inferior outcomes[52] in MCL.

ATM Mutations

Ataxia telangiectasia mutated (ATM) tumor suppressor gene is located on 11q22-q23 and ATM mutations are observed in approximately 30% to 50% of MCL cases. ATM is involved in the detection of DNA damage and plays an important role in the regulation of cell cycle progression.

Apoptosis Resistance

In MCL, resistance[53] to apoptosis may occur as a result of overexpression of B-cell lymphoma 2 (BCL2), upregulation of the PI-3 kinase/AKT prosurvival signaling pathway, and/or activation of nuclear factor-κB (NF-κB) and/or mutations in *TP53*. Gain-of-function truncating mutations in *NOTCH1* and *NOTCH2* genes are also relevant in mediating apoptosis resistance in MCL.[54,55] NOTCH activation may also induce overexpression of MYC.

Epigenetic Perturbations and Other Molecular Alterations

Integrated genomics approaches have revealed that complex genomic variants[30,56] and higher degree of DNA methylation is associated with higher proliferation and aggressive behavior of MCL cells.[27] Common mutations that affect the epigenetic pathways in MCL include *KMT2D*,[57] *NSD2*,[58] and mutations in *SWI-SNF* chromatic remodeling complex[59]; *SMARCA4, SMARCA2*, and *ARID2* mutations are associated with resistance to ibrutinib-venetoclax in MCL. Other mutations such as *MEF2B and UBR5*[60] are infrequent in MCL and influence transcription and post-transcription processes. Other aberrant somatic mutations include *MAP2K14, NOTCH2, BIRC3, KMT2D, CARD11, SMARCA4*, and *BTK*.[61] Activation of PI3K/AKT and the integrin-β1 signaling pathway[62] has been shown as another mechanism of acquired ibrutinib resistance. Of note, mutation profile in case of ibrutinib resistance or venetoclax resistance in MCL is different from that of CLL because BTKC481S mutations were infrequent in MCL[58] (10%–15%) and BCL2 mutations were also infrequent in venetoclax-resistant MCL.[63] Altered splicing of the HNRNPH1 gene associated with RNA processing is also observed in patients with MCL.[64]

Microenvironmental Impact and BCR Signaling Kinases

The tissue microenvironment cellular composition and cytokine milieu play a vital role in MCL cell growth and survival and promote drug resistance. In contrast to peripheral blood, the lymph node microenvironment in patients with MCL is unique, having a differential expression of genes involved in BCR signaling and canonical NF-κB pathways.[65] This feature in MCL provides activation signals to MCL cells and

is involved in drug resistance. In addition, because the M2 polarized macrophages (CD163+), which are tumor-associated macrophages, play an important role in promoting MCL cell survival via colony-stimulating factor-1,[66] therefore, inhibition of colony-stimulating factor-1 receptor might be clinically useful. Targeting various components of BCR signaling[67,68] and interactions with stromal cells can overcome treatment resistance and eradicate dormant residual cells.[69] Additional studies on the cytokine-chemokine milieu and its interaction with MCL cells and stromal cells in tissue microenvironment are under investigations. Finally, an immune "cold" microenvironmental signature was shown to be associated with ibrutinib resistance in MCL.[70]

Furthermore, using RNA sequencing, we showed that a dysregulated metabolic programming exists in MCL cells and contributes to ibrutinib resistance. Inhibition of oxidative phosphorylation in MCL cells can provide an opportunity to inhibit ibrutinib-resistant MCL cell growth in patient-derived mouse models.[71]

CLINICAL WORKUP AND DIAGNOSIS OF MCL

Clinical manifestations of MCL are summarized in Table 10–1[72] and commonly present as symptomatic progressive generalized lymphadenopathy, cytopenia, and bone marrow infiltration. Enlarged spleen, tonsils, and parts of the gastrointestinal tract (lymphomatous polyposis)[73,74] are common. Extranodal involvement of the kidneys and central nervous system (CNS) is rare.[75,76] The pure asymptomatic, non-nodal leukemic phase, in which the absolute monoclonal lymphocyte count is higher than 5000 cells/μL is infrequent and may masquerade as CLL. The asymptomatic indolent or smoldering nodal/extranodal[77] or leukemic non-nodal presentation[26,78] is seen in about 10% to 20% of cases and generally does not require immediate systemic treatment, and can simply be safely observed.[79] Conversely, most patients with MCL (~80%) present with symptomatic lymphadenopathy or extranodal disease requiring systemic therapy. Appropriate diagnostic workup of patients with MCL is the initial critical step to determine the diagnosis and the prognosis. Figure 10–2 outlines our clinical approach to the patient with MCL.

The initial workup includes history and physical examination, assessment of performance status, comorbidities, and B symptoms. Laboratory workup must include a complete blood cell count with differential count, comprehensive metabolic panel, serum lactate dehydrogenase (LDH) levels, β_2 microglobulin levels, and hepatitis panel. Bone marrow aspiration/biopsy and involved tissue biopsy is routinely performed at initial diagnosis. Immunophenotype on peripheral blood/bone marrow/involved tissue biopsy is critical. The typical MCL immunophenotype[26] is CD5, CD20, CD19, sIgM/sIgD, FMC-7 + B-cells with monoclonal kappa/lambda light chains, dim/negative

Table 10–1 Clinical Presentations in MCL Patients

Clinical Presentation	Clinicopathologic Features
Smoldering MCL[77]	Asymptomatic and with absence of B symptoms (drenching night sweats, unintentional weight loss of >10% of normal body weight over a period of ≤6 months or less, fever >38 °C), main indicator for smoldering MCL Normal serum LDH, β_2 microglobulin levels White blood cell count <30,000 K/μL Low MIPI (mantle cell lymphoma international prognostic index) score Ki-67% on lymphoma cells in nonmarrow tissue biopsy of <30% Nonblastoid/pleomorphic cytomorphologic pattern in tissue biopsy Maximum lymph node diameter <3 cm, spleen size <20 cm PET scan showing the maximum standardized uptake value <6 Absence of *TP53* or *NOTCH1/2* mutations by DNA sequencing Absence of deletion 17p or MYC translocation/amplification by FISH testing, absence of complex karyotype
Asymptomatic purely leukemic nonblastoid MCL	Monoclonal B lymphocytosis (with typical MCL immunophenotype and nonblastoid morphology) in peripheral blood with or without splenomegaly
Conventional MCL (most common)	Symptomatic bulky nodal/extranodal disease Classic or blastoid/pleomorphic cytomorphology At initial diagnosis or at clinical progression

Reproduced with permission from Jain P, Wang M: Mantle cell lymphoma: 2019 update on the diagnosis, pathogenesis, prognostication, and management, *Am J Hematol* 2019 Jun;94(6):710-725.

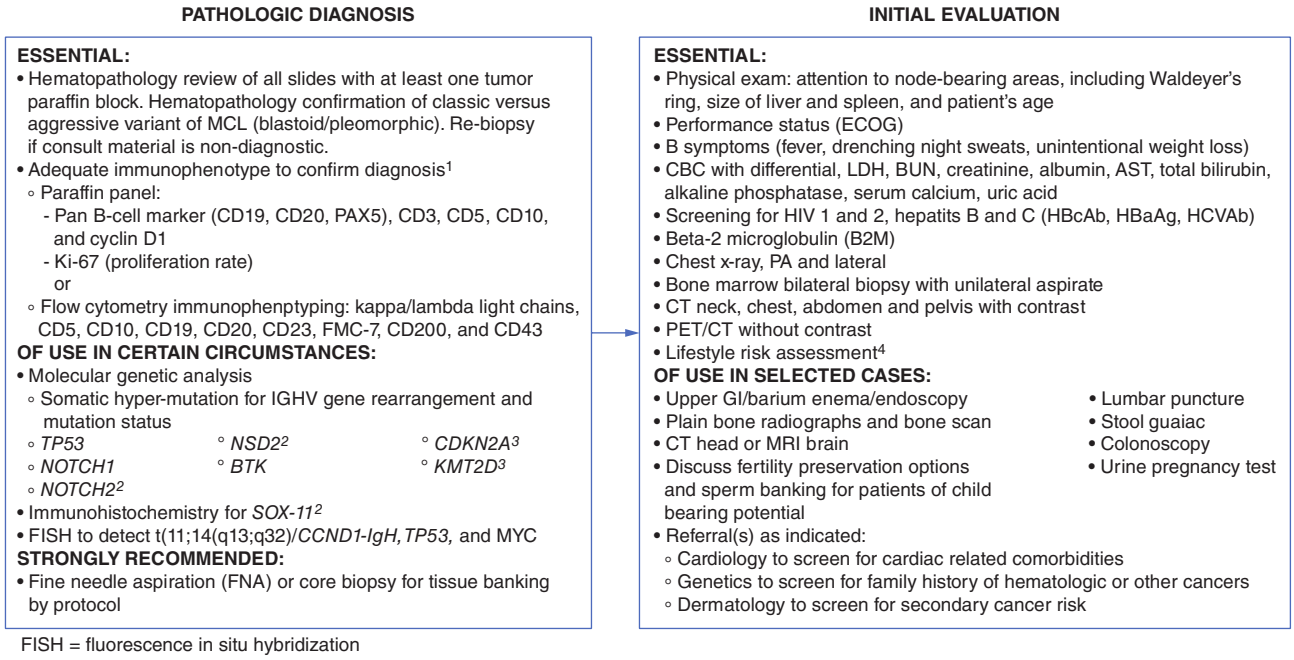


FIGURE 10–2 Outlines of our approach in the initial evaluation of a patients with a newly diagnosed mantle cell lymphoma (MCL). Immunophenotype: CD5++, CD20++, CD43++, CD23–/+/+, cyclin D 1+. Note: Some cases of MCL may be CD5–, CD10++, or CD23. If the diagnosis is suspected, cyclin D 1 staining or FISH to demonstrate t(11;14, q13, q32) should be performed. Currently approved. Currently not available for routine testing. Ongoing reassessments of lifestyle risks (smoking, physical activity, and nutrition should be a part of routine clinical practice).

CD23, dim/negative CD200, and strong cyclin D1 expression. Immunohistochemical analysis of involved nodal/extranodal tissues shows a strong nuclear staining for cyclin D1 (BCL-1 or PRAD-1), and generally MCL cells are positive for SOX-11. Cytogenetic assessment for karyotype or FISH showing translocation t(11;14) (q13; q32) is an important diagnostic hallmark of MCL (90%). At MDACC, if the BM involvement is higher than 10% by MCL cells then we also perform somatic mutation of IGHV genes, percent deviation from germline IGHV sequence, and type of VH gene usage. Targeted DNA sequencing from involved tissues for somatic mutations such as *TP53*, *NOTCH1/2*, *BIRC3, CDKN2A*, *NSD2*, *BTK*, and *ATM* genes is very useful.

Comprehensive histopathologic assessment of involved tissue biopsy is required. Morphology at initial diagnosis can change at disease progression/relapse to an aggressive morphology (blastoid/pleomorphic), ie, transformed MCL (t-MCL). Figure 10–3 shows the morphologic spectrum of MCL. The histology can vary from classic morphology (nodal, mantle zone, interstitial, diffuse) to an aggressive histology (blastoid or pleomorphic). MCL cell size can vary from small to medium with irregular nuclei to lymphoblast-like cells (medium to large) that are blastoid or pleomorphic. It is mandatory to obtain the Ki-67%[80] of MCL cells from the involved nonmarrow tissue biopsies for prognosis. Imaging studies should be obtained for staging and include assessment with whole-body positron emission tomography-computed tomography (PET-CT) scan or CT scan only. Serial imaging studies will demonstrate response to treatment (Lugano lymphoma response criteria).[81] A pregnancy test, magnetic resonance imaging of the brain, electrocardiogram, echocardiogram, and endoscopic evaluation of the gastrointestinal tract (essential to confirm stage I-II disease) should be conducted depending on the clinical presentation and/or requirement by the clinical trial protocol (if applicable). Cardiac status should be evaluated by a cardiologist before starting Bruton tyrosine kinase (BTK) inhibitor therapy. Consider stem cell transplantation (SCT) consultation for high-risk patients. Lumbar puncture is performed in cases with clinically suspected CNS involvement. In addition to morphology, immunophenotype should be performed from any fluid assessments (cerebrospinal fluid and/or ascitic or pleural fluid).

Finally, exploratory investigations in MCL would include serial plasma samples and genomic evaluation of tissue biopsies at diagnosis and relapse, analysis of minimal residual disease (MRD) and copy number changes, as well as for chromosomal aberrations and clonal evolution assessment. Multiomic assessment with single-cell sequencing is performed at MDACC.

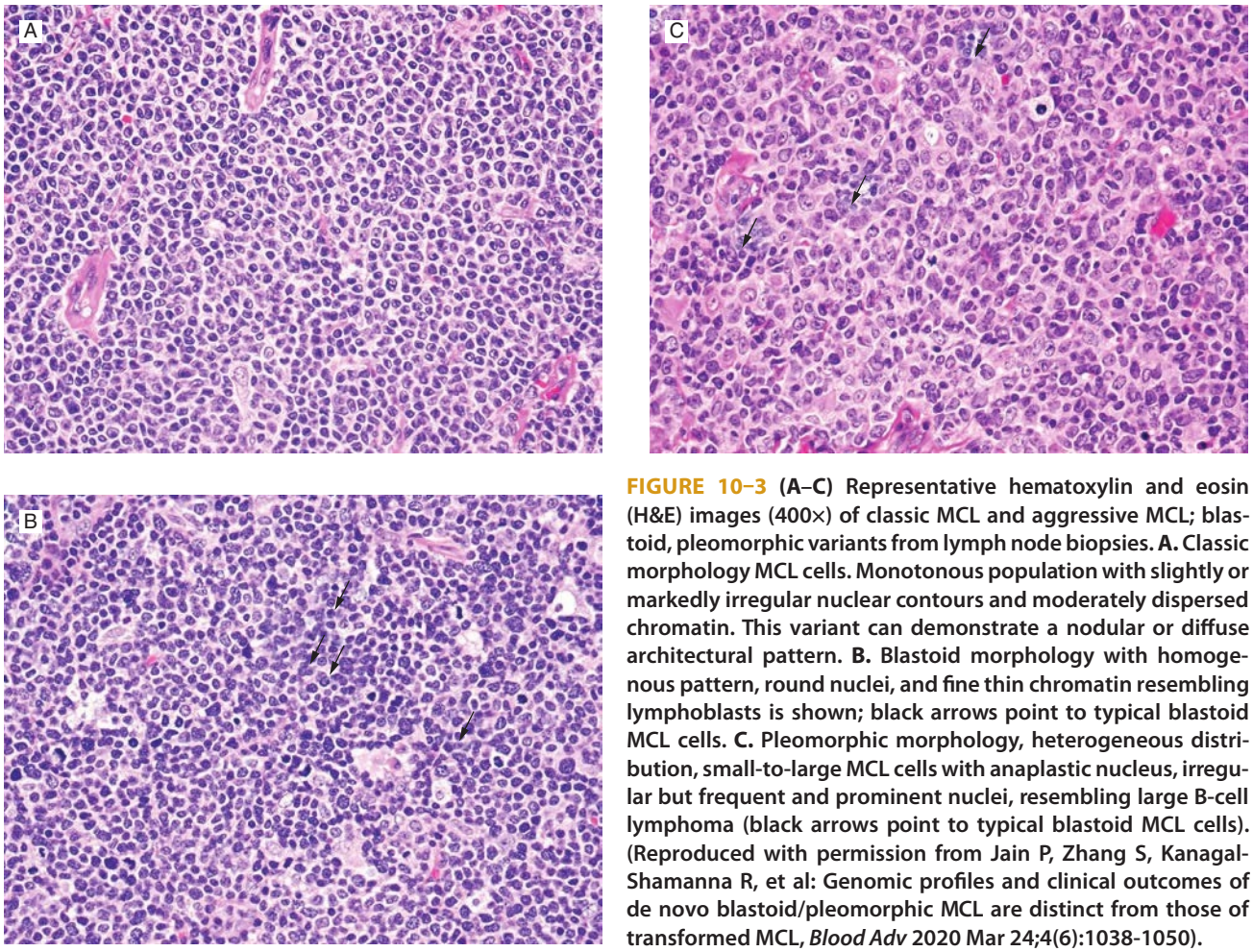


FIGURE 10–3 (A–C) Representative hematoxylin and eosin (H&E) images (400×) of classic MCL and aggressive MCL; blastoid, pleomorphic variants from lymph node biopsies. A. Classic morphology MCL cells. Monotonous population with slightly or markedly irregular nuclear contours and moderately dispersed chromatin. This variant can demonstrate a nodular or diffuse architectural pattern. B. Blastoid morphology with homogenous pattern, round nuclei, and fine thin chromatin resembling lymphoblasts is shown; black arrows point to typical blastoid MCL cells. C. Pleomorphic morphology, heterogeneous distribution, small-to-large MCL cells with anaplastic nucleus, irregular but frequent and prominent nuclei, resembling large B-cell lymphoma (black arrows point to typical blastoid MCL cells). (Reproduced with permission from Jain P, Zhang S, Kanagal-Shamanna R, et al: Genomic profiles and clinical outcomes of de novo blastoid/pleomorphic MCL are distinct from those of transformed MCL, *Blood Adv* 2020 Mar 24;4(6):1038-1050).

Differential Diagnoses

MCL can be distinguished from other masquerading lymphoid malignancies such as SLL/CLL,[25] follicular lymphoma, marginal zone lymphoma, and B-cell–prolymphocytic leukemia. Translocation t(11;14) (q13;q32) can be observed in a fraction of patients with multiple myeloma (20%–25%), SLL/CLL (2%–5%), and plasma cell leukemia and B-cell–prolymphocytic leukemia (20% with t (11;14) and cyclin D1+ cells, and these are considered as the leukemic phase of MCL[82]). Cyclin D1 expression is also observed in a subset of patients with myeloma, hairy cell leukemia, and splenic lymphoma, and SOX-11 expression can be seen in Burkitt lymphoma (20%–25%), hairy cell leukemia, and lymphoblastic lymphoma.

Atypical MCL

Variations from the typical immunophenotype of MCL are included under this category. These variations are largely based on flow cytometric evaluation of the involved tissues and include CD10+ MCL,[83] CD5-negative MCL,[84] cyclin D1–negative MCL,[40,85] CD200+ MCL,[31] SOX-11–negative MCL,[28,86] and CD23–positive MCL.[87] In some cases, biopsies may reveal presence of cyclin D1+ cells in the inner mantle zone of lymphoid follicles (termed as *in situ mantle cell neoplasia*),[26,32] which should not lead to a diagnosis of MCL.

PROGNOSTIC FACTORS IN MCL

Determining the prognosis is of vital importance. Various parameters that can reliably predict patient prognosis are summarized in Table 10–2. We have implemented the inclusion of these risk factors to select therapy in the ongoing clinical trials at MDACC. We believe that in the future, the selection of therapy will be based on risk factors. Thus far, the relevance of prognostic factors is well established in patients treated with chemoimmunotherapy. We also anticipate that with the advent of newer therapies, the prognostic impact of risk factors may change.

Table 10–2 Summary of Prognostic Markers in Newly Diagnosed Patients With MCL

Currently Used	May Be Included Under Initial Workup if Available in Clinical Practice
Performance status Advanced age with comorbidities MIPI risk categories[88] Blastoid/pleomorphic cytomorphology Ki-67% >30%[90] *TP53* mutations, *TP53* by FISH or overexpression of *TP53* by immunohistochemistry[52]	Complex karyotype[103] MYC translocation or overexpression[104] Unmutated IGHV status[28] Additional somatic hypermutations - *NOTCH1* and *NOTCH2* mutations,[55] *CCND1, NSD2 (WHSC1)*[55a], *SWI/SNF (SMARCA4)*[a], *BIRC3, KMT2D/MLL2, BTK*[a],[58] *CDKN2A*[a], *MAP3K14*[a], *CARD11*[a] MCL35 RNA expression assay[113] Tumor metabolic volume by PET-CT scans MRD testing by flow cytometry, PCR for IgH, t(11;14), IgH clonocseq or by ctDNA miRNA18b[91]

[a]Gene mutations associated with ibrutinib-venetoclax resistance in patients with relapsed MCL.

CHAPTER 10

As of this writing, the following factors are used in routine clinical practice to determine high risk in MCL patients: high-risk MIPI (mantle cell lymphoma international prognostic score), blastoid or pleomorphic histology, high Ki-67% (≥30%) score, and *TP53* mutations. In addition, in relapsed patients, t-MCL and/or complex karyotype and/or early progression within 12 to 24 months after starting first-line chemoimmunotherapy or detection of additional somatic mutations in addition to *TP53* such as *CDKN2A*, *KMT2D*, *NSD2*, *NOTCH1/2*, *BIRC3*, or *SMARCA4* are highly indicative of high-risk MCL.

The MIPI risk scoring is commonly used. The simplified MIPI score is based on a weighted sum (of performance status, age, LDH levels higher than upper limit of normal and white blood cell count) and divides the patients into low-, intermediate-, and high-risk categories.[88] The score can be used as a continuous variable. Patients with MIPI scores less than 5.70 were classified as low risk, patients with MIPI scores of at least 5.70 but lower than 6.20 as intermediate risk, and patients with MIPI score of at least 6.20 as high risk. The 5-year overall survival (OS) rate in low-, intermediate- and high-risk MIPI categories was 81%, 63%, and 35%, respectively, and this was validated in the context of European randomized clinical trials with chemoimmunotherapy.[89] The prognostic value of the simplified MIPI risk score is further improved by adding the value of Ki-67%, and this modified MIPI score is also called biologic MIPI or MIPIb.[90] In general, a Ki-67% more than 30% is considered as the high-risk category and a cutoff value of more than 50% is used at MDACC. The 5-year survival percentage in low-, intermediate-, and high-risk MIPIb categories was 81%, 83%, and 37%, respectively. Further modifications of MIPI—combined MIPI (MIPIc) with binary Ki-67% and MIPI score and MIPIb with expression of miR-18b[91]—are reported. The presence of aggressive-histology MCL, ie, blastoid or pleomorphic variants, exhibit an inferior prognosis compared with classic histology MCL. We described patients with de novo aggressive-histology MCL who had superior survival (48 months) compared with patients with t-MCL (14 months). These aggressive histologies coexist with additional high-risk features, especially with CNS involvement (5%). In addition, high-risk genomic profile is frequently observed in aggressive-histology MCL[92] (reviewed in detail in reference 93). Because most of the patients with aggressive-histology MCL also exhibit high Ki-67%, patients with either one or both of these risk factors are considered as high-risk MCL.

Finally, *TP53* gene mutations are well established in MCL.[94,95] Reported frequency of *TP53* mutations at initial diagnosis is about 15% to 25%, and the frequency of these mutations increases up to 45% at relapse.[96] High tumor burden of *TP53* mutations indicates a worse prognosis.[97] A Nordic group[52] has reported that the frequency of *TP53* mutations at initial diagnosis was 11%, and these patients have a poor response to standard frontline chemoimmunotherapy. The median OS was 1.8 years in *TP53* aberrant versus 12.7 years in patients without *TP53* aberrancy. *TP53* gene mutations may coexist with other aberrations such as *NOTCH1* mutation (71%), deletion of *CDKN2A* (del9p21) (31%), and deletion of *TP53* (del17p13) (31%). The presence of both *TP53* deletion (detected by FISH) and *TP53* mutations (by DNA sequencing) was associated with the worst survival. In addition, we have demonstrated that *TP53* mutations may coexist with *NSD2* mutations in three of four patients with ibrutinib-resistant t-MCL.[58]

Other Important Prognostic Factors

SOX-11

Absence of SOX-11 expression with mutated IGHV identified a subset of patients with MCL with a favorable prognosis.[28,98] The clinical relevance of SOX-11

in nodal MCL in the era of newer therapies remains unclear.[99] *IGHV somatic mutation status* and the type of VH gene usage type are important variables. Patients with mutated MCL (>3% deviation from the germline sequence)[100] exhibit a better outcome compared with patients with unmutated IGHV; however, the systematic studies on IGHV mutation status in MCL are lacking, especially in the context of newer therapies.[28] Complex karyotype, defined as having three or more chromosomal abnormalities in addition to t (11;14) or additional chromosomal abnormalities detected by conventional karyotype,[101] also coexist with *TP53* mutations and generally exhibit poorer outcomes.[102,103] Miscellaneous factors associated with frequent relapses and disease resistance include *CDKN2A* (locus 9p21) deletions[43,59]; *MYC* gene rearrangements; and amplification of MYC,[104–108] *NOTCH1*,[54] and/or *NOTCH2*[55] mutations; *NSD2* mutations[55,109]; *CCND1* mutations[110]; and *KMT2D*[57] *SWI/SNF* (SWitch/sucrose nonfermentable) chromatic remodeling complex mutations (including *SMARCA4* gene); these are associated with ibrutinib-venetoclax resistance,[59] *BIRC3* (Baculoviral IAP repeat containing three mutations are seen in 10%–15% of patients with MCL). *BIRC3* deletions of 11q21–q23 are common alterations in MCL, and in addition to *ATM*, *BIRC3* is also located in this region (11q22.2). *BIRC3* aberrations in MCL may result in decreased response to ibrutinib because of a failure to suppress the alternate NF-κB pathway mediated by *MAP3K14,* which is proposed as a therapeutic target in *BIRC3*-mutated lymphomas.[111] Elevated absolute monocyte count is also prognostic.[112]

Gene proliferation signature (MCL35 assay) is predictive of prognosis. Using a NanoString RNA expression–based molecular assay (MCL35[113–115]), a 17-gene proliferation signature was validated to predict prognosis in patients with MCL treated with first-line chemoimmunotherapy. In another study, a six-gene signature (*AKT3, BCL2, BTK, CD79B, PIK3CD,* and *SYK)* was predictive of poor outcome,[116] but exhibited higher sensitivity to ibrutinib.[117] Micro-RNA (miRNA) profile is investigational.[29,118] Patients with an overexpression of miR-18b[91] were identified as a high risk in the MCL3 prospective clinical trial. The impact of complete metabolic response after treatment completion is also known to correlate with a better clinical outcome[119]; however, this aspect requires further validation for MCL in prospective studies. Detailed discussion of mechanistic relevance of each prognostic factor in the context of MCL is beyond the scope of this chapter.

Post-Treatment Prognostic Factors

Early Disease Progression

Disease relapse or progression within 12 to 24 months after receiving first-line therapy such as intensive chemoimmunotherapy (with/without) SCT can portend a poor outcome and increased risk of relapse on subsequent lines of therapies.[120] Visco et al.[121] demonstrated that among the 188 patients who received intensive chemoimmunotherapies (with/without consolidative SCT), patients with early disease progression (<24 months from diagnosis; n = 90) had significantly shorter OS (from the time of disease progression after first-line therapy to death from any cause) compared with late progressors (n = 98) (median survival 12 months and not reached, respectively; $P < .001$). Patients with early failure had an increased risk of death.

MRD-Positive Status

This is proposed as an important prognostic factor to predict relapses. The optimal technique to detect MRD in MCL is investigational—either flow cytometry from bone marrow (if involved at baseline), peripheral blood polymerase chain reaction (PCR) for IgH or IgH clonoseq by next-generation sequencing, or tracking ctDNA (circulating tumor DNA or liquid biopsy). MRD estimation and optimization in MCL is investigational. In a phase 3 randomized trial,[122] patients (n = 240) who had received four cycles of rituximab – dexamethasone, cisplatin, ara-C (R-DHAP) induction followed by auto-SCT were randomly assigned to observation versus rituximab maintenance groups. The rituximab maintenance group received 375 mg/m^2 rituximab once every 2 months for 3 years. This study demonstrated that rituximab maintenance can improve survival after SCT. Achieving MRD-negative status improves outcome and may obviate the need for maintenance therapy after SCT. MRD assessment in MCL has not been systematically implemented in clinical practice; however, a few studies[123] have shown the clinical significance of MRD-positive disease status and risk of predicting future relapses.[124–126] Kolstad et al has shown that preemptive rituximab treatment has shown benefit in turning MRD-positive status post auto-SCT to MRD-negative status; however, 69% of patients relapsed after rituximab therapy. Detailed discussion of methodology of MRD and various studies in MCL with MRD is beyond the scope of this chapter and is discussed elsewhere.[127]

Progression on BTK inhibitors

The approval of the BTK inhibitor ibrutinib is a major advance in MCL[128]; however, progression an outcome of patients who progress on ibrutinib has become a therapeutic challenge as these patients generally exhibit poor outcomes. The pattern and mechanisms of resistance of ibrutinib in MCL are under active investigation. The median survival after progression on ibrutinib was 2.9 months in 114 patients with MCL.[129] In a cohort of 80 patients with relapsed MCL

at MDACC who discontinued ibrutinib,[58] the outcomes of patients who progressed on ibrutinib (n = 41) were very poor, with a median survival of 9 months (range 6–10). Response rates to subsequent treatments were about 30% with chemoimmunotherapy, bendamustine, lenalidomide, or bortezomib. Furthermore, development of anti–CD19-CAR-T has demonstrated excellent results in managing BTK inhibitor–refractory MCL[130]; however, longer follow-up of this modality is awaited.

TREATMENT OF PATIENTS WITH MCL

Various factors should be considered before selecting therapy. These include patient related factors: performance status, age, comorbidities, disease status (smoldering nodal MCL vs leukemic non-nodal vs conventional nodal MCL presentation), organ dysfunction, prior therapies (if relapsed), toxicities from prior therapy, eligibility for SCT, financial constraints, and availability of a clinical trial. Feasibility for clinical trial or referral to a specialized center that treats patients with MCL should always be explored. A recent study from the United Kingdom showed that patients who received treatment at specialized centers had better outcomes compared with those treated at nonspecialized centers.[131]

Chemoimmunotherapy still remains a standard frontline treatment in most centers. Chemotherapy-associated toxicities, prolonged myelosuppression, infection-associated mortality, therapy-related myelodysplasia, and second cancers remain a serious concern.

Considerable advances are made in the treatment for patients with MCL. Currently, the focus is headed toward chemotherapy-free treatments in the frontline and relapsed settings. In the relapsed setting, BTK inhibitors, venetoclax, and FDA approval of brexucabtagene autoleucel are major achievements. Initially, BTK inhibitors were shown as effective in canine lymphoma models.[132] This seminal study drove human trials with BTK inhibitors in lymphoma.[133] Our group led the initial clinical trial of ibrutinib in relapsed MCL.[128,134] Subsequently, we also led the FDA approval for acalabrutinib.[135] Venetoclax is also investigated in refractory MCL.[63,136,137] Furthermore, we characterized ibrutinib[58] acalabrutinib,[138] and venetoclax-refractory[139] MCL patients and their genomic features to possibly explore mechanisms of resistance. Finally, our group led the pivotal Zuma-2 study and the FDA approval of brexucabtagene autoleucel (anti–CD19-CAR-T) in relapsed or refractory MCL.

Despite these advances, more research and newer clinical trials are needed in MCL. High-risk patients, patients who are triple resistant (refractory to BTK inhibitors, venetoclax and anti–CD19-CAR-T), and patients who have CNS disease continue to remain a huge therapeutic challenge.

At MDACC, we approach patients with MCL using the following five clinical categories: (1) smoldering MCL; (2) previously untreated patients (age <65 or age ≥65 years) in all risk categories; (3) previously treated relapsed MCL–BTK inhibitor-naïve; (4) previously treated relapsed MCL–BTK inhibitor refractory; and (5) triple-relapsed-refractory MCL.

Smoldering MCL

For patients with excellent performance status (0), no B symptoms or asymptomatic, nonbulky disease (<5 cm) with normal LDH levels, low Ki-67% (<30%), and nonaggressive cytomorphology, we do not recommend systemic therapy and these patients can simply be observed.[77] These patients can also exhibit an asymptomatic, non-nodal leukemic phase or localized gastrointestinal involvement. We counsel these patients about the risks and benefits of observation alone.[140] It is also important to distinguish smoldering MCL from MCL in situ neoplasia because in situ neoplasia does not qualify to be referred to as MCL.

Observation as an initial strategy in MCL is described by eight different studies. Most recently, a series of 94 patients by Kumar et al[141] was reported. The median time of observation alone was 23 months and non-nodal clinical presentation was associated with longer time to initiate treatment. Although patients with high Ki-67% (>30%) tend to receive immediate therapy versus observation alone, among the patients who were under observation alone, the time to first treatment was similar, irrespective of Ki-67%. This finding indicated that extent of clinical symptoms and clinical features, rather than Ki-67% or *TP53* status, should determine whether patients can be observed. In another study from British Columbia,[79] 440 patients were reviewed (75 with observation alone for ≥3 months, 365 with early treatment). Overall, 80% of patients underwent observation for more than 12 months, including 10 patients who were observed for more than 5 years. The median follow-up in the observation group was 48 months, and the median time to first treatment was 35 months (range 5–79). The median OS was significantly longer in the observation group compared with the early treatment group (72 vs 52.5 months; $P = .04$). Patients with non-nodal clinical presentation or those with negative *TP53* by immunohistochemistry had longer survival in the observation group. Another study using the National Cancer Database reported that among 8029 patients with MCL, 492 were deemed as wait-and-watch-alone. Younger age, male gender, and lack of comorbidities were predictive of OS.[142]

A group from Spain reported the initial results of ibrutinib with rituximab in indolent MCL (n = 40).[143] They demonstrated that in patients with indolent MCL, ibrutinib with rituximab therapy led to deep MRD-negative responses (87%). At MDACC, we are conducting a phase 2 study with single-agent ibrutinib in high-risk smoldering MCL (NCT03282396). High-risk smoldering MCL refers to patients who have clinically smoldering MCL but exhibit high-risk features, with *TP53* mutations and/or high Ki-67% (≥30%). In this study, we are investigating whether the use of ibrutinib in smoldering MCL instead of observation alone can prolong the time to first treatment in high-risk patients with MCL.

Limited-stage disease, ie, stages I/II, is uncommon. These patients can fall into the smoldering MCL category; however, there are patients who have limited-stage disease but significant symptoms and they need treatment—either local radiation or systemic therapy alone. Management of limited disease is detailed in reference 144.

Previously Untreated Patients (Age <65 or Age ≥65 Years)—All Risk Categories

Factors to consider before selecting frontline therapy are age, performance status, eligibility for SCT, risk categories especially for high-risk patients, and available clinical trials. Limited-stage, nonbulky disease may benefit from the addition of radiation to chemotherapy; however, this strategy has not been confirmed in large randomized studies.[145] Chemoimmunotherapy with or without autologous SCT and with or without maintenance therapy is the most commonly used standard-of-care frontline treatment; however, at MDACC, clinical trials or chemo-free therapies are the first choice. In Table–3,[72] we have summarized the findings from major frontline clinical trials in patients with MCL.

Previously Untreated Young Patients (Age <65 Years)—All Risk Categories

At MDACC, the standard of protocol treatment for physically fit, transplant-eligible patients is intensive chemoimmunotherapy with rituximab with HCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone) as part A and methotrexate-ara-C as part B (R-HCVAD/methotrexate-ara-C). We do not recommend consolidation with SCT after R-HCVAD. At other centers, intensive chemoimmunotherapy is followed by auto-SCT and rituximab maintenance in high-risk MCL.[146] The choice of chemoimmunotherapy regimen is based on feasibility, physician choice, and patient choice.

The use of Hyper-CVAD with alternating Mtx/ara-C followed by consolidation auto-SCT, was initially reported from MDACC in 1998.[147] We conducted a phase 2 clinical trial with R-HCVAD/methotrexate-ara-C regimen in 97 patients. After a median follow-up of 13.4 years,[148] the overall response rates (ORR) and complete remission (CR) rates were 97% and 87%, respectively. The failure-free survival in young patients was 30% after 10 years and appeared to reach a plateau. In another study, bortezomib was added to R-HCVAD/methotrexate-ara-C,[149] but the response rates did not improve over R-HCVAD alone.

The R-HCVAD regimen was also tested in two multicenter phase 2 studies—one from Italy[150] (n = 60) and another from SWOG[151] (n = 49). The ORRs were 83% and 86%, respectively. Because of severe hematologic toxicities, 40% to 60% of patients could not tolerate the treatment and could not complete the regimen.

More commonly, a Nordic regimen is utilized in clinical practice.[152,153] In a phase 2 trial with R-maxi CHOP alternating with R-high dose ara-C was used and showed 97% response rate; however, 9% of patients had development of second cancers over long-term follow-up. One phase 2 French study[154] used three cycles of R-CHOP and three cycles of R-DHAP followed by auto-SCT in 60 patients, with 90% to 94% ORR. With a median follow-up of 67 months, the 5-year OS was 75%. In a phase 3 trial from the European MCL network,[155] R-CHOP/R-DHAP followed by auto-SCT was compared against R-CHOP alone followed by auto-SCT. Time to treatment failure was significantly longer with R-CHOP/R-DHAP. In one recent retrospective analysis of young patients with MCL (n = 1254),[146] consolidation auto-SCT was shown to be associated with improved progression-free survival (PFS) but not OS in a multivariate analysis. Considering the durable remissions with auto-SCT, many physicians prefer that young MCL patients receive auto-SCT after intensive induction chemotherapy. In addition, rituximab maintenance for 3 years after four cycles of R-DHAP followed by auto-SCT led to significant improvement in survival outcomes compared with observation alone.[122]

Bendamustine was combined with rituximab (BR) followed by rituximab and high-dose ara-C and auto-SCT in 23 patients.[156] The median follow-up was 13 months, and the PFS was 96%, with a median OS not reached. MRD-negative status after chemotherapy alone was 93%. We do not have data on whether BR induction is a better choice before auto-SCT compared with R-CHOP. In a randomized SWOG study, BR was compared with R-HCVAD before auto-SCT, but the study was stopped prematurely because the stem cell mobilization failure was 29% after R-HCVAD.[157]

Table 10–3 Summary of Pivotal Published Studies in the Frontline Setting in MCL

Protocol Used	Number of Patients	Median Follow-up	ORR (CR), %	Median Remission Duration/PFS	Median OS	Comments
R-HCVAD/Mtx-ara-C[148,229,230] (no auto-SCT)	97	13.4 y	97 (87)	4.8 y	10.7 y	In young (<65 y; n = 65) patients, median FFS 6.5 y and OS 13.4 whereas in older adult (>65 y; n = 32), median FFS 3 y and OS 4.9 y 6.2% rate of myelodysplasia and acute myeloid leukemia Blastoid/pleomorphic histology (n = 15) not associated with survival FFS plateaued after 10 y
R-maxi-CHOP/R-HiDAC (with auto-SCT), Nordic regimen[152,153,231]	160	11.4 y	96 (54/89*)	8.5 y	12.7 y	145 patients received auto-SCT, and median PFS and OS were 11 y and NR 9.4% rate of second cancers (n = 20 with 15 solid tumors and 5 myeloid cancers) Plateau in survival curves not reached, 50% patients relapsed after 12 y
R-CHOP + auto-SCT **R-CHOP/R-DHAP + auto-SCT[155]**	234 232	6.1 y	97 (61) vs 98 (63)	4.3 vs 9.1 y	NR vs 9.8 y	Time to treatment failure longer in ara-C group (9.1 vs 4.3 y) OS was not significantly different 2.4% secondary leukemia and 4.3% other cancers with ara-C group
R-DHAP (4 cycles) + auto-SCT followed by rituximab maintenance vs observation alone[122]	120 each	50 mo	89 (77) after 4[b] R-DHAP	4 y % (83% vs 64%)	4 y % (89% vs 80%)	Maintenance rituximab after R-DHAP induction therapy, followed by R-BEAM consolidation therapy, prevented relapses and was associated with a low risk of major infection
BR vs R-CHOP (StiL)[159]	46 vs 48	45 mo	93[b] (40) vs 91 (30)	35.1 vs 22.1 mo	NR in both	Response rates were reported from both indolent and MCL patients Trend of longer time to next treatment with BR but OS was similar in BR vs R-CHOP Long-term follow-up and detailed subset analysis is not reported

Table 10–3 Summary of Pivotal Published Studies in the Frontline Setting in MCL (*Cont.*)

Protocol Used	Number of Patients	Median Follow-up	ORR (CR), %	Median Remission Duration/PFS	Median OS	Comments
BR vs R-CHOP (BRIGHT)[160,161]	37 vs 37	65 mo	[b]97 (31) vs 91 (25)	5 y 40% vs 14%	82% vs 85% alive at 5 y	Higher second cancers in BR group Detailed subset analysis is not reported Lesser toxicities with BR
Bortezomib-R-CHOP vs R-CHOP alone[164]	[c]243 vs 244	82 mo	92 (53) vs 89 (42)	25 vs 14.4 mo	[c]91 vs 56 mo	Improved overall survival with bortezomib-R-CHOP in patients with high Ki-67% (>30%) 42% died in bortezomib group vs 57% in R-CHOP alone group Similar incidence of second cancers
Lenalidomide-Rituximab[167,168]	38	64	92 (64)	5 y 64%	5 y 77%	6 patients (16%) had second primary cancers (mostly skin cancers) 42% grade ≥3 neutropenia Th2 to Th1 cytokine/chemokine switch after 3 cycles of induction showing immune modulation and effect on inflammation

[a]CR 89% after auto-SCT
[b]In both indolent and MCL patients
[c]140 and 128 patients were included at 82-month follow-up.
The table excludes data in relapsed-refractory MCL and unpublished studies on frontline BTK inhibitors at the time of this writing.
NR is not reached, ORR is overall response rate, CR is complete response rate, yrs. Years, R-HCVAD/Mtx-ara-C (rituximab with hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with highdose methotrexate and cytosine arabinoside), R-DHAP (rituximab – dexamethasone, cisplatin, ara-C), StiL (study group indolent lymphoma).
Reproduced with permission from Jain P, Wang M: Mantle cell lymphoma: 2019 update on the diagnosis, pathogenesis, prognostication, and management, *Am J Hematol* 2019 Jun;94(6):710-725.

Clinical Trials at MDACC for Young MCL

We have a portfolio of clinical trials for frontline therapy in young, physically fit patients with MCL. We have incorporated orally available targeted therapies in the frontline setting to minimize or obviate the need for chemotherapy except in high-risk patients. These clinical trials include the following.

Window-1 Trial

Ibrutinib with rituximab (IR) induction (Part A) followed by short-course four cycles of R-HCVAD-Methotrexate/ara-C (Part B) were used in 131 patients. After a median follow-up of 22 months, the ORR on part A of therapy was 100% (88% CR and 12% PR) and after completion of both parts A and part B, ORR was 100% (94% CR). Overall, the median PFS and OS were not reached (3 year, 85% and 97%, respectively) and nine patients had relapse after treatment and 21 patients left the study for various reasons. None of the patients had grade 3 or higher atrial fibrillation or bleeding.[158] Longer follow-up of this study is pending. This regimen is included in the 2020 NCCN guidelines for treating MCL (NCT02427620).

Window-2 Trial

Ibrutinib and rituximab induction is followed by venetoclax and risk-stratified use of R-HCVAD-Methotrexate/ara-C. For high-risk patients (4 cycles) and for moderate risk, only two cycles of chemotherapy are approved, whereas the low-risk patients do not receive chemotherapy (NCT03710772).

Other Important Trials in Young MCL Patients in the Frontline Setting

TRIANGLE Study

The TRIANGLE study is a phase 3 trial in young, transplant-eligible patients in Europe. It is a three-arm randomized trial with six cycles of R-CHOP/R-DHAP

+ auto-SCT versus six cycles of R-CHOP + ibrutinib/R-DHAP + auto-SCT + 2 years of ibrutinib maintenance versus six cycles of R-CHOP + ibrutinib/R-DHAP + 2 years of ibrutinib maintenance. Results of this trial would indicate whether ibrutinib and ara-C–based induction is efficacious and can improve the previous results with chemoimmunotherapy alone in induction before auto-SCT (NCT02858258).

E4151 Study

This phase 3 randomized study by a United States intergroup is evaluating maintenance rituximab in patients who achieve MRD-negative CR after induction therapy and who are then randomly assigned to auto-SCT + MR versus MR alone. This study may provide insight into the role of consolidation SCT after achieving MRD-negative CR (NCT03267433).

Previously Untreated Elderly Patients (Age ≥65 Years)—All Risk Categories

Older adult patients usually exhibit comorbidities and therefore may not be eligible for SCT; their tolerability to chemotherapy is generally poorer compared with young and physically fit patients. Older adult patients (n = 32) had significantly inferior failure-free and OS compared with patients younger than 65 years in the long-term follow-up of R-HCVAD/Mtx-ara-C.[148] In general, bendamustine with rituximab (BR) combination is used in the routine clinical practice for older patients with MCL, largely because of its less intensive schedule. The BR regimen was tested in two different phase 3 randomized trials: one in Germany[159] and another in North America.[160,161] In 2013, Rummel and colleagues[159] reported that BR significantly improved PFS in patients with MCL compared with R-CHOP,[159] and showed that BR was less toxic compared with R-CHOP. A nine-year follow-up of this study confirmed these findings.[162] Similar results demonstrating superiority of BR over R-CHOP for improved PFS were reported after a 5-year follow-up of the BRIGHT study.[161] The incidence of second cancers was 19% in the BR group versus 11% in the R-CHOP group in the BRIGHT study. One of the caveats of the BRIGHT study was that this included a combination of patients—indolent and MCL. BR was also studied in combination with low-dose ara-C[163] (R-BAC-500; n = 57; BR + ara-C 500 mg/m^2 on days 2–4 4 weekly), the ORR and CR were 91%, with 50% of patients developing grade 3–4 neutropenia. R-BAC followed by venetoclax as consolidation in high-risk elderly MCL is evaluated (NCT03567876).

Promising OS was noted in a combination of bortezomib with R-CHOP compared with R-CHOP alone, but an increase in hematologic toxicity with combination was noted.[164,165] the European MCL network demonstrated that rituximab maintenance for two years or beyond after induction with R-CHOP significantly improved PFS (5 years) and OS (9.8 years) versus no maintenance (PFS 1.9 years and OS 7 years).[166] Maintenance rituximab after BR has not shown benefit.

Lenalidomide was also investigated in older adults with MCL. A combination of lenalidomide with rituximab was investigated in 38 elderly patients. The 5-year follow-up of this study showed that the majority (75%) of these patients completed more than 3 years of treatment. In a subset of patients (8/10), MRD was negative at the last follow-up assessment.[167,168] However, lenalidomide-based regimens are currently less favored in MCL, largely because of the availability of better, well-tolerated BTK inhibitors and the concern about second cancers with lenalidomide. The combination of lenalidomide with chemotherapy was also investigated. Lenalidomide with BR in one study[169] (n = 51) reported that 42% of patients experienced grade 3–4 infections and 16% of patients developed second cancers. Lenalidomide in combination with bortezomib and dexamethasone[170] showed a 2-year PFS of 70%, but 51% of patients experienced grade 3–4 neutropenia.

Clinical Trials at MDACC for Previously Untreated Older Adults With MCL

We have incorporated orally available targeted therapies in the frontline setting to minimize or obviate the need for chemotherapy. Our clinical trials include the following.

Ibrutinib With Rituximab in Nonblastoid/Pleomorphic MCL

Our group has conducted a phase 2 clinical trial[171] with a combination of ibrutinib and rituximab in 50 patients (NCT01880567). Ibrutinib was administered as 560 mg orally daily for 28 days (one cycle) and was continued until disease progression or discontinuation for any reason. Rituximab was given on days 1, 8, 15, and 22 plus or minus 1 day by IV injection at a fixed dose of 375 mg/m^2 (Cycle 1, followed by rituximab on day 1 of every cycle starting in Cycles 3–8). After Cycle 8, rituximab was given on day 1 of every other cycle for up to two years. The ORR was 98% (60% CR, 38% PR, 2% stable disease). With a median follow-up of 28 months, the median PFS and OS were not reached. Four patients progressed during the study and two patients died. Overall, 19 patients (39%) discontinued therapy. Atrial fibrillation was noted in seven patients (3 had new onset and four had prior history of atrial fibrillation), and bleeding was noted in three patients. The combination of IR was an excellent frontline

treatment option for older adult patients; however, patients taking this combination are strongly recommended to closely follow up with a cardiologist. Longer follow-up of this study is pending.

SYMPATICO Study

This is an ongoing global multicenter phase 3 study with a combination of ibrutinib and venetoclax (NCT03112174). The efficacy of a combination of ibrutinib with venetoclax in transplant-ineligible, previously untreated patients with MCL who are 65 years or older (n = 50) and patients under the age of 65 who have *TP53*-mutated MCL is tested (n = 25). Of note, patients with blastoid variant and those with CNS involvement are excluded.

Zanubrutinib-Rituximab Versus BR Study

This is an ongoing randomized phase 3 study comparing ZR with BR in transplant-ineligible patients. Patients either between 65 and 69 years of age or 70 years or older with comorbidities precluding auto-SCT are eligible (NCT04002297).

ECOG-E1411 Study

The ECOG-E1411 study is a four-arm randomized phase 2 trial in patients age 60 years or older. Arm 1 is BR induction followed by rituximab maintenance, arm 2 is BR + bortezomib followed by rituximab maintenance, arm 3 is BR followed by lenalidomide + rituximab maintenance, and arm 4 is BR + bortezomib followed by lenalidomide + rituximab maintenance. This study will provide information on ideal maintenance strategy with lenalidomide (NCT 01415752).

MCL-R2 Older Adult Trial

This is a phase 3 randomized trial to assess the efficacy of ara-C induction and lenalidomide maintenance. This study is evaluating whether the addition of lenalidomide to rituximab maintenance is useful in older adult patients with MCL (NCT01865110).

Miscellaneous Studies

These studies are investigating various combinations of newer BTK inhibitors, with venetoclax and/or obinutuzumab with/without chemotherapy.

Previously Treated Relapsed MCL—BTK Inhibitor–Naïve

The success story of BTK inhibitors and venetoclax in MCL in the last 5 to 7 years is a landmark feat. Ibrutinib,[133,172] acalabrutinib,[135] and zanubrutinib[173] are approved BTK inhibitors[136,174] in patients with relapsed MCL. Their main advantages are oral availability, excellent efficacy, better tolerability, and safety profile compared with chemotherapy and feasibility for the older adult age group. Conventionally, after first-line failure, patients were treated with salvage regimens such as R-ICE or R-DHAP or with bortezomib (ORR 25%–50% with a CR of 4%–8%),[175–177] temsirolimus (ORR 22%),[178] lenalidomide (ORR 28% with single agent and 57% with rituximab),[179,180] or their combinations with rituximab.[181] These modalities in the relapsed setting demonstrated modest response rates, but intolerance is a major issue.[182]

Treatment Options in Relapsed BTK-Naïve MCL

Lenalidomide With Rituximab (LR)

In a phase 1/2 study,[181] the LR combination was tested in 52 patients. Forty-four patients were enrolled in a phase 2 cohort with an ORR of 57% and CR of 36%. The median PFS was 11.1 months and the median OS was 24.3 months.

Ibrutinib

This is an irreversible, covalent inhibitor of BTK (a TEC kinase) and binds to cysteine 481 on the ATP binding site of the BTK kinase domain. Ibrutinib has off-target effects on other TEC kinases (BMX, ITK, and BLK), which are distributed in various tissues, leading to off-target effects such as bleeding, cardiac arrythmias (mainly atrial fibrillation),[183,184] and ventricular arrhythmias.[185,186] Inhibition of BTK leads to abrogation of MCL cell survival, proliferation, and growth.[187] Ibrutinib also leads to redistribution lymphocytosis after interfering with the chemokine-receptor interactions and homing of MCL cells.[145] Lymphocytosis after ibrutinib is not considered a sign of disease progression.

Initial results from single-agent ibrutinib in patients with relapsed MCL (n = 111) were reported in 2013.[128] The median age of patients was 68 years, with a median of three prior lines of therapies. The ORR was 68% and CR was 21%. Grade 3 or 4 adverse events included 16% neutropenia, 11% thrombocytopenia, 10% anemia, and 5% bleeding. On the longer follow-up of 26.7 months,[134] the CR rate improved to 23%, and 22% of patients continued treatment for more than 2 years. Two-year PFS and OS were 31% and 47%, respectively, and the median duration of response was 17.5 months. Six percent of patients had grade 3 or 4 bleeding events (none fatal), 11% had atrial fibrillation (grade 3 in 6%), and second cancers developed in 5%.

Ibrutinib was also compared with temsirolimus (m-TOR inhibitor) in a randomized study (RAY study[188]) and ibrutinib was superior to temsirolimus. A three-year follow-up of this study demonstrated that survival and safety data were better with ibrutinib.

Long-term follow-up from a pooled analysis of 370 ibrutinib-treated patients with relapsed MCL with

a median follow-up of 41.5 months was reported.[172] Seventeen percent of patients continued to receive treatment for more than 4 years. The median PFS and OS were 12.5 and 26.7 months, respectively. A higher number of prior lines of therapy was associated with shorter PFS in the multivariate analysis. Ibrutinib after failure of first-line therapy has a superior response rate 77% (37% CR) and longer duration of response (36 months) compared with ibrutinib administered after failure of multiple lines of therapies. Among blastoid MCL, the response rate was inferior compared with nonblastoid histology (50% vs 68%). In addition, OS was shorter in blastoid versus nonblastoid MCL (12.8 vs not reached, respectively). Of note, 14% of patients were *TP53*-mutated and demonstrated inferior response rates (55%), shorter PFS (4 months), and shorter OS (10.3 months). Patients with wild-type *TP53* showed a 70.2% response rate, PFS of 12 months, and OS of 33.6 months. Atrial fibrillation occurred in 11% of patients (any grade; 5% grade 3) but none of the patients discontinued ibrutinib owing to atrial fibrillation.[189] Ibrutinib can induce platelet dysfunction[186,190,191] and impaired thrombus formation, contributing to bleeding tendency, and concomitant anticoagulant and antiplatelet agents must be carefully evaluated in patients taking ibrutinib.[192] Cardiovascular effects, arrythmias[193,194] (mainly atrial fibrillation), and hypertension are critical to watch for in patients taking ibrutinib. These cardiac adverse events are likely associated with inhibition of other TEC kinases present in cardiac myocytes.[183,195,196]

We conducted a phase 2 study at MDACC using a combination of IR in relapsed MCL (with a median of three prior therapies). A 4-year follow-up of this study showed that the CR improved from 44%[197] to 58%[198]. The median PFS was 43 months and the median OS was not reached. High-risk patients, high Ki-67% (>50%) and/or patients with aggressive histology had inferior survival outcomes. The addition of lenalidomide to IR was investigated in the PHILEMON study, a European phase 2 multicenter trial.[199] In 50 previously treated patients with relapsed MCL, the ORR was 76% (56% CR) after a median follow-up of 17.8 months; 38% of patients had grade 3–4 neutropenia on this combination.

Finally, ibrutinib was investigated in a combination with venetoclax in relapsed MCL (AIM study from Australia). This combination of ibrutinib and venetoclax was based on preclinical data showing synergy between the two.[200] The I+V regimen was ibrutinib (560 mg daily) with venetoclax (weekly dose escalation up to 400 mg daily dose). Among 23 patients with relapsed MCL, 75% had high-risk MIPI score and 50% had *TP53* mutations. The median follow-up duration was 15.9 months. The combination[174] resulted in an ORR of 71% with 62% CR (with PET-based assessment) at week 16. In all patients, MRD-negative response was 67% by flow cytometry and 38% by PCR. The median PFS was not reached, with a 12-month PFS of 75%. Interestingly, among the patients with *TP53* mutation (n = 12), 50% achieved CR. Grade 3–4 diarrhea was noted in 71%, and neutropenia was noted in 33% of patients. Resistance mechanisms for the combination demonstrated that the mutations in the SWI/SNF chromatin-remodeling complex was associated with drug resistance.[59] In addition, ibrutinib was also investigated in combination with palbociclib. In a phase 1 trial, the ORR was 67% and CR was 37%, whereas the two-year PFS was 59%.[201]

Of interest is the activity of ibrutinib to penetrate the blood-brain barrier; it has been investigated in CNS lymphomas, and ibrutinib has a potential for further testing in MCL involving CNS.[202–205]

In relapsed MCL, various combinations of ibrutinib with chemotherapy—ibrutinib with venetoclax, and obinutuzumab and ibrutinib with anti-CD19-CAR-T therapy (because of a potential to improve CAR-T efficacy by the off-target effects of ibrutinib), and ibrutinib with palbociclib (a CDK4/6 inhibitor)[201] are being investigated. In the Australian TARMAC study (NCT04234061), ibrutinib is administered before CAR-T in patients with relapsed MCL.

Few challenges with ibrutinib include disease progression and ibrutinib discontinuation caused by side effects, patient choice,[58,129] ibrutinib-refractory MCL, and the mechanisms of ibrutinib resistance.[61] Unlike CLL/SLL, BTK C481S mutation is infrequent in ibrutinib-resistant MCL.[58,206] At MDACC, we are working to further understand the mechanisms of ibrutinib resistance[105] and strategies to overcome ibrutinib resistance in MCL.[207,208]

Acalabrutinib

A more selective, FDA-approved and orally administered agent, acalabrutinib is a covalent, irreversible inhibitor of BTK and binds to C481S in the ATP binding pocket. Minimal off-target kinase activity of acalabrutinib is a distinct advantage over ibrutinib.[209] Acalabrutinib preserves *Src* family kinase (collagen to platelet adhesion) activity and thus avoids the unstable platelet thrombus formation seen with ibrutinib therapy.[210] These activities may explain the low incidence of atrial fibrillation and less risk of bleeding compared with ibrutinib; however, randomized studies with head-to-head comparison of acalabrutinib and ibrutinib may reveal the actual risk of these adverse events.

In the pivotal multicenter phase 2 trial in relapsed MCL (n = 124), patients had a median of two lines of prior therapy.[135] After a median follow-up of 15.2 months, the ORR was 81% with 40% CR, and at the 26-month follow-up analysis,[211] the median PFS was 19.5 months, and the median OS was not reached.

About 40% of patients continued on acalabrutinib. Three patients experienced grade 3 bleeding events, and none had atrial fibrillation. Headache and diarrhea were observed in 38% and 30% patients, respectively.

Various combinations of acalabrutinib with rituximab and/or acalabrutinib-venetoclax, acalabrutinib-lenalidomide, or a combination of acalabrutinib with venetoclax and rituximab are investigated. Longer follow-up and the analysis of outcomes after acalabrutinib progression[138] are important to fully explore the potential of acalabrutinib in MCL.

Zanubrutinib

Zanubrutinib is a newly FDA-approved selective and irreversible BTK inhibitor. In the phase 1 trial,[212] with a median follow-up of about 16 months in 37 patients with relapsed MCL, the response rate was 87%, with 30% CR with single-agent zanubrutinib, whereas in eight previously untreated patients, the response rate was 87.5% with 37% CR. In a phase 2 study[213] of 86 patients from China, zanubrutinib demonstrated 84% ORR and 68% CR in relapsed MCL (median two prior lines). The median follow-up was 18 months and the median PFS was 22 months. In 15 *TP53*-mutated patients, ORR was 80% versus 87% in *TP53* wild-type, and the median PFS was 14.2 versus 22.1 months in *TP53* wild-type patients. Of note, because of minimal off-target effects, none of the patients exhibited grade 3 or higher bleeding or cardiac arrythmias.

Tirabrutinib[214] and orelabrutinib[215] are other irreversible BTK inhibitors with higher selectivity against BTK and better side effect profiles compared with ibrutinib. These are under clinical investigation.

Previously Treated Relapsed MCL–BTK Inhibitor Refractory

As our experience with BTK inhibitors is growing, we are seeing patients with BTK inhibitor–refractory MCL. Newer therapies are urgently required to treat these complex patients.

Venetoclax

This drug is an orally available, selective inhibitor of the anti-apoptotic BCL-2 protein. Initial experience with venetoclax in MCL was demonstrated in a phase 1 study.[136] Twenty-eight relapsed-refractory MCL patients (none BTK inhibitor refractory; median age, 72 years and median of 3 prior lines of treatments) were enrolled, and patients achieved an ORR of 75%, CR of 21%, and a median PFS of 14 months. Venetoclax has very promising activity in MCL. One retrospective study[137] described venetoclax monotherapy in 20 patients with relapsed MCL (median of 3 prior lines of therapy). The ORR was 53% and CR was 18%. The majority (85%) of patients in this study were resistant to BTK inhibitors, and the median PFS was 3.2 months. At MDACC, we reported our experience in 24 patients with heavily treated MCL (median 5 prior lines of therapy). The majority of patients had high-risk disease and 67% were refractory to BTK inhibitors. After a median follow-up after venetoclax of 17 months, the ORR was 50% (21% CR). The median PFS was 8 months. Using whole-exome sequencing, we demonstrated that non-BCL2 mutations (*SMARCA4, TP53, CDKN2A, KMT2D, CELSR3, CCND1,* and *NOTCH2*) were noted after progression on venetoclax. BCL2 mutations were infrequent (only one-third of patients). Venetoclax is actively investigated with various combinations in MCL, with BTK inhibitors in the frontline and in the relapsed-refractory setting.

LOXO-305

LOXO-305 is the latest and novel, reversible, noncovalent, and orally administered BTKi that inhibits both wild-type and C481-mutated BTK in preclinical studies. LOXO-305 has minimum off-target kinase and nonkinase inhibitory activity. This molecule is currently undergoing a phase 1 clinical trial in B-cell lymphoid malignancies.[216]

In the phase 1 trial, in 38 relapsed-refractory MCL patients, the median number of prior lines of therapy was two (range 2–8), and 92% of patients were treated with a prior BTK inhibitor. Among the 35 efficacy-evaluable patients with MCL treated across all dose levels, the ORR was 51%, including nine CRs. Among the subset of 20 efficacy-evaluable patients with MCL who started at 200 mg daily, the ORR was 65% including seven CRs, six PRs, four SDs, one PD, and two NEs. Because of lesser off-target effects, LOXO-305 has better safety data compared with ibrutinib. Fatigue and diarrhea were common adverse events noticed in less than 20% of patients. Final data were reported at the 2020 American Society of Hematology meeting. The phase 2 dose was 200 mg orally daily. LOXO-305 and its combinations hold great promise for patients with BTK inhibitor–refractory MCL.

R-BAC Regimen

In a multi-institutional retrospective report from 36 patients whose disease failed prior BTK inhibitors, this regimen demonstrated 83% ORR and 60% CR, and 31% bridged to allo-SCT. The median OS was 12.5 months.[217]

Stem Cell Transplantation

Autologous SCT is conventionally used as a consolidation strategy after completing intensive chemoimmunotherapy. Some retrospective and few

prospective studies have described their experience with SCT in MCL, although the data of SCT in BTK inhibitor-refractory MCL are not well described. In a multicenter retrospective analysis,[218] 70 patients with relapsed MCL who received allo-SCT were described. Patients with chemosensitive disease demonstrated superior outcomes compared with patients who had PR or no response. Allogenic SCT can be useful in high-risk, transplant-eligible *TP53*-mutated relapsed MCL. Allo-SCT can provide long-term disease control in about 30% of patients with MCL.[219,220] Ibrutinib before allo-SCT can be efficacious as a bridging therapy, as reported in a study of 22 patients.[221] Pretransplant disease response is important in predicting response to allo-SCT in MCL. As of this writing, the role of allo-SCT in relapsed MCL is limited because of its availability, mortality, morbidity, and the advent of relatively safe and efficacious brexucabtagene autoleucel an anti–CD19-CAR-T therapy.

Chimeric Antigen Receptor T-Cell (CAR-T) Therapy

CAR-T therapy is the most recent and most potent landmark development for highly refractory patients with MCL. The recent FDA approval of anti–CD19-CAR-T, brexucabtagene autoleucel (KTE-X19), was the highlight of the year 2020 and was recently approved by the FDA for adult patients with relapsed or refractory MCL.

The ZUMA-2 study is a single-arm, international, multicenter, open-label, phase 2 trial in which 68 patients with relapsed MCL received CAR-T therapy. All patients had progressed on BTK inhibitors and they had a median of 3 prior lines of therapy (range 1–5). Forty-two patients were primary refractory to BTK inhibitors, and 18 patients (26%) had relapsed after an initial response to BTK inhibitor. The patients underwent leukapheresis and lymphocyte-depleting chemotherapy followed by CAR-T infusion at a target dose of 2×10^6 CAR-T cells/kg. Patients who had high-risk MCL were included : 17 (25%) had blastoid histology, six with *TP53* mutations, and 32 had Ki-67% of at least 50%. The ORR was 93% and the CR was 67%. With a follow-up of 12 months, 57% patients remained in remission. Furthermore, the ORR was higher than 93% in blastoid, *TP53*-mutated, and high Ki-67% patients. The PFS and OS were not reached. Most common grade 3 or higher adverse events were cytopenias (69%) and infections (32%), and grade 3 or higher cytokine release syndrome in 15%, whereas neurotoxicity was noted in 31% patients. A longer follow-up on this study is required to further evaluate the durability of responses achieved by this modality. The process with CAR-T is less complicated and well tolerated compared with similar data from traditional allo-SCT. Conversely, the cost of CAR-T, limited experience in the community, and its availability at specialized centers are the major limitations.

Newer Cellular Therapies

Lisocabtagene maraleucel (JCAR-017)[222] is a CD19-directed 4-1BB CAR-T product undergoing clinical trials in MCL. In the phase 1 study, median follow-up was 18 months (n = 17) and the ORR was 71% (CR 53%). Grade 3 or higher toxicities were 6% cytokine release syndrome and 12% neurotoxicity. Other newer cellular therapies include CD19 CAR-NK cells,[223] allogeneic CAR-T, and humanized binding domain in CD19 CAR-T cells (Hu19-CD828Z).[224] Most recently, clinical trials have also started investigating the combination of BTK inhibitors with anti–CD19-CAR-T. Other antigens relevant in MCL and being investigated are CD20, CD22, ROR1, BAFF,[225] and CD79b,[226] or bispecific antibodies (CD3-CD20).

Triple-Refractory Relapsed MCL

Recently, in our clinical experience, we have also observed a very-high-risk subset in patients with MCL that we call "triple-refractory MCL," referring to patients who have progressed on BTK inhibitors, venetoclax, and CAR-T therapy. Treatment options for these patients are highly limited. Currently, newer clinical trials are required to address the issue of triple resistance. In the coming years, we will be able to observe the pattern of resistance observed in triple-resistant MCL patients.

CNS Prophylaxis in MCL

This is controversial and no definitive guidelines exist. The practice varies at different centers, especially in patients with aggressive-histology MCL. Few retrospective studies[76,227,228] demonstrated that some baseline characteristics of patients with MCL (blastoid MCL, very high LDH levels, high Ki-67%) correlate with a higher frequency of CNS involvement. The outcomes of CNS-MCL are very poor. In one study with 57 patients who developed CNS involvement by MCL,[76] 20% had prior intrathecal chemotherapy and 18% had prior R-HCVAD; therefore, complete prevention of CNS involvement by routine intrathecal chemotherapy may not be attainable. However, patients with blastoid MCL are advised to undergo prophylactic intrathecal chemotherapy by some physicians. In addition, because ibrutinib has been shown to penetrate the blood-brain barrier[202,205] and is increasingly used in MCL, the role of CNS prophylaxis in ibrutinib-treated MCL patients remains unknown. As of this writing, we do not administer intrathecal chemotherapy in patients if they have received ibrutinib-based therapies, and/or have had

R-HCVAD therapy; however, in specific clinical situations such as patients with high-risk MCL receiving only chemotherapy, paraspinal disease, or paranasal involvement, we consider intrathecal chemotherapy.

SUMMARY

The field of MCL is changing rapidly. Advances in our understanding of the pathobiology, molecular events, and tissue microenvironment have improved our understanding of MCL, leading to improvement in risk stratification, further advances in the field, and help in accurately predicting the prognosis. In addition, newer therapies have significantly improved survival outcomes and response rates. The evolution of BTK inhibitors, venetoclax and anti-CD19 CAR-T, have demonstrated phenomenal results and are shifting the focus to investigate these therapies in the frontline setting. We hope that this momentum of advancement in understanding MCL will continue and we may find a cure for it in the coming years.

MD ANDERSON PRACTICE TIPS

- To obtain full risk factor assessment with relevant investigations and collect various parameters at initial diagnosis (outlined in Fig. 10–2). This is important for determining prognosis and future considerations on clinical trials.
- To obtain information on the high-risk features at initial diagnosis: high-risk MIPI score, blastoid/pleomorphic histology, high Ki-67% at least 30%, and *TP53* mutation status. This information is highly relevant because it can affect the clinical outcome.
- To obtain a detailed cardiology assessment and cardiology clearance before starting BTK inhibitors on any patient with MCL. Cardiac arrythmias, hypertension, and bleeding tendencies can be life threatening for older adult patients with MCL.
- To obtain gastrointestinal tract (upper and lower) endoscopies with random biopsies, along with PET-CT scan and bone marrow assessment (flow cytometry, cytogenetics, molecular testing) to confirm CR in patients with MCL. About 30% of MCL can have delayed clearance of the GI tract, and residual disease in the GI tract disqualifies patients to achieve CR.
- The focus in the treatment of MCL is gradually shifting from frontline chemotherapies to "chemo-free" therapies such as BTK inhibitors and venetoclax as their initial therapy. We recommend enrolling patients in clinical trials and exploring the option for recently approved anti–CD19-CAR-T (brexucabtagene autoleucel) therapy in relapsed patients and/or patients who progressed on BTK inhibitors and/or patients who are high risk and relapsed after standard therapies.
- Explore the option for enrollment in clinical trials and refer the patient to specialized centers for MCL treatment in the US or elsewhere. We have the center of excellence in MCL at MDACC. For further enquiries, please contact miwang@mdanderson.org and/or pjain@mdanderson.org.

ACKNOWLEDGMENTS

Funding for various MCL studies at MD Anderson Cancer Center was provided in part by the generous philanthropy donated to the MD Anderson Cancer Center B-Cell Lymphoma Moon Shot Program; R21 CA202104 (Michael Wang, PI); and philanthropy funds from The Gary Rogers Foundation and the Fox Family Foundation.

CONFLICTS OF INTEREST DISCLOSURES

MW – honoraria from Pharmacyclics, Janssen, AstraZeneca/Acerta Pharma, Targeted Oncology, and OMI; consultancy or advisory role for Pharmacyclics, Celgene, Janssen, AstraZeneca/Acerta Pharma, MoreHealth, Loxo Oncology, Kite, a Gilead Company, Oncternal, InnoCare and Pulse Biosciences; research funding from Pharmacyclics, Janssen, AstraZeneca/Acerta Pharma, BioInvent, Novartis, Kite, a Gilead Company, Juno, Celgene, Loxo Oncology, Oncternal, InnoCare and VelosBio; expert testimony for AstraZeneca/Acerta Pharma; and travel support from Janssen, Pharmacyclics, Celgene, Targeted Oncology, and OMI.;**P.J.** – none.

REFERENCES

1. Teras LR, DeSantis CE, Cerhan JR, et al. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. *CA Cancer J Clin.* 2016;66(6):443-459.
2. Sant M, Allemani C, Tereanu C, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. *Blood.* 2010;116(19):3724-3734.
3. Smith A, Howell D, Patmore R, et al. Incidence of haematological malignancy by sub-type: a report from the Haematological Malignancy Research Network. *Br J Cancer.* 2011;105(11):1684-1692.
4. Fu S, Wang M, Lairson DR, et al. Trends and variations in mantle cell lymphoma incidence from 1995 to 2013: A comparative study between Texas and National SEER areas. *Oncotarget.* 2017;8(68):112516-112529.
5. Epperla N, Hamadani M, Fenske TS, et al. Incidence and survival trends in mantle cell lymphoma. *Br J Haematol.* 2018;181(5):703-706.
6. Lee H, Park HJ, Park E-H, et al. Nationwide statistical analysis of lymphoid malignancies in Korea. *Cancer Res Treat.* 2018;50(1):222-238.
7. Meng J, Chang C, Pan H, et al. Epidemiologic characteristics of malignant lymphoma in Hubei, China: A single-center 5-year retrospective study. *Medicine (Baltimore).* 2018;97(35):e12120.
8. Sun J, Yang Q, Lu Z, et al. Distribution of lymphoid neoplasms in China: analysis of 4,638 cases according to the World Health Organization classification. *Am J Clin Pathol.* 2012;138(3):429-434.
9. Nair R, Arora N, Mallath MK. Epidemiology of Non-Hodgkin's lymphoma in India. *Oncology.* 2016;91(suppl 1):18-25.
10. Wang Y, Ma S. Racial differences in mantle cell lymphoma in the United States. *BMC Cancer.* 2014;14:764.
11. Glimelius I, Smedby KE, Eloranta S, et al. Comorbidities and sex differences in causes of death among mantle cell lymphoma patients—a nationwide population-based cohort study. *Br J Haematol.* 2020;189(1):106-116.
12. Wang Y, Ma S. Risk factors for etiology and prognosis of mantle cell lymphoma. *Expert Rev Hematol.* 2014;7(2):233-243.
13. Schöllkopf C, Melbye M, Munksgaard L, et al. Borrelia infection and risk of non-Hodgkin lymphoma. *Blood.* 2008;111(12):5524-5529.
14. Smedby KE, Sampson JN, Turner JJ, et al. Medical history, lifestyle, family history, and occupational risk factors for mantle cell lymphoma: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. *J Natl Cancer Inst Monogr.* 2014;2014(48):76-86.
15. Skibola CF, Bracci PM, Nieters A, et al. Tumor necrosis factor (TNF) and lymphotoxin-alpha (LTA) polymorphisms and risk of non-Hodgkin lymphoma in the InterLymph Consortium. *Am J Epidemiol.* 2010;171(3):267-276.
16. Wang SS, Slager SL, Brennan P, et al. Family history of hematopoietic malignancies and risk of non-Hodgkin lymphoma (NHL): a pooled analysis of 10 211 cases and 11 905 controls from the International Lymphoma Epidemiology Consortium (InterLymph). *Blood.* 2007;109(8):3479-3488.
17. Smedby KE, Hjalgrim H, Askling J, et al. Autoimmune and chronic inflammatory disorders and risk of non-Hodgkin lymphoma by subtype. *J Natl Cancer Inst.* 2006;98(1):51-60.
18. Kleinstern G, Maurer MJ, Liebow M, et al. History of autoimmune conditions and lymphoma prognosis. *Blood Cancer J.* 2018;8(8):73.
19. Hadzidimitriou A, Agathangelidis A, Darzentas N, et al. Is there a role for antigen selection in mantle cell lymphoma? Immunogenetic support from a series of 807 cases. *Blood.* 2011;118(11):3088-3095.
20. Fichtner M, Spies E, Seismann H, et al. Complementarity determining region-independent recognition of a superantigen by B-cell antigen receptors of mantle cell lymphoma. *Haematologica.* 2016;101(9):e378-e381.
21. Leshchenko VV, Kuo P-Y, Shaknovich R, et al. Genome-wide DNA methylation analysis reveals novel targets for drug development in mantle cell lymphoma. *Blood.* 2010;116(7):1025-1034.
22. Shah BK, Khanal A. Second primary malignancies in mantle cell lymphoma: a US population-based study. *Anticancer Res.* 2015;35(6):3437-3440.
23. Navarro A, Beà S, Jares P, et al. Molecular pathogenesis of mantle cell lymphoma. *Hematol Oncol Clin North Am.* 2020;34(5):795-807.
24. Jares P, Colomer D, Campo E. Molecular pathogenesis of mantle cell lymphoma. *J Clin Invest.* 2012;122(10):3416-3423.
25. Puente XS, Jares P, Campo E. Chronic lymphocytic leukemia and mantle cell lymphoma: crossroads of genetic and microenvironment interactions. *Blood.* 2018;131(21):2283-2296.
26. Swerdlow SH, Campo C, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood.* 2016;127(20):2375-2390.
27. Queirós AC, Beekman R, Vilarrasa-Blai R, et al. Decoding the DNA methylome of mantle cell lymphoma in the light of the entire B cell lineage. *Cancer Cell.* 2016;30(5):806-821.
28. Navarro A, Clot G, Royo C, et al. Molecular subsets of mantle cell lymphoma defined by the IGHV mutational status and SOX11 expression have distinct biologic and clinical features. *Cancer Res.* 2012;72(20):5307-5316.
29. Navarro A, Clot G, Prieto M, et al. microRNA expression profiles identify subtypes of mantle cell lymphoma with different clinicobiological characteristics. *Clin Cancer Res.* 2013;19(12):3121-3129.
30. Nadeu F, Martin-Garcia D, Clot G, et al. Genomic and epigenomic insights into the origin, pathogenesis and clinical behavior of mantle cell lymphoma subtypes. *Blood.* 2020;136(12):1419-1432.
31. Hu Z, Sun Y, Schlette EJ, et al. CD200 expression in mantle cell lymphoma identifies a unique subgroup of patients with frequent IGHV mutations, absence of SOX11 expression, and an indolent clinical course. *Mod Pathol.* 2018;31(2):327-336.
32. Carvajal-Cuenca A, Sua LF, Silva NM, et al. In situ mantle cell lymphoma: clinical implications of an incidental finding with indolent clinical behavior. *Haematologica.* 2012;97(2):270-278.
33. Body S, Esteve-Arenys A, Miloudi H, et al. Cytoplasmic cyclin D1 controls the migration and invasiveness of mantle lymphoma cells. *Sci Rep.* 2017;7(1):13946.
34. Allinne J, Pichugin A, Iarovaia O, et al. Perinucleolar relocalization and nucleolin as crucial events in the transcriptional activation of key genes in mantle cell lymphoma. *Blood.* 2014;123(13):2044-2053.
35. Slotta-Huspenina J, Koch I, de Leval L, et al. The impact of cyclin D1 mRNA isoforms, morphology and p53 in mantle cell lymphoma: p53 alterations and blastoid morphology are strong predictors of a high proliferation index. *Haematologica.* 2012;97(9):1422-1430.
36. Wiestner A, Tehrani M, Chiorazzi M, et al. Point mutations and genomic deletions in CCND1 create stable truncated cyclin D1 mRNAs that are associated with increased proliferation rate and shorter survival. *Blood.* 2007;109(11):4599-606.
37. Peterson JF, Baughn LB, Ketterling RP, et al. Characterization of a cryptic IGH/CCND1 rearrangement in a case of mantle cell lymphoma with negative CCND1 FISH studies. *Blood Adv.* 2019;3(8):1298-1302.
38. Marrero WD, Cruz-Chacon A, Cabanillas F. Mantle cell lymphoma with t(11;22) (q13;q11.2) an indolent clinical variant? *Leuk Lymphoma.* 2018;59(10):2509-2511.

39. Iaccarino I, Afify L, Aukema SM, et al. t(11;14)-positive mantle cell lymphomas lacking cyclin D1 (CCND1) immunostaining because of a CCND1 mutation or exclusive expression of the CCND1b isoform. *Haematologica.* 2018;103(9):e432-e435.
40. Salaverria I, Royo C, Carvajal-Cuenca A, et al. CCND2 rearrangements are the most frequent genetic events in cyclin D1(-) mantle cell lymphoma. *Blood.* 2013;121(8):1394-1402.
41. Martín-Garcia D, Navarro A, Valdés-Mas R, et al. CCND2 and CCND3 hijack immunoglobulin light-chain enhancers in cyclin D1(-) mantle cell lymphoma. *Blood.* 2019;133(9):940-951.
42. Delfau-Larue MH, Klapper W, Berger F, et al. High-dose cytarabine does not overcome the adverse prognostic value of CDKN2A and TP53 deletions in mantle cell lymphoma. *Blood.* 2015;126(5):604-611.
43. Pinyol M, Hernandez L, Cazorla M, et al. Deletions and loss of expression of p16INK4a and p21Waf1 genes are associated with aggressive variants of mantle cell lymphomas. *Blood.* 1997;89(1):272-280.
44. Hernández L, Beà S, Pinyol M, et al. CDK4 and MDM2 gene alterations mainly occur in highly proliferative and aggressive mantle cell lymphomas with wild-type INK4a/ARF locus. *Cancer Res.* 2005;65(6):2199-2206.
45. Chiron D, Di Liberto M, Martin P, et al. Cell-cycle reprogramming for PI3K inhibition overrides a relapse-specific C481S BTK mutation revealed by longitudinal functional genomics in mantle cell lymphoma. *Cancer Discov.* 2014;4(9):1022-1035.
46. Ek S, Dictor M, Jerkeman M, et al. Nuclear expression of the non B-cell lineage Sox11 transcription factor identifies mantle cell lymphoma. *Blood.* 2008;111(2):800-805.
47. Vegliante MC, Palomero J, Pérez-Galán P, et al. SOX11 regulates PAX5 expression and blocks terminal B-cell differentiation in aggressive mantle cell lymphoma. *Blood.* 2013;121(12):2175-2185.
48. Kuo P-Y, Jatiani SS, Rahman AH, et al. SOX11 augments BCR signaling to drive MCL-like tumor development. *Blood.* 2018;131(20):2247-2255.
49. Palomero J, Vegliante JC, Eguileor Á, et al. SOX11 defines two different subtypes of mantle cell lymphoma through transcriptional regulation of BCL6. *Leukemia.* 2016;30(7):1596-1599.
50. Palomero J, Vegliante MC, Rodríguez ML, et al. SOX11 promotes tumor angiogenesis through transcriptional regulation of PDGFA in mantle cell lymphoma. *Blood.* 2014;124(14):2235-2247.
51. Balsas P, Palomero J, Eguileor Á, et al. SOX11 promotes tumor protective microenvironment interactions through CXCR4 and FAK regulation in mantle cell lymphoma. *Blood.* 2017;130(4):501-513.
52. Eskelund CW, Dahl C, Hansen JW, et al. TP53 mutations identify younger mantle cell lymphoma patients who do not benefit from intensive chemoimmunotherapy. *Blood.* 2017;130(17):1903-1910.
53. Hofmann WK, de Vos S, Tsukasaki K, et al. Altered apoptosis pathways in mantle cell lymphoma detected by oligonucleotide microarray. *Blood.* 2001;98(3):787-794.
54. Kridel R, Meissner B, Rogic S, et al. Whole transcriptome sequencing reveals recurrent NOTCH1 mutations in mantle cell lymphoma. *Blood.* 2012;119(9):1963-1971.
55. Beà S, Valdés-Mas R, Navarro A, et al. Landscape of somatic mutations and clonal evolution in mantle cell lymphoma. *Proc Natl Acad Sci U S A.* 2013;110(45):18250-18255.
56. Streich L, Sukhanova M, Lu X, et al. Aggressive morphologic variants of mantle cell lymphoma characterized with high genomic instability showing frequent chromothripsis, CDKN2A/B loss, and TP53 mutations: a multi-institutional study. *Genes Chromosomes Cancer.* 2020;59(8):484-494.
57. Ferrero S, Rossi D, Rinaldi A, et al. KMT2D mutations and TP53 disruptions are poor prognostic biomarkers in mantle cell lymphoma receiving high-dose therapy: a FIL study. *Haematologica.* 2020;105(6):1604-1612.
58. Jain P, Kanagal-Shamanna R, Zhang S, et al. Long-term outcomes and mutation profiling of patients with mantle cell lymphoma (MCL) who discontinued ibrutinib. *Br J Haematol.* 2018;183(4):578-587.
59. Agarwal R, Chan-Y-C, Tam CS, et al. Dynamic molecular monitoring reveals that SWI-SNF mutations mediate resistance to ibrutinib plus venetoclax in mantle cell lymphoma. *Nat Med.* 2019;25(1):119-129.
60. Swenson SA, Gilbreath TJ, Vahle H, et al. UBR5 HECT domain mutations identified in mantle cell lymphoma control maturation of B cells. *Blood.* 2020;136(3):299-312.
61. Hershkovitz-Rokah O, Pulver D, Lenz G, et al. Ibrutinib resistance in mantle cell lymphoma: clinical, molecular and treatment aspects. *Br J Haematol.* 2018;181(3):306-319.
62. Zhao X, Lwin T, Silva A, et al. Unification of de novo and acquired ibrutinib resistance in mantle cell lymphoma. *Nat Commun.* 2017;8:14920.
63. Zhao S, Kanagal-Shamanna R, Navsaria L, et al. Efficacy of venetoclax in high risk relapsed mantle cell lymphoma (MCL) - outcomes and mutation profile from venetoclax resistant MCL patients. *Am J Hematol.* 2020;95(6):623-629.
64. Pararajalingam P, Coyle KM, Arthur SE, et al. Coding and noncoding drivers of mantle cell lymphoma identified through exome and genome sequencing. *Blood.* 2020;136(5):572-584.
65. Saba NS, Liu D, Herman SEM, et al. Pathogenic role of B-cell receptor signaling and canonical NF-kappaB activation in mantle cell lymphoma. *Blood.* 2016;128(1):82-92.
66. Papin A, Tessoulin B, Bellanger C, et al. CSF1R and BTK inhibitions as novel strategies to disrupt the dialog between mantle cell lymphoma and macrophages. *Leukemia.* 2019;33(10):2442-2453.
67. Rudelius M, Tillmann Rosenfeldt M, Leich E, et al. Inhibition of focal adhesion kinase overcomes resistance of mantle cell lymphoma to ibrutinib in the bone marrow microenvironment. *Haematologica.* 2018;103(1):116-125.
68. Kurtova AV, Tamayo AT, Ford RJ, et al. Mantle cell lymphoma cells express high levels of CXCR4, CXCR5, and VLA-4 (CD49d): importance for interactions with the stromal microenvironment and specific targeting. *Blood.* 2009;113(19):4604-4613.
69. Bernard S, Danglade D, Gardano L, et al. Inhibitors of BCR signalling interrupt the survival signal mediated by the micro-environment in mantle cell lymphoma. *Int J Cancer.* 2015;136(12):2761-2774.
70. Nomie K. Multiomics analysis of mantle cell lymphoma reveals an immune-cold tumor microenvironment associated with ibrutinib resistance. 2020; ASCO Virtual Scientific Program: American Society of Clinical Oncology.
71. Zhang L, Yao Y, Zhang S, et al. Metabolic reprogramming toward oxidative phosphorylation identifies a therapeutic target for mantle cell lymphoma. *Sci Transl Med.* 2019;11(491):eaau1167.
72. Jain P, Wang M. Mantle cell lymphoma: 2019 update on the diagnosis, pathogenesis, prognostication, and management. *Am J Hematol.* 2019;94(6):710-725.
73. Ruskoné-Fourmestraux A, Delmer A, Lavergne A, et al. Multiple lymphomatous polyposis of the gastrointestinal tract: prospective clinicopathologic study of 31 cases. Groupe D'etude des Lymphomes Digestifs. *Gastroenterology.* 1997;112(1):7-16.
74. Romaguera JE, Medeiros LJ, Hagemeister FB, et al. Frequency of gastrointestinal involvement and its clinical significance in mantle cell lymphoma. *Cancer.* 2003;97(3):586-591.
75. Gill S, Herbert KE, Prince HM, et al. Mantle cell lymphoma with central nervous system involvement: frequency and clinical features. *Br J Haematol.* 2009;147(1):83-88.
76. Cheah CY, George A, Giné E, et al. Central nervous system involvement in mantle cell lymphoma: clinical features,

prognostic factors and outcomes from the European Mantle Cell Lymphoma Network. *Ann Oncol.* 2013;24(8):2119-2123.
77. Ye H, Desai A, Zeng D, et al. Smoldering mantle cell lymphoma. *J Exp Clin Cancer Res*. 2017;36(1):185.
78. Ondrejka SL, Lai R, Smith SD, et al. Indolent mantle cell leukemia: a clinicopathological variant characterized by isolated lymphocytosis, interstitial bone marrow involvement, kappa light chain restriction, and good prognosis. *Haematologica.* 2011;96(8):1121-1127.
79. Abrisqueta P, Scott DW, Slack GW, et al. Observation as the initial management strategy in patients with mantle cell lymphoma. *Ann Oncol.* 2017;28(10):2489-2495.
80. Klapper W, Hoster E, Determann O, et al. Ki-67 as a prognostic marker in mantle cell lymphoma-consensus guidelines of the pathology panel of the European MCL Network. *J Hematop*. 2009;2(2):103-111.
81. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol.* 2014;32(27):3059-3068.
82. van der Velden VH, Hoogeveen PG, de Ridder D, et al. B-cell prolymphocytic leukemia: a specific subgroup of mantle cell lymphoma. *Blood.* 2014;124(3):412-419.
83. Akhter A, Mahe E, Street L, et al. CD10-positive mantle cell lymphoma: biologically distinct entity or an aberrant immunophenotype? Insight, through gene expression profile in a unique case series. *J Clin Pathol.* 2015;68(10):844-848.
84. Liu Z, Dong HY, Gorczyca W, et al. CD5- mantle cell lymphoma. *Am J Clin Pathol.* 2002;118(2):216-224.
85. Fu K, Weisenburger DD, Greiner TC, et al. Cyclin D1-negative mantle cell lymphoma: a clinicopathologic study based on gene expression profiling. *Blood.* 2005;106(13):4315-4321.
86. Xu J, Wang L, Li J, et al. SOX11-negative mantle cell lymphoma: clinicopathologic and prognostic features of 75 patients. *Am J Surg Pathol.* 2019;43(5):710-716.
87. Schlette E, Fu K, Medeiros LJ. CD23 expression in mantle cell lymphoma: clinicopathologic features of 18 cases. *Am J Clin Pathol.* 2003;120(5):760-766.
88. Hoster E, Dreyling M, Klapper W, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. *Blood.* 2008;111(2):558-565.
89. Hoster E, Klapper W, Hermine O, et al. Confirmation of the mantle-cell lymphoma International Prognostic Index in randomized trials of the European Mantle-Cell Lymphoma Network. *J Clin Oncol.* 2014;32(13):1338-1346.
90. Hoster E, Rosenwald A, Berger F, et al. Prognostic value of Ki-67 index, cytology, and growth pattern in mantle-cell lymphoma: results from randomized trials of the European Mantle Cell Lymphoma Network. *J Clin Oncol.* 2016;34(12):1386-1394.
91. Husby S, Ralfkiaer U, Garde C, et al. miR-18b overexpression identifies mantle cell lymphoma patients with poor outcome and improves the MIPI-B prognosticator. *Blood.* 2015;125(17):2669-2677.
92. Jain P, Zhang S, Kanagal-Shamanna R, et al. Clinical and genomic characteristics in de novo blastoid/pleomorphic (MCL) and transformed blastoid/pleomorphic (t-MCL) mantle cell lymphoma (MCL) in the ibrutinib era: comprehensive analysis of 168 patients. *Blood.* 2018;132(suppl 1):1599.
93. Jain P, Wang M. Blastoid mantle cell lymphoma. *Hematol Oncol Clin North Am.* 2020;34(5):941-956.
94. Aukema SM, Hoster E, Rosenwald A, et al. Expression of TP53 is associated with the outcome of MCL independent of MIPI and Ki-67 in trials of the European MCL Network. *Blood.* 2018;131(4):417-420.
95. Clot G, Jares P, Giné E, et al. A gene signature that distinguishes conventional and leukemic nonnodal mantle cell lymphoma helps predict outcome. *Blood.* 2018;132(4):413-422.
96. Hill HA, Qi X, Jain P, et al. Genetic mutations and features of mantle cell lymphoma: a systematic review and meta-analysis. *Blood Adv.* 2020;4(13):2927-2938.
97. Obr A, Klener P, Furst T, et al. A high TP53 mutation burden is a strong predictor of primary refractory mantle cell lymphoma. *Br J Haematol.* 2020;191(5):e103-e106.
98. Nygren L, Baumgartner Wennerholm S, Klimkowska M, et al. Prognostic role of SOX11 in a population-based cohort of mantle cell lymphoma. *Blood.* 2012;119(18):4215-4223.
99. Nordström L, Sernbo S, Eden P, et al. SOX11 and TP53 add prognostic information to MIPI in a homogenously treated cohort of mantle cell lymphoma—a Nordic Lymphoma Group study. *Br J Haematol.* 2014;166(1):98-108.
100. Thorsélius M, Walsh S, Eriksson I, et al. Somatic hypermutation and V(H) gene usage in mantle cell lymphoma. *Eur J Haematol.* 2002;68(4):217-224.
101. Schraders M, Pfundt R, Straatman HMP, et al. Novel chromosomal imbalances in mantle cell lymphoma detected by genome-wide array-based comparative genomic hybridization. *Blood.* 2005;105(4):1686-1693.
102. Sarkozy C, Terré C, Jardin F, et al. Complex karyotype in mantle cell lymphoma is a strong prognostic factor for the time to treatment and overall survival, independent of the MCL international prognostic index. *Genes Chromosomes Cancer.* 2014;53(1):106-116.
103. Greenwell IB, Staton AD, Lee MJ, et al. Complex karyotype in patients with mantle cell lymphoma predicts inferior survival and poor response to intensive induction therapy. *Cancer.* 2018;124(11):2306-2315.
104. Choe J-Y, Yun JY, Na HY, et al. MYC overexpression correlates with MYC amplification or translocation, and is associated with poor prognosis in mantle cell lymphoma. *Histopathology.* 2016;68(3):442-449.
105. Lee J, Zhang LL, Wu W, et al. Activation of MYC, a bona fide client of HSP90, contributes to intrinsic ibrutinib resistance in mantle cell lymphoma. *Blood Adv.* 2018;2(16):2039-2051.
106. Hu Z, Medeiros LJ, Chen Z, et al. Mantle cell lymphoma with MYC rearrangement: a report of 17 patients. *Am J Surg Pathol.* 2017;41(2):216-224.
107. Nagy B, Lundán T, Larramendy ML, et al. Abnormal expression of apoptosis-related genes in haematological malignancies: overexpression of MYC is poor prognostic sign in mantle cell lymphoma. *Br J Haematol.* 2003;120(3):434-441.
108. Wang L, Tang G, Medeiros LJ, et al. MYC rearrangement but not extra MYC copies is an independent prognostic factor in patients with mantle cell lymphoma. *Haematologica.* 2020:doi: 10.3324/haematol.2019.243071.
109. Yang P, Zhang W, Wang J, et al. Genomic landscape and prognostic analysis of mantle cell lymphoma. *Cancer Gene Ther.* 2018;25(5-6):129-140.
110. Mohanty A, Sandoval N, Das M, et al. CCND1 mutations increase protein stability and promote ibrutinib resistance in mantle cell lymphoma. *Oncotarget.* 2016;7(45):73558-73572.
111. Rahal R, Frick M, Romero R, et al. Pharmacological and genomic profiling identifies NF-kappaB-targeted treatment strategies for mantle cell lymphoma. *Nat Med.* 2014;20(1):87-92.
112. von Hohenstaufen KA, Conconi A, de Campos CP, et al. Prognostic impact of monocyte count at presentation in mantle cell lymphoma. *Br J Haematol.* 2013;162(4):465-473.
113. Scott DW, Abrisqueta P, Wright GW, et al. New molecular assay for the proliferation signature in mantle cell lymphoma applicable to formalin-fixed paraffin-embedded biopsies. *J Clin Oncol.* 2017;35(15):1668-1677.
114. Rauert-Wunderlich H, Mottok A, Scott DW, et al. Validation of the MCL35 gene expression proliferation assay in randomized trials of the European Mantle Cell Lymphoma Network. *Br J Haematol.* 2019;184(4):616-624.

115. Holte H, Beiske K, Boyle M, et al. The MCL35 gene expression proliferation assay predicts high-risk MCL patients in a Norwegian cohort of younger patients given intensive first line therapy. *Br J Haematol.* 2018;183(2):225-234.
116. Bomben R, Ferrero S, D'Agaro T, et al. A B-cell receptor-related gene signature predicts survival in mantle cell lymphoma: results from the Fondazione Italiana Linfomi MCL-0208 trial. *Haematologica.* 2018;103(5):849-856.
117. D'Agaro T, Zucchetto A, Vit F, et al. A B-cell receptor-related gene signature predicts response to ibrutinib treatmeant in mantle cell lymphoma cell lines. *Haematologica.* 2019;104(9):e410-e414.
118. Goswami RS, Atenafu EG, Xuan Y, et al. MicroRNA signature obtained from the comparison of aggressive with indolent non-Hodgkin lymphomas: potential prognostic value in mantle-cell lymphoma. *J Clin Oncol.* 2013;31(23):2903-2911.
119. Lamonica D, Graf DA, Munteanu MC, et al. 18F-FDG PET for measurement of response and prediction of outcome to relapsed or refractory mantle cell lymphoma therapy with bendamustine-rituximab. *J Nucl Med.* 2017;58(1):62-68.
120. Kumar A, Sha F, Toure A, et al. Patterns of survival in patients with recurrent mantle cell lymphoma in the modern era: progressive shortening in response duration and survival after each relapse. *Blood Cancer J.* 2019;9(6):50.
121. Visco C, Tisi MC, Evangelista A, et al. Time to progression of mantle cell lymphoma after high-dose cytarabine-based regimens defines patients risk for death. *Br J Haematol.* 2019;185(5):940-944.
122. Le Gouill S, Thieblemont C, Oberic L, et al. Rituximab after autologous stem-cell transplantation in mantle-cell lymphoma. *N Engl J Med.* 2017;377(13):1250-1260.
123. Hoster E, Pott C. Minimal residual disease in mantle cell lymphoma: insights into biology and impact on treatment. *Hematology Am Soc Hematol Educ Program.* 2016;2016(1):437-445.
124. Ferrero S, Dreyling M, North European Mantle Cell Lymphoma. Minimal residual disease in mantle cell lymphoma: are we ready for a personalized treatment approach? *Haematologica.* 2017;102(7):1133-1136.
125. Kolstad A, Bredo Pedersen L, Eskelund CW, et al. Molecular monitoring after autologous stem cell transplantation and preemptive rituximab treatment of molecular relapse; results from the Nordic Mantle Cell Lymphoma Studies (MCL2 and MCL3) with median follow-up of 8.5 years. *Biol Blood Marrow Transplant.* 2017;23(3):428-435.
126. Liu H, Johnson JJ, Koval G, et al. Detection of minimal residual disease following induction immunochemotherapy predicts progression free survival in mantle cell lymphoma: final results of CALGB 59909. *Haematologica.* 2012;97(4):579-585.
127. Ladetto M, Tavarozzi R, Pott C. Minimal residual disease in mantle cell lymphoma: methods and clinical significance. *Hematol Oncol Clin North Am.* 2020;34(5):887-901.
128. Martin P, Maddocks K, Leonard JP, et al. Postibrutinib outcomes in patients with mantle cell lymphoma. *Blood.* 2016;127(12):1559-1563.
129. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. *N Engl J Med.* 2020;382(14):1331-1342.
130. McCulloch R, Smith A, Crosbie, N, et al. Receiving treatment at a specialist centre confers an overall survival benefit for patients with mantle cell lymphoma. *Br J Haematol.* 2019;185(5):1002-1004.
131. Honigberg LA, Smith AM, Sirisawad M, et al. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. *Proc Natl Acad Sci U S A.* 2010;107(29):13075-13080.
132. Harrington BK, Gardner HL, Izumi R, et al. Preclinical evaluation of the novel BTK inhibitor acalabrutinib in canine models of B-cell non-Hodgkin lymphoma. *PLoS One.* 2016;11(7):e0159607.
133. Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N Engl J Med.* 2013;369(6):507-516.
134. Wang ML, Blum KA, Martin P, et al. Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results. *Blood.* 2015;126(6):739-745.
135. Wang M, Rule S, Zinzani PL, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. *Lancet.* 2018;391(10121):659-667.
136. Davids MS, Roberts AW, Seymour JF, et al. Phase I first-in-human study of venetoclax in patients with relapsed or refractory non-Hodgkin lymphoma. *J Clin Oncol.* 2017;35(8):826-833.
137. Eyre TA, Walter HS, Iyengar S, et al. Efficacy of venetoclax monotherapy in patients with relapsed, refractory mantle cell lymphoma after Bruton tyrosine kinase inhibitor therapy. *Haematologica.* 2019;104(2):e68-e71.
138. Jain P, Kanagal-Shamanna R, Zhang S, et al. Outcomes, causes of discontinuation and mutation profile of patients with mantle cell lymphoma who progressed on acalabrutinib. *Blood.* 2018;132(suppl 1):4151.
139. Pham LV, Huang S, Zhang H, et al. Strategic therapeutic targeting to overcome venetoclax resistance in aggressive B-cell lymphomas. *Clin Cancer Res.* 2018;24(16):3967-3980.
140. Martin P, Chadburn A, Christos P, et al. Outcome of deferred initial therapy in mantle-cell lymphoma. *J Clin Oncol.* 2009;27(8):1209-1213.
141. Kumar A, Ying Z, Alperovich A, et al. Clinical presentation determines selection of patients for initial observation in mantle cell lymphoma. *Haematologica.* 2019;104(4):e163-e166.
142. Cohen JB, Han X, Jemal A, et al. Deferred therapy is associated with improved overall survival in patients with newly diagnosed mantle cell lymphoma. *Cancer.* 2016;122(15):2356-2363.
143. Giné E, de Fatima De La Cruz M, Grande C, et al. Efficacy and safety of ibrutinib in combination with rituximab as frontline treatment for indolent clinical forms of mantle cell lymphoma (MCL): preliminary results of Geltamo IMCL-2015 Phase II Trial. *Blood.* 2019;134(suppl 1):752.
144. Romancik JT, Cohen JB. Is limited-stage mantle cell lymphoma curable and how is it best managed? *Hematol Oncol Clin North Am.* 2020;34(5):849-859.
145. Leitch HA, Gascoyne RD, Chhanabhai M, et al. Limited-stage mantle-cell lymphoma. *Ann Oncol.* 2003;14(10):1555-1561.
146. Gerson JN, Handorf E, Villa D, et al. Survival outcomes of younger patients with mantle cell lymphoma treated in the rituximab era. *J Clin Oncol.* 2019;37(6):471-480.
147. Khouri IF, Romaguera J, Kantarjian H, et al. Hyper-CVAD and high-dose methotrexate/cytarabine followed by stem-cell transplantation: an active regimen for aggressive mantle-cell lymphoma. *J Clin Oncol.* 1998;16(12):3803-3809.
148. Chihara D, Cheah CY, Westin JR, et al. Rituximab plus hyper-CVAD alternating with MTX/Ara-C in patients with newly diagnosed mantle cell lymphoma: 15-year follow-up of a phase II study from the MD Anderson Cancer Center. *Br J Haematol.* 2016;172(1):80-88.
149. Romaguera JE, Wang M, Feng L, et al. Phase 2 trial of bortezomib in combination with rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with bortezomib, rituximab, methotrexate, and cytarabine for untreated mantle cell lymphoma. *Cancer.* 2018;124(12):2561-2569.
150. Merli F, Luminari S, Ilariucci F, et al. Rituximab plus Hyper-CVAD alternating with high dose cytarabine and methotrexate for the initial treatment of patients with mantle cell lymphoma, a multicentre trial from Gruppo Italiano Studio Linfomi. *Br J Haematol.* 2012;156(3):346-353.

151. Bernstein SH, Epner E, Unger JM, et al. A phase II multicenter trial of hyperCVAD MTX/Ara-C and rituximab in patients with previously untreated mantle cell lymphoma; SWOG 0213. *Ann Oncol.* 2013;24(6):1587-1593.
152. Geisler CH, Kolstad A, Laurell A, et al. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. *Blood.* 2008;112(7):2687-2693.
153. Eskelund CW, Kolstad A, Jerkeman M, et al. 15-year follow-up of the Second Nordic Mantle Cell Lymphoma trial (MCL2): prolonged remissions without survival plateau. *Br J Haematol.* 2016;175(3):410-418.
154. Delarue R, Haioun C, Ribrag V, et al. CHOP and DHAP plus rituximab followed by autologous stem cell transplantation in mantle cell lymphoma: a phase 2 study from the Groupe d'Etude des Lymphomes de l'Adulte. *Blood.* 2013;121(1):48-53.
155. Hermine O, Hoster E, Walewski J, et al. Addition of high-dose cytarabine to immunochemotherapy before autologous stem-cell transplantation in patients aged 65 years or younger with mantle cell lymphoma (MCL Younger): a randomised, open-label, phase 3 trial of the European Mantle Cell Lymphoma Network. *Lancet.* 2016;388(10044):565-575.
156. Armand P, Redd R, Bsat J, et al. A phase 2 study of rituximab-bendamustine and rituximab-cytarabine for transplant-eligible patients with mantle cell lymphoma. *Br J Haematol.* 2016;173(1):89-95.
157. Chen RW, Li H, Bernstein SH, et al. RB but not R-HCVAD is a feasible induction regimen prior to auto-HCT in front-line MCL: results of SWOG Study S1106. *Br J Haematol.* 2017;176(5):759-769.
158. Wang ML, Jain P, Lee HJ, et al. Frontline treatment with ibrutinib plus rituximab (IR) followed by short course R-Hypercvad/MTX is extremely potent and safe in patients (age ≤ 65 years) with mantle cell lymphoma (MCL)—results of phase-II Window-1 Clinical Trial. *Blood.* 2019;134(suppl 1):3987.
159. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet.* 2013;381(9873):1203-1210.
160. Flinn IW, van der Jagt R, Kahl BS, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. *Blood.* 2014;123(19):2944-2952.
161. Flinn IW, van der Jagt R, Kahl B, et al. First-line treatment of patients with indolent non-Hodgkin lymphoma or mantle-cell lymphoma with bendamustine plus rituximab versus R-CHOP or R-CVP: results of the BRIGHT 5-year follow-up study. *J Clin Oncol.* 2019;37(12):984-991.
162. Rummel MJ, Maschmeyer G, Ganser A, et al. Bendamustine plus rituximab (B-R) versus CHOP plus rituximab (CHOP-R) as first-line treatment in patients with indolent lymphomas: nine-year updated results from the StiL NHL1 study. *J Clin Oncol.* 2017;35(suppl 15):7501.
163. Visco C, Chiappella A, Nassi L, et al. Rituximab, bendamustine, and low-dose cytarabine as induction therapy in elderly patients with mantle cell lymphoma: a multicentre, phase 2 trial from Fondazione Italiana Linfomi. *Lancet Haematol.* 2017;4(1):e15-e23.
164. Robak T, Jin J, Pylypenko H, et al. Frontline bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) versus rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in transplantation-ineligible patients with newly diagnosed mantle cell lymphoma: final overall survival results of a randomised, open-label, phase 3 study. *Lancet Oncol.* 2018;19(11):1449-1458.
165. Robak T, Huang H, Jin J, et al. Bortezomib-based therapy for newly diagnosed mantle-cell lymphoma. *N Engl J Med.* 2015;372(10):944-953.
166. Kluin-Nelemans HC, Hoster E, Hermine O, et al. Treatment of older patients with mantle cell lymphoma (MCL): long-term follow-up of the Randomized European MCL Elderly Trial. *J Clin Oncol.* 2020;38(3):248-256.
167. Ruan J, Martin P, Shah B, et al. Lenalidomide plus rituximab as initial treatment for mantle-cell lymphoma. *N Engl J Med.* 2015;373(19):1835-1844.
168. Ruan J, Martin P, Christos P, et al. Five-year follow-up of lenalidomide plus rituximab as initial treatment of mantle cell lymphoma. *Blood.* 2018;132(19):2016-2025.
169. Albertsson-Lindblad A, Kolstad A, Laurell A, et al. Lenalidomide-bendamustine-rituximab in patients older than 65 years with untreated mantle cell lymphoma. *Blood.* 2016;128(14):1814-1820.
170. Gressin R, Daguindau N, Tempescul A, et al. A phase 2 study of rituximab, bendamustine, bortezomib and dexamethasone for first-line treatment of older patients with mantle cell lymphoma. *Haematologica.* 2019;104(1):138-146.
171. Jain P, Lee HJ, Steiner RE, et al. Frontline treatment with ibrutinib with rituximab (IR) combination is highly effective in elderly (≥65 years) patients with mantle cell lymphoma (MCL)—results from a phase II trial. *Blood.* 2019;134(suppl 1):3988.
172. Rule S, Dreyling M, Goy A, et al. Ibrutinib for the treatment of relapsed/refractory mantle cell lymphoma: extended 3.5-year follow-up from a pooled analysis. *Haematologica.* 2019;104(5):e211-e214.
173. Song Y, Zhou K, Zou D, et al. Safety and activity of the investigational Bruton tyrosine kinase inhibitor zanubrutinib (BGB-3111) in patients with mantle cell lymphoma from a phase 2 trial. *Blood.* 2018;132(suppl 1):148.
174. Tam CS, Anderson MA, Pott C, et al. Ibrutinib plus venetoclax for the treatment of mantle-cell lymphoma. *N Engl J Med.* 2018;378(13):1211-1223.
175. Goy A, Bernstein SH, Kahl BS, et al. Bortezomib in patients with relapsed or refractory mantle cell lymphoma: updated time-to-event analyses of the multicenter phase 2 PINNACLE study. *Ann Oncol.* 2009;20(3):520-525.
176. Fisher RI, Bernstein SH, Kahl BS, et al. Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. *J Clin Oncol.* 2006;24(30):4867-4874.
177. O'Connor OA, Moskowitz C, Portlock C, et al. Patients with chemotherapy-refractory mantle cell lymphoma experience high response rates and identical progression-free survivals compared with patients with relapsed disease following treatment with single agent bortezomib: results of a multicentre Phase 2 clinical trial. *Br J Haematol.* 2009;145(1):34-39.
178. Hess G, Herbrecht R, Romaguera J, et al. Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell lymphoma. *J Clin Oncol.* 2009;27(23):3822-3829.
179. Trněny M, Lamy T, Walewski J, et al. Lenalidomide versus investigator's choice in relapsed or refractory mantle cell lymphoma (MCL-002; SPRINT): a phase 2, randomised, multicentre trial. *Lancet Oncol.* 2016;17(3):319-331.
180. Goy A, Sinha R, Williams ME, et al. Single-agent lenalidomide in patients with mantle-cell lymphoma who relapsed or progressed after or were refractory to bortezomib: phase II MCL-001 (EMERGE) study. *J Clin Oncol.* 2013;31(29):3688-3695.
181. Wang M, Fayad L, Wagner-Bartak N, et al. Lenalidomide in combination with rituximab for patients with relapsed or refractory mantle-cell lymphoma: a phase 1/2 clinical trial. *Lancet Oncol.* 2012;13(7):716-723.

182. Kahl BS, Spurgeon SE, Furman RR, et al. A phase 1 study of the PI3Kdelta inhibitor idelalisib in patients with relapsed/refractory mantle cell lymphoma (MCL). *Blood.* 2014;123(22):3398-3405.
183. McMullen JR, Boey EJH, Ooi JYY, et al. Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling. *Blood.* 2014;124(25):3829-3830.
184. Tuomi JM, Xenocostas A, Jones DL. Increased susceptibility for atrial and ventricular cardiac arrhythmias in mice treated with a single high dose of ibrutinib. *Can J Cardiol.* 2018;34(3):337-341.
185. Cheng C, Woronow D, Nayernama A, et al. Ibrutinib-associated ventricular arrhythmia in the FDA Adverse Event Reporting System. *Leuk Lymphoma.* 2018;59(12):3016-3017.
186. Levade M, David E, Garcia C, et al. Ibrutinib treatment affects collagen and von Willebrand factor-dependent platelet functions. *Blood.* 2014;124(26):3991-3995.
187. Chang BY, Francesco M, De Rooij MFM, et al. Egress of CD19(+)CD5(+) cells into peripheral blood following treatment with the Bruton tyrosine kinase inhibitor ibrutinib in mantle cell lymphoma patients. *Blood.* 2013;122(14):2412-2424.
188. Rule S, Jurczak W, Jerkeman M, et al. Ibrutinib versus temsirolimus: 3-year follow-up of patients with previously treated mantle cell lymphoma from the phase 3, international, randomized, open-label RAY study. *Leukemia.* 2018;32(8):1799-1803.
189. Rule S, Dreyling M, Goy A, et al. Outcomes in 370 patients with mantle cell lymphoma treated with ibrutinib: a pooled analysis from three open-label studies. *Br J Haematol.* 2017;179(3):430-438.
190. Kamel S, Horton L, Ysebaert L, et al. Ibrutinib inhibits collagen-mediated but not ADP-mediated platelet aggregation. *Leukemia.* 2015;29(4):783-787.
191. Dobie G, Kuriri FA, Omar MMA, et al. Ibrutinib, but not zanubrutinib, induces platelet receptor shedding of GPIb-IX-V complex and integrin alphaIIbbeta3 in mice and humans. *Blood Adv.* 2019;3(24):4298-4311.
192. Caron F, Leong DP, Hillis C, et al. Current understanding of bleeding with ibrutinib use: a systematic review and meta-analysis. *Blood Adv.* 2017;1(12):772-778.
193. Lampson BL, Yu L, Glynn RJ, et al. Ventricular arrhythmias and sudden death in patients taking ibrutinib. *Blood.* 2017;129(18):2581-2584.
194. Guha A, Derbala MH, Zhao Q, et al. Ventricular arrhythmias following ibrutinib initiation for lymphoid malignancies. *J Am Coll Cardiol.* 2018;72(6):697-698.
195. Leong DP, Caron F, Hillis C, et al. The risk of atrial fibrillation with ibrutinib use: a systematic review and meta-analysis. *Blood.* 2016;128(1):138-140.
196. Dickerson T, Wiczer T, Waller A, et al. Hypertension and incident cardiovascular events following ibrutinib initiation. *Blood.* 2019;134(22):1919-1928.
197. Wang ML, Lee H, Chuang H, et al. Ibrutinib in combination with rituximab in relapsed or refractory mantle cell lymphoma: a single-centre, open-label, phase 2 trial. *Lancet Oncol.* 2016;17(1):48-56.
198. Jain P, Romaguera J, Srour SA, et al. Four-year follow-up of a single arm, phase II clinical trial of ibrutinib with rituximab (IR) in patients with relapsed/refractory mantle cell lymphoma (MCL). *Br J Haematol.* 2018;182(3):404-411.
199. Jerkeman M, Eskelund CW, Hutchings M, et al. Ibrutinib, lenalidomide, and rituximab in relapsed or refractory mantle cell lymphoma (PHILEMON): a multicentre, open-label, single-arm, phase 2 trial. *Lancet Haematol.* 2018;5(3):e109-e116.
200. Cervantes-Gomez F, Lamothe B, Woyach JA, et al. Pharmacological and protein profiling suggests venetoclax (ABT-199) as optimal partner with ibrutinib in chronic lymphocytic leukemia. *Clin Cancer Res.* 2015;21(16):3705-3715.
201. Martin P, Bartlett NL, Blum KA, et al. A phase 1 trial of ibrutinib plus palbociclib in previously treated mantle cell lymphoma. *Blood.* 2019;133(11):1201-1204.
202. Lionakis MS, Dunleavy K, Roschewski M, et al. Inhibition of B cell receptor signaling by ibrutinib in primary CNS lymphoma. *Cancer Cell.* 2017;31(6):833-843.
203. Grommes C, Pastore A, Palaskas N, et al. Ibrutinib unmasks critical role of Bruton tyrosine kinase in primary CNS lymphoma. *Cancer Discov.* 2017;7(9):1018-1029.
204. Grommes C, Tang SS, Wolfe J, et al. Phase 1b trial of an ibrutinib-based combination therapy in recurrent/refractory CNS lymphoma. *Blood.* 2019;133(5):436-445.
205. Bernard S, Goldwirt L, Amorim S, et al. Activity of ibrutinib in mantle cell lymphoma patients with central nervous system relapse. *Blood.* 2015;126(14):1695-1698.
206. Kanagal-Shamanna R, Jain P, Patel KP, et al. Targeted multigene deep sequencing of Bruton tyrosine kinase inhibitor-resistant chronic lymphocytic leukemia with disease progression and Richter transformation. *Cancer.* 2019;125(4):559-574.
207. Dobrovolsky D, Wang ES, Morrow S, et al. Bruton tyrosine kinase degradation as a therapeutic strategy for cancer. *Blood.* 2019;133(9):952-961.
208. Ming M, Wu W, Xie B, et al. XPO1 inhibitor selinexor overcomes intrinsic ibrutinib resistance in mantle cell lymphoma via nuclear retention of IkappaB. *Mol Cancer Ther.* 2018;17(12):2564-2574.
209. Barf T, Covey T, Izumi R, et al. Acalabrutinib (ACP-196): a covalent Bruton tyrosine kinase inhibitor with a differentiated selectivity and in vivo potency profile. *J Pharmacol Exp Ther.* 2017;363(2):240-252.
210. Bye AP, Unsworth AJ, Desborough MJ, et al. Severe platelet dysfunction in NHL patients receiving ibrutinib is absent in patients receiving acalabrutinib. *Blood Adv.* 2017;1(26):2610-2623.
211. Wang M, Rule S, Zinzani PL, et al. Long-term follow-up of acalabrutinib monotherapy in patients with relapsed/refractory mantle cell lymphoma. *Blood.* 2018;132(suppl 1):2876-2876.
212. Tam CS, Trotman J, Opat S, et al. Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL. *Blood.* 2019;134(11):851-859.
213. Song Y, Zhou K, Zou D, et al. Treatment of patients with relapsed or refractory mantle cell lymphoma with zanubrutinib, a selective inhibitor of Bruton's tyrosine kinase. *Clin Cancer Res.* 2020;26(16):4216-4224.
214. Rule SA, Cartron G, Fegan C, et al. Long-term follow-up of patients with mantle cell lymphoma (MCL) treated with the selective Bruton's tyrosine kinase inhibitor tirabrutinib (GS/ONO-4059). *Leukemia.* 2020;34(5):1458-1461.
215. Song Y, Song Y, Liu L, et al. Safety and efficacy of orelabrutinib monotherapy in Chinese patients with relapsed or refractory mantle cell lymphoma: a multicenter, open-label, phase II study. *Blood.* 2019;134(suppl 1):755.
216. Mato AR, Flinn IW, Pagel JM, et al. Results from a first-in-human, proof-of-concept phase 1 trial in pretreated B-cell malignancies for Loxo-305, a next-generation, highly selective, non-covalent BTK inhibitor. *Blood.* 2019;134(suppl 1):501.
217. McCulloch R, Visco C, Eyre TA, et al. Efficacy of R-BAC in relapsed, refractory mantle cell lymphoma post BTK inhibitor therapy. *Br J Haematol.* 2020;189(4):684-688.
218. Le Gouill S, Kröger N, Dhedin N, et al. Reduced-intensity conditioning allogeneic stem cell transplantation for relapsed/refractory mantle cell lymphoma: a multicenter experience. *Ann Oncol.* 2012;23(10):2695-2703.
219. Robinson SP, Boumendil A, Finel H, et al. Long-term outcome analysis of reduced-intensity allogeneic stem cell transplantation in patients with mantle cell lymphoma: a retrospective study from the EBMT Lymphoma Working Party. *Bone Marrow Transplant.* 2018;53(5):617-624.
220. Lin RJ, Ho C, Hilden PD, et al. Allogeneic haematopoietic cell transplantation impacts on outcomes of mantle cell lymphoma with TP53 alterations. *Br J Haematol.* 2019;184(6):1006-1010.

221. Dreger P, Michallet M, Bosman P, et al. Ibrutinib for bridging to allogeneic hematopoietic cell transplantation in patients with chronic lymphocytic leukemia or mantle cell lymphoma: a study by the EBMT Chronic Malignancies and Lymphoma Working Parties. *Bone Marrow Transplant.* 2019;54(1):44-52.
222. Wang M, Gordon LI, Palomba ML, et al. Safety and preliminary efficacy in patients (pts) with relapsed/refractory (R/R) mantle cell lymphoma (MCL) receiving lisocabtagene maraleucel (Liso-cel) in TRANSCEND NHL 001. *J Clin Oncol.* 2019;37(suppl 15):7516.
223. Liu E, Marin D, Banerjee P, et al. Use of CAR-transduced natural killer cells in CD19-positive lymphoid tumors. *N Engl J Med.* 2020;382(6):545-553.
224. Brudno JN, Lam N, Vanasse D, et al. Safety and feasibility of anti-CD19 CAR T cells with fully human binding domains in patients with B-cell lymphoma. *Nat Med.* 2020;26(2):270-280.
225. Qin H, Dong Z, Wang X, et al. CAR T cells targeting BAFF-R can overcome CD19 antigen loss in B cell malignancies. *Sci Transl Med.* 2019;11(511):eaaw9414.
226. Ormhøj M, Scarfò I, Cabral ML, et al. Chimeric antigen receptor T cells targeting CD79b show efficacy in lymphoma with or without cotargeting CD19. *Clin Cancer Res.* 2019;25(23):7046-7057.
227. Chihara D, Asano N, Ohmachi K, et al. Ki-67 is a strong predictor of central nervous system relapse in patients with mantle cell lymphoma (MCL). *Ann Oncol.* 2015;26(5):966-973.
228. Ferrer A, Bosch F, Villamor N, et al. Central nervous system involvement in mantle cell lymphoma. *Ann Oncol.* 2008;19(1):135-141.
229. Romaguera JE, Fayad L, Rodriguez MA, et al. High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. *J Clin Oncol.* 2005;23(28):7013-7023.
230. Romaguera JE, Fayad LE, Feng L, et al. Ten-year follow-up after intense chemoimmunotherapy with Rituximab-HyperCVAD alternating with Rituximab-high dose methotrexate/cytarabine (R-MA) and without stem cell transplantation in patients with untreated aggressive mantle cell lymphoma. *Br J Haematol.* 2010;150(2):200-208.
231. Geisler CH, Kolstad A, Laurell A, et al. Nordic MCL2 trial update: six-year follow-up after intensive immunochemotherapy for untreated mantle cell lymphoma followed by BEAM or BEAC + autologous stem-cell support: still very long survival but late relapses do occur. *Br J Haematol.* 2012;158(3):355-362.

11 Nodal Peripheral T-Cell Lymphoma

Ranjit Nair
Francisco Vega
Swaminathan P. Iyer

KEY CONCEPTS

- Nodal peripheral T-cell lymphomas (PTCLs) are categorized into three basic subtypes: systemic anaplastic large-cell lymphoma (sALCL) anaplastic lymphoma kinase ALK (+) and ALK (-), angioimmunoblastic T-cell lymphoma; and peripheral T-cell lymphoma not otherwise specified (PTCL-NOS).
- The prognosis for patients with nodal PTCLs remains suboptimal compared with its aggressive B cell counterparts despite the use of aggressive chemotherapy. The introduction of novel agents such as CD30(+) antibody–drug conjugates and histone deacetylase inhibitors have brought unprecedented enthusiasm in bench to bedside research for this disease.
- It is recently recognized that angioimmunoblastic T–cell lymphoma has its cell of origin from CD4+ T-follicular helper (TFH) cells and as a result a third of the PTCL-NOS are more aptly diagnosed as angioimmunoblastic T-cell lymphoma because of the expression of TFH markers.
- Understanding of the genomic landscape has recently helped to identify better prognostic markers. Whereas the presence of ALK or DUSP-22 in sALCL is associated with favorable prognosis, expression of GATA-3 or GATA-3 target genes in PTCL-NOS is associated with a worse prognosis.
- Except for ALK (+) ALCL and ALK (-) ALCL with DUSP22 rearrangement, patients with PTCL generally have a chemoresistance, short-term remission, and early relapse when treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like chemotherapy.
- Combination therapies using novel agents holds the future to improve clinical response and outcomes in both frontline and relapsed or refractory disease. Whereas BV-CHP (brentuximab vedotin plus cyclophosphamide, doxorubicin, prednisone) is currently the standard of care treatment in patients with CD30(+) PTCLs, Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), with or without the addition of etoposide, is commonly used in those with CD30(-) PTCLs.

Peripheral T-cell lymphoma (PTCL) comprises a rare and heterogeneous group of mature T- and natural killer (NK)-cell neoplasms with diverse clinical presentation, response to treatment, and prognosis.[1] PTCLs have historically been a challenging disease because of their rarity, often grouped by their shared immunophenotype of neoplastic T-cells, despite the biologically differences and lack of standard treatment approaches.[2] Getting a second opinion and reviews by expert hematopathologists improve the accuracy of subtyping, and referral to academic or specialty centers is recommended. Even though there is no current standard of care for patients with PTCL, first-line approaches still revolve around anthracycline-based therapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like combination chemotherapies. Although many patients initially respond to induction chemotherapy, responses are often brief, and many patients relapse or become refractory to treatment. The introduction of agents based on the novel targets such as CD30 and brentuximab vedotin (BV) has given us tremendous hope recently leading to the only Food and Drug Administration (FDA)–approved chemotherapy combination for first-line treatment. Significant advances in our understanding of this disease biology have also led to revisions in the classification of mature T-cell and NK-cell neoplasms and introduction of provisional entities. According to the 2016 World Health Organization classification (WHO) classification of lymphoid neoplasms, based on morphologic, immunophenotypic, molecular, and clinical features,

TABLE 11–1 Summary of 2016 World Health Organization Classification of Mature T-Cell and Natural Killer Cell Neoplasms[a]

Leukemic	Nodal	Extranodal	Cutaneous
T-cell prolymphocytic leukemia	PTCL-NOS	Extranodal NK-/T-cell lymphoma, nasal type	Subcutaneous panniculitis-like T-cell lymphoma
T-cell large granular lymphocytic leukemia	AITL	Enteropathy-associated T-cell lymphoma	Mycosis fungoides
Chronic lymphoproliferative disorder of NK cells	**Follicular T-cell lymphoma[b]**	Monomorphic epitheliotropic intestinal T-cell lymphoma[b]	Sezary syndrome
Aggressive NK-cell leukemia	**Nodal peripheral T-cell lymphoma with TFH phenotype[b]**	Hepatosplenic T-cell lymphoma	Primary cutaneous CD30(+) T-cell lymphoproliferative disorders
Adult T-cell leukemia/lymphoma	Anaplastic large-cell lymphoma, ALK (+)	Systemic EBV (+) T-cell lymphoma of childhood[b]	Lymphomatoid papulosis
	Anaplastic large-cell lymphoma, ALK (-)[b]	Hydroa vacciniforme–like lymphoproliferative disorder[b]	Primary cutaneous anaplastic large-cell lymphoma
		Breast implant–associated anaplastic large-cell lymphoma[b]	Primary cutaneous γδ T-cell lymphoma
		Indolent T-cell lymphoproliferative disorder of the GI tract[b]	**Primary cutaneous CD8(+) aggressive epidermotropic cytotoxic T-cell lymphoma**
			Primary cutaneous CD4(+) small-/medium T-cell lymphoproliferative disorder[b]

[a]Provisional entities are listed in bold.
[b]Changes from the 2008 classification.
AITL, angioimmunoblastic T-cell lymphoma; ALK, anaplastic lymphoma kinase; EBV, Epstein-Barr virus; GI, gastrointestinal; NK, natural killer cell; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified.

there are total 19 subtypes of mature T-cell and NK-cell neoplasms and eight provisional entities that are currently recognized (Table 11–1). PTCLs, although uncommon in young individuals, can be diagnosed as early as childhood, and rates continue to increase until about age 70 years.[3]The most common subtype of nodal PTCL, aside from mycosis fungoides (MF), is PTCL not otherwise specified (PTCL-NOS) followed by systemic anaplastic large-cell lymphoma (sALCL), and angioimmunoblastic T-cell lymphoma (AITL). T-cell acute lymphoblastic leukemia/lymphoma are derived from T-cell precursors (eg, thymocytes) is not included in the mature lymphoma group and hence will not be discussed in this chapter.[4,5]

EPIDEMIOLOGY

PTCL represent approximately 10% to 15% of non-Hodgkin lymphomas (Fig. 11–1). These are further subclassified as nodal, extranodal, leukemic, and cutaneous T-cell lymphomas. The most common histologic subtype is PTCL-NOS followed by AITL and sALCL anaplastic lymphoma kinase (ALK) (+) and ALK (-). These three accounts for approximately two-thirds of the T-cell lymphomas.[6] With better diagnostic markers and molecular criteria, the combined entity of three nodal lymphomas expressing signatures typical for T-follicular helper (TFH) cells, including AITL, nodal PTCL with a TFH phenotype, and follicular T-cell lymphoma, is starting to outnumber the PTCL-NOS cases.[7,8]

There is significant geographic variation in the incidence and prevalence of the different type of PTCL, which is attributed to a combination of genetic and environmental factors. AITL tends to be more frequent in Europe (28.7% of all PTCLs) followed by Asia (17.9%) and North America (16.0%).[9] PTCL-NOS is more common in in Western countries than Asian countries (30% vs 20%–25% of PTCL). sALCL tends to be more common the United States (24% of PTCL) and with less incidence in Europe and Asia.[10] Other PTCL subtypes—adult T-Cell Lymphoma/Leukemia (ATLL) and extranodal natural killer/T-cell lymphoma (ENKL)—occur at higher frequencies in Asia and Central and South America than in Western countries, paralleling the distribution of human T-lymphotropic virus 1 (HTLV1) and the Epstein-Barr virus (EBV) respectively. Enteropathy-associated T-cell lymphoma (EATL) is seen more in Northern Europe, where celiac disease is more prevalent.[6,11]

INCIDENCE AND OUTCOMES

According to the US Surveillance Epidemiology and End Registry, the age-adjusted incidence of PTCL is fewer than one case per 100,000 people in the United States, with approximately over 10,000 new cases diagnosed each year.[3] In recent years, although the

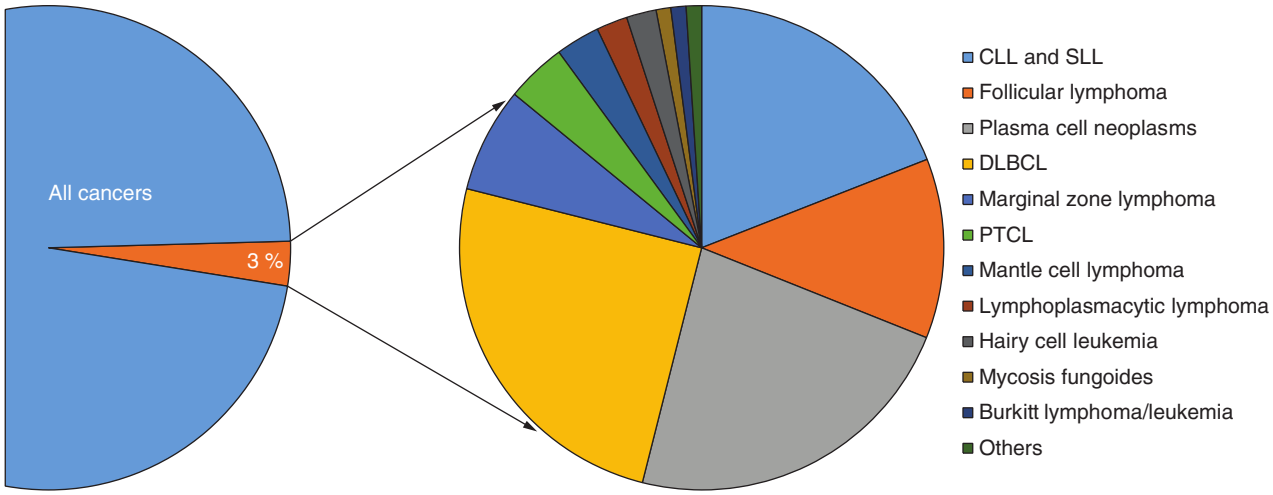


FIGURE 11–1 Distribution of subtypes of mature non- Hodgkin lymphoid neoplasms. CLL, chronic lymphocytic leukemia. DLBCL, diffuse large B- cell lymphoma; PTCL, peripheral T-cell lymphoma; SLL, small lymphocytic lymphoma. (Data from Teras LR, DeSantis CE, Cerhan JR, et al: 2016 US lymphoid malignancy statistics by World Health Organization subtypes, *CA Cancer J Clin* 2016 Nov 12;66(6):443-459.)

incidence rates of many B-cell lymphomas have begun to decline or plateau at best, the incidence rates for T-cell lymphomas have continued to rise globally. This is likely a consequence of the aging population, improved health care access, and improved diagnostics tools. Worldwide there is still no consensus on first-line or salvage therapies for patients because of the rarity of the disease and the lack of randomized clinical trials, which translates to worse overall survival (OS) among patients with nodal PTCL (36%–56% 5- year survival). In contrast, the outcomes for MF are overall better (79%–92% 5- year survival rate).[3]

PATHOGENESIS AND HISTOLOGY

The exact pathogenesis of PTCL is largely elusive, and the putative cellular derivation of the different pathological subtypes remains poorly characterized. There have been significant attempts with gene expression profiling (GEP; RNA sequencing, microarray analysis, micro-RNA profiling, mutation analysis, copy number alterations) and epigenetics analysis to help identify new biomarkers and mutations.[12–15] PTCLs are derived from mature T-cells, and deregulation at T-cell differentiation or maturation level is a critical event in lymphomagenesis. The pathogenic events in general can be classified into three categories:

1. Intrinsic or recurrent molecular events in the pivotal intracellular signaling pathways
   a. TCR/CD3 pathway
   b. Notch pathway
   c. Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway
   d. RHOA pathway
   e. Phosphoinositide 3-kinase (PI3K) pathway
   f. Epigenetic regulation
   g. AP-1–mediated transcriptional programs
2. Extrinsic or microenvironmental changes
3. Virus-mediated (eg, EBV, HTLV-1–induced T-cell neoplastic transformation)[16]

ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA

AITL is characterized by its cellular derivation from CD4+ TFH cells, which is the effector T-cell subset, and the diagnostic criteria remain unchanged in the 2016 WHO classification. TFH cells are a critical peripheral checkpoint for B-cell activation and differentiation within a germinal center.[17] Dysregulated TFH cell that triggers the transformation to AITL is proposed to be the cell of origin (COO) with subsequent disruption of immunologic tolerance and uncontrolled constitutively activated immune system presenting as autoimmune phenomenon.[18] The tumor cells retain characteristic phenotype of TFH cells with the expression of markers PD-1 (programmed death-1), BCL6, CXCL13, CD10, ICOS, SAP, and CXCR5, CD279 (PD-1, PDCD1) CD40L, and NFATC1. A subset of what used to be classified as PTCL-NOS on molecular analysis expresses TFH-associated markers and shares recurrent genetic abnormalities with AITL. This has been given provisional category in WHO 2016 called nodal T-cell lymphomas with a TFH phenotype. Another category called follicular T-cell lymphoma has also been added to this group, which primarily involves the

follicles and could resemble its B cell counterpart–the follicular lymphoma (see Table 11–1). GEP has shown that the malignant TFH cell often carry mutations in the genes encoding methyl cytosine dioxygenase TET2 (47%–73%), isocitrate dehydrogenase 2 (IDH2) (20%–40%), DNA methyltransferase 3A (DNMT3A) (33%), or RHOA-G17V mutation (~60%).[19] CXCL13 produced by AITL cells has a known association with hypergammaglobulinemia and autoimmune hemolytic anemia because this protein stimulates B-cell expansion and plasmacytic differentiation in the tumor microenvironment.[20,21] EBV-positive clonal/oligoclonal B-lymphoblastoid cells are present in majority of AITL cases, but their exact pathogenetic role is elusive. Given that EBV virtually affects only B-cell population, it is postulated to rather play a protumorigenic role in the microenvironment than a primary role in the lymphomagenesis.

Microscopically (Fig. 11–2A–D), there is a polymorphic immune infiltrate in lymph node specimens with effacement of germinal centers and prominent neovascularization, with a rich microenvironment composed not only of tumor cells but also of small reactive lymphocytes, histiocytes, eosinophils, an expanded follicular dendritic cell meshwork, and prominent endothelial venules.[22] In addition to the tumor cells expressing TFH cell markers, T-cell receptor gene rearrangements (TCRs) are present in about 80% of the tumor cells, and trisomy of chromosomes 3 and 5 are the commonly observed cytogenetic abnormality. EBV positivity is universally present in the large B immunoblasts in the lymph node but not in the neoplastic T-cells.[23]

Peripheral T-Cell Lymphoma Not Otherwise Specified

PTCL-NOS is a heterogeneous entity and includes a watershed area of different mature T-cell neoplasms that do not have a characteristic immunophenotype or do not meet the criteria of a specific PTCL entity. Despite the absence of a distinct COO or recurrent cytogenetic abnormality, GEP studies have defined two novel molecular clusters in this group with distinct features using PTCL-GATA3 and PTCL-TBX21. The cluster with high expression of GATA3-related target genes (CCR4, IL18RA, CXCR7, and IK) had poorer outcomes with the 5-year OS of nearly half of the TBX21 cluster (19% vs 38%). Within the TBX21 subgroup, expression of cytotoxic CD8+ T-cells is associated with adverse outcomes.[24] Immunohistochemistry (IHC) algorithms are currently being identified to distinguish these two subtypes in paraffin tissue using antibodies to key transcriptional factors (GATA3 and TBX21) and their target proteins (CCR4 and CXCR3).[25]

The PTCL-NOS diagnosis is known to have the highest rate of dilemma and discordance rate among pathologists. This reflects the heterogeneity and the presence of different PTCL subtypes at different stages of disease progression.[6] One third of PTCL-NOS case are more aptly diagnosed as AITL because of the expression of TFH markers. The lymph nodes usually appear diffusely effaced with pleomorphic cells, which are medium-sized or large cells with irregular nuclei containing prominent nucleoli and many mitoses. There is often presence of hyperplastic endothelial venules with an admixture of eosinophils, plasma cells, small lymphocytes, B cells, histiocytes, and activated macrophages. A morphologic variant of PTCL-NOS that is known to have a favorable prognosis called lymphoepithelioid cell lymphoma (Lennert's lymphoma) presents with more abundant epithelioid histiocytes and neoplastic cells that portray a CD8-positive cytotoxic (TIA1, granzyme B, and/or perforin) phenotype.[26]

In PTCL-NOS, there is variable loss of expression of T-cell–associated antigens, more frequently CD5 or CD7 and rarely CD2 or CD3. In majority of the cases, T-cells express CD4, αβ-TCR (TCR-β positive), or both than in minority with CD8 and/or γδ phenotype. CD30 is less commonly expressed, and its prognostic impact is currently unclear. Half of PTCL-NOS cases are EBV-positive, an observation shown to be associated with a poor survival.[7] Other markers that are rarely expressed include B-cell markers such as CD20, CD19, CD79a, or PAX5. A recent genome-wide next-generation sequencing analysis of PTCL-NOS led to the identification of recurrent translocations involving rearrangements of the *TP63* gene (a TP53 family member) with *TBL1XR1* and *ATXN1* genes (10% cases).[27] These gene fusions encode proteins that inhibit the p53 pathway and are associated with adverse clinical outcomes. Screening a large series of cases for TP63 rearrangements by fluorescence in situ hybridization showed similar frequencies in ALK (-) ALCL (12.5%) and primary cutaneous ALCL (10.5%).[27]

Systemic Anaplastic Large-Cell Lymphoma

sALCL shows ALK expression in more than 30% of cases.[28] The translocation leads to the expression of the constitutively active NPM-ALK kinase, triggering downstream signaling pathways that regulate cell growth, survival, and malignant transformation.[29,30] This leads to a downward cascade involving STAT3/5, CEBPB, and AP1.[31–33] In sALCL, GEP studies of tumor cells to identify COO have largely been largely unsuccessful. A recent gene set enrichment analysis points to a Th17 origin, which is a lineage of interleukin (IL)-17–producing CD4+ T helper cell program.[34,35] Whether this Th17 expression is from an already known recurrent chromosomal rearrangements involving the ALK

gene with nucleophosmin (NPM1) (t(2;5)(p23q35)) is unclear.[36] GEP indicates that ALK (+) ALCL and ALK (-) ALCL display similar genome signatures, thus suggesting a common COO.[35] ALK (-) subtype was a provisional entity in the WHO 2008 and is now a recognized entity in the 2016 WHO classification. The prognosis is intermediate between ALK (+) ALCL and PTCL. One third of ALK (-) ALCL harbors the DUSP22-IRF4 locus on a 6p25.3 rearrangement and has a favorable prognosis with survival comparable to ALK (+) ALCL

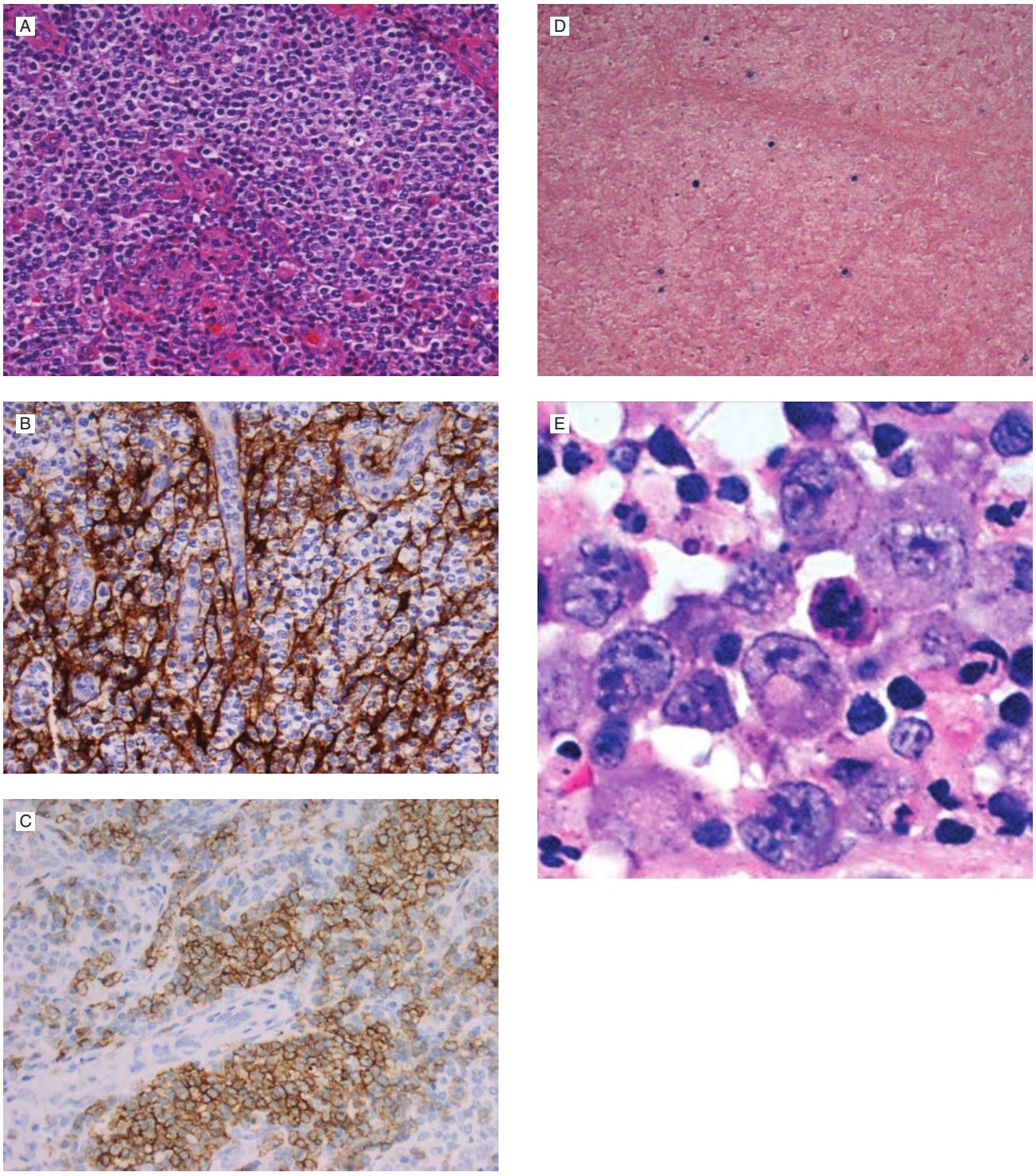


FIGURE 11–2 Microscopic histopathology of peripheral T-cell lymphoma. Angioimmunoblastic T-cell lymphoma (AITL): AITL (**A**; hematoxylin and eosin [H&E] stain), immunohistochemistry (IHC) for CD21 (**B**), ICH for PD1 (**C**), and in situ hybridization for Epstein-Barr virus (EBV)-encoded RNA (**D**). Systemic anaplastic large-cell lymphoma (sALCL): sALCL (**E**; H&E), IHC for CD30

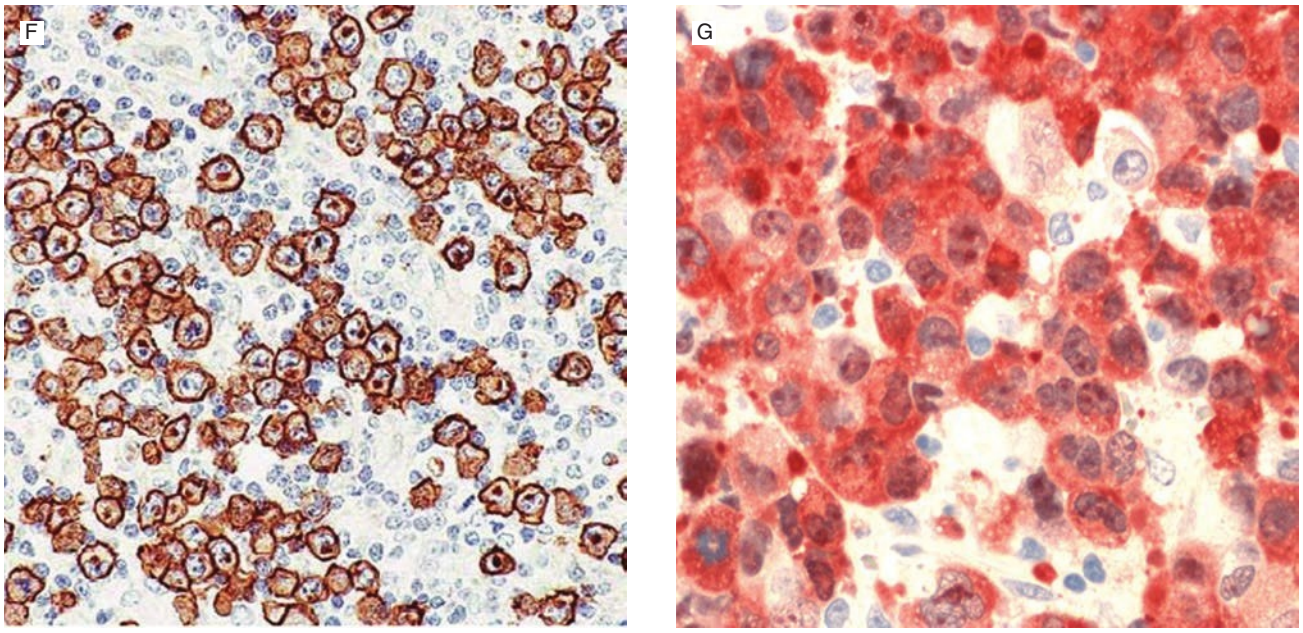


FIGURE 11–2 (Continued) (F), and IHC for anaplastic lymphoma kinase 1 (ALK1) (G). (Used with permission from Dr. Francisco Vega, MDACC.)

counterpart. About 8% to 12% cases demonstrate the TP53 homolog TP63 on 3q28 and are associated with an aggressive clinical behavior and poor outcomes (5-year OS rate, 17%).[37] The subset of ALK(-) ALCL that does not carry none of the above rearrangements is termed triple-negative ALCL (ALK, TP63 and DUSP22 negative) and carries an intermediate prognosis (5-year OS rate, 33%), poorer than ALK(+) ALCL and DUSP22-rearranged ALCL but better than TP63-rearranged ALCL and similar to ALK(-) ALCL as a whole.[37]

The majority of the cases of ALCL display a classical morphology under the microscope characterized by the presence of large cells with abundant cytoplasm (see Figure 11–2E–G). The common or classic type is characterized by sheets of large pleomorphic tumor cells and the presence of hallmark cells with eccentric kidney-shaped nucleus (with multiple prominent nucleoli) and a prominent and pale Golgi region (paranuclear halo). Variations of multinucleated cells, Reed-Sternberg–like cells, and doughnut cells that often preferentially involve the lymph node sinuses and paracortex are often seen. Uncommon morphologic variants include small-cell, monomorphic, lymphohistiocytic, neutrophil-rich, clear cell, signet ring cell, giant cell–rich, Hodgkin-like, and sarcomatoid variants. On IHC, CD30 is universally and strongly expressed in a membrane and Golgi pattern, with frequent expression of TIA1, granzyme B, perforin, EMA, and low expression of CD8 and CD56. Cells are negative for B-cell surface markers (CD19, CD20, CD22). There is heterogenous expression of T-cell antigens and in some cases is defined as a null group none of the lineage-specific markers are detected. Whereas the majority of ALCL have clonally rearranged TCR genes, roughly 10% in the null group have no rearrangement of TCR.[10,38,39]

CLINICAL COURSE

The clinical presentation of mature T-cell lymphomas is extremely variable and largely depends on the subtype (Table 11–2). PTCL-NOS, AITL, and ALCL

TABLE 11–2 Five-Year Outcomes by Different Peripheral T-Cell Lymphoma Subtypes

	ITCP: 5-Year FFS (%)	ITCP: 5-Year OS (%)	BCCA: 5-Year FFS (%)	BCCA: 5-Year OS (%)
AITL	18	32	13	36
PTCL-NOS	20	32	29	35
ALK (-) ALCL	36	49	28	43
ALK (+) ALCL	60	70		

AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; FFS, failure-free survival; ITCP, International T-Cell Project; OS, overall survival; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified.

all often present with generalized lymphadenopathy and B symptoms and can involve extranodal sites, including the skin, gastrointestinal tract, liver, spleen, and bone marrow. Patients commonly present with advanced-stage disease (stages III and IV; AITL, 89%; PTCL-NOS, 69%; ALK (+) ALCL, 65%; ALK (-) ALCL, 58%).[10] It is common for PTCL to be mistaken for other types of lymphoma, which often can lead to a delay in diagnosis because of suboptimal rates of concordant pathological diagnosis.[40] Infrequently, patients present with or develop during the course features of hemophagocytic lymphohistiocytosis (HLH) and can have a high fatality rate. In one series, 23% patients had PTCL was associated with lymphoma-associated hemophagocytic syndrome, PTCL-NOS accounted for the majority.[41]

Angioimmunoblastic T-Cell Lymphoma

Patients with AITL are typically middle-aged to older adults. There is a nearly equal incidence between both genders. The majority of patients present with an aggressive clinical course characterized by generalized lymphadenopathy, B symptoms (fevers, unintentional weight loss, drenching night sweats), bone marrow involvement, and hepatosplenomegaly. There are anecdotal reports of a patients presenting with a smoldering course with waxing and waning lymphadenopathy. This is one of the commonest lymphomas that masquerades as other pathologic entities, posing a diagnostic challenge and presenting with atypical symptoms. This includes symptoms of immunodeficiency, opportunistic infections, skin rash, and hemolytic anemia.[42] Skin rash can be a presenting symptom, usually pruritic. Rash is seen in 20% to 50% of patients with AITL, ranging from urticarial lesions to nodular tumors. Hematologic abnormalities (eg, Coombs-positive hemolytic anemia and polyclonal hypergammaglobulinemia) can be seen in up to 45% of cases.[9]

Peripheral T-Cell Lymphoma Not Otherwise Specified

The median age of the patients with PTCL-NOS is 60 years. The male-to-female ratio is 2 to 1, and it has an aggressive clinical course .Although the majority of patients have nodal sites of involvement (87%), extranodal disease can be present in 62%.[43] Biochemical abnormalities include the presence of circulating tumor cells (10%); elevated serum β2-microglobulin (36%), C-reactive protein (50%), or calcium (5%) levels; hypogammaglobulinemia (9%); monoclonal serum immunoglobulin (4%); hemolytic anemia (3%); and hemophagocytic syndrome (3%).[43]

Anaplastic Large-Cell Lymphoma

ALK (+) ALCL is clinically distinctive with a more common incidence in younger patients (median age, 34 years).[10,44,45] Both ALK (+) and ALK (-) have frequent B symptoms, and one in five affected patients has involvement of the bone marrow, skin, soft tissues, bone, bone marrow, liver, and lungs. In adults, breast involvement has been described, with most cases being ALK (-) ALCL and frequently seen in association with breast implants. The outer shell of the implant (smooth vs textured) is implicated in the risk of Breast implant–associated - ALCL with no risk reported in patients who had smooth implants.[46–48] Primary cutaneous ALCL are morphologically similar but a clinically distinct subtype of ALCL without systemic involvement at the time of diagnosis. They lack the expression of ALK and do not have gene rearrangements involving the *ALK* gene.[49,50]

DIAGNOSIS AND STAGING

The diagnosis of PTCL is often challenging because of the spectrum of clinical manifestations, heterogenous pathological appearance, and often overlap with more common nonmalignant conditions, both clinically and pathologically. The workup of all patients who may have PTCL includes excisional lymph node biopsy if feasible, which is the gold standard test. The pathologic diagnosis is based on characteristic morphologic features and immunohistochemical patterns in correlation with the clinical signs and symptoms on presentation. Several factors add to a diagnostic gap in this lymphoma, including its rarity and need for detailed immunophenotypic markers. Current guidelines support the use of diagnostic panels to improve diagnostic accuracy and often require an expert hematopathologist. The initial workup of patients with PTCL should include physical examination; complete blood counts; and chemistry, including lactate dehydrogenase (LDH), β_2-microglobulin, bone marrow aspirate, and biopsy. Serologic tests for human immunodeficiency virus, HTLV11, hepatitis B and C can aid in identifying the subtypes of PTCLs. Positron emission tomography (PET) with 2-deoxy-2-[fluorine-18] fluoro-D-glucose should be considered at diagnosis, and further imaging should be done with PET or computed tomography scan for treatment monitoring at mid-treatment and the end of therapy in all cases. One should have a low threshold to workup if there is any suspicion of HLH and should consider tests including EBV polymerase chain reaction (PCR), ferritin, fibrinogen, triglycerides, and cytokine 12 profile, including soluble interleukin-2 receptor (IL-2sR). In men and women of childbearing potential, the possibility of infertility should be

discussed, and referral for fertility preservation consultation and therapy should be considered.

PROGNOSIS

The specific subtypes of aggressive PTCL along with the molecular markers discussed so far can provide information on the prognosis, with ALK (+) ALCL having the best prognosis. Clinical factors are also developed such as B-cell lymphoma to risk stratify patients called the International Prognostic Index (IPI), which is based on age, performance status (PS), LDH, stage, and extranodal involvement.[6] This was developed in aggressive B lymphomas and is less popularly used in T-cell lymphomas because of its limited ability to identify PTCL patients with their risk of treatment failure. They were validated in smaller studies, and the prognostication was not so satisfactory for the nodal entities. Hence, scores based on the biologic features of the tumors are currently being explored. An Italian cooperative group proposed a revision of the IPI for PTCL-NOS, the Prognostic Index for T-cell lymphoma (PIT) score, which includes age, PS, LDH, and bone marrow involvement.[51] The National Comprehensive Cancer Network (NCCN)-IPI, which subspecified features with respect to age, serum LDH, and inclusion of specific extranodal sites (central nervous system, bone marrow, liver, gastrointestinal tract, lung), seemed to separate prognostic groups slightly better on a visual scale. Both the PIT and the NCCN- IPI are able to discriminate the risk groups better in PTCL- NOS and ALCL than in AITL.[51,52] Although these clinical models are useful in estimating the prognosis, they have not impacted treatment approaches, and better tools incorporating immunophenotypic and molecular markers are much needed.

CLINICAL MANAGEMENT

Despite the advancements in the knowledge of the biology of PTCLs, the clinical course varies extensively depending on PTCL subtype and therapeutic intervention. It is imperative that the choice of frontline treatments to be critically appraised based on the subtype and the expression of CD30. Except for ALK (+) ALCL and ALK (-) ALCL with DUSP22 rearrangement, patients with PTCL generally have a chemoresistance, short-term remission, early relapse when treated with chemotherapy with CHOP or CHOP-like chemotherapy.[53] Historically, most of our knowledge on the treatment outcomes from the International T-Cell Project (ITCP) and the British Columbia Cancer Agency (BCCA) series (see Table 11–1). In the BCCA group, the majority of patients with ALK (+) disease had low-risk IPI scores and had an excellent 5-year OS (75%). However, the remainder of the patients with PTCL mostly had IPI scores greater than 2, and the 5-year OS rate were 25%, underscoring the high unmet need in this group.[39,43]

Expression of CD30

CD30 is a transmembrane glycoprotein belonging to the tumor necrosis factor receptor superfamily. It is expressed normally in activated B and T lymphocytes and in pathological states on many PTCL subtypes, including sALCL, in which it is characteristically uniform and high. Ligation of CD30 activates downstream nuclear factor κB (NF-κB) signaling pathways to promote cell growth and survival. Because signaling through CD30 can be oncogenic in some T-cell lymphomas, with limited expression in normal cells, it is one of the ideal targets. The CD30-directed antibody–drug conjugate BV has changed the approach to PTCL, essentially drawing a therapeutic line between CD30(+) and CD30(-) groups.

CD30 + Peripheral T-Cell Lymphoma

BV is an antibody–drug conjugate with the CD30-specific monoclonal antibody attached by a linker peptide to the chemotherapeutic agent monomethyl auristatin E (MMAE). Upon binding to CD30, BV undergoes endocytosis and is taken up by the lysosomal complexes. Under low pH conditions, the proteases cleave the linker and release MMAE to cytoplasm. Single-agent BV was approved for patients with sALCL after failure of one or more previous multiagent chemotherapy regimens. A phase I study evaluating BV in combination with CHP (CHOP without vincristine) in newly diagnosed patients with CD30(+) T-cell lymphomas showed an overall response rate (ORR) of 86%, with complete response rate (CRR) of 57%. The toxicities were manageable; adverse events (AEs) of grade 3 or higher commonly included neutropenia (21%), thrombocytopenia (14%), peripheral sensory neuropathy (12%), and anemia (7%). The long term 5-year follow-up in 38 patients who achieved CR showed progression-free survival (PFS) of 57% and OS of 79%.

A large, randomized, phase III study (ECHELON-2) comparing BV-CHP with CHOP BV plus CHP demonstrated superior response rates, higher rates of PFS, higher and OS without added toxicity for BV-CHP.[54] This is an important practice changing milestone in PTCL history, and BV-CHP is currently the standard of care treatment in patient with CD30 (+) PTCLs. CD30 is universally expressed in ALCLs, both ALK (+) and (-). In non-sALCL subtypes, CD30 expression is estimated to be approximately 58% to 64% in PTCL-NOS and 43% to 63% in AITL.[55,56] The ECHELON-2

study required the expression of CD30 to be at least 10% or greater in the neoplastic cells to be included in the study. About 75% of the patients in the ECHELON-2 study had advanced-stage disease, 30% were 65 years of age or older, and 70% had sALCL (48% ALK (-)). Twenty-two percent of patients were ALK (+) were required to have IPI scores of 2 or greater. Others in the study included patients with PTCL-NOS (16%), AITL (12%), ATLL (<2%), and EATL (<1%). The ORR and CRR were significantly higher with BV-CHP than CHOP (ORR, 83% vs 72%; CR rate, 68% vs 56%). The study met the primary endpoint showing significant improvement of PFS with BV-CHP. With a median follow-up period of 36.2 months, the median PFSs were 48.2 months versus 20.8 months (BV-CHP vs CHOP; hazard ratio [HR], 0.71, 95% confidence interval [CI], 0.54–0.93; $P = .011$). There was also a significant improvement in OS with HR (0.66; 95% CI, 0.46–0.95; $P = .0244$ for BV-CHP versus CHOP). The OS benefit was predominantly seen in sALCL but not in PTCL-NOS (HR, 0.83; 95% CI, 0.38–1.80) and AITL (HR, 0.87; 95% CI, 0.29–2.58). The treatment-related AE rates were similar between the two groups: AEs of grade 3 or greater occurred in 66% of the BV group versus 65% of the CHOP group. Febrile neutropenia occurred in 18% versus 15% and any grade peripheral neuropathy in 52% versus 55%. Serious AE occurred in 39% vs 38%; treatment discontinuation because of AEs occurred in 6% and 7% of patients in BV-CHP and CHOP arms, respectively. Treatment-related AEs leading to death were similar in both cohorts (3% vs 4%). The study clearly breaks the traditional norm in PTCL trials and established CD30-based treatment for frontline treatment of patients with T-cell lymphomas. However, it remains to be noted that AITL and PTCL-NOS subgroups were suboptimally represented, so the study is not powered to compare efficacy between histologic subtypes along with the potential benefit of BV in non- ALCL CD30(+) PTCL subtypes.[54] In November 2018, the FDA approved BV with CHP for patients with previously untreated sALCL or other CD30-expressing PTCLs, including AITL and PTCL-NOS (Fig. 11–3).

CD30-Negative T-Cell Lymphoma

For the vast majority of both cases of AITL and PTCL-NOS that are CD30 (-), CHOP-based chemotherapy remains the standard of care. Although more intensive therapies have been attempted, these did not fare better than those treated with CHOP therapy.[57] Both the registry study from Sweden and the German High-Grade Non-Hodgkin Lymphoma Study Group's ad-hoc analysis showed improved event-free survival (EFS) with the incorporation of etoposide in CHOP, especially if age is younger than 60 years, and normal

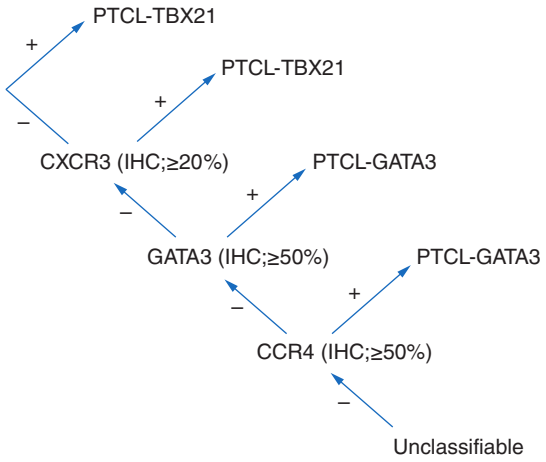


FIGURE 11–3 Cell of origin for peripheral T-cell lymphoma (PTCL) not otherwise specified. IHC, immunohistochemistry.

levels of LDH. The positive effect of etoposide on EFS was confirmed when patients with ALK(+) ALCL were considered (3-year EFS, 91.2% vs 57.1%; $P = .012$); the comparison showed a similar numerical trend when the other subtypes were taken together (3-year EFS, 60.7% vs 48.3%; $P = .057$).[58,59] In older adult patients, the addition of etoposide is considered debatable and can often cause toxicity; its use should be evaluated on a case-by-case basis. Many centers use it to achieve deeper remissions rates in anticipation for consolidation with high-dose chemotherapy with hematopoietic stem-cell transplant (HDC SCT). More intensive induction regimens (eg, infusional EPOCH, hyper-CVAD [hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone]) provide comparable clinical outcomes, but no prospective studies have directly compared the regimens. Moreover, these intensive regimens are associated with increased AEs.[60] CHOP is generally administered every 3 weeks, similar to Cyclophosphamide, Doxorubicin, Vincristine, Etoposide and Prednisone (CHOEP), in which the additional etoposide is administered on days 1 through 3 every 3 weeks[58] (Fig. 11–4).

UPFRONT CONSOLIDATION AND MAINTENANCE

The majority of patients receiving frontline chemotherapy (see Fig. 11–4), except for those with ALK (+) ALCL, fail to achieve long- term remissions in PTCL.[61] Studies have looked at the role of consolidation with radiation therapy (RT) and HDC SCT in eligible patients; however, it is worth noting that there is a lack of adequately powered randomized controlled trials to make a strong recommendation.

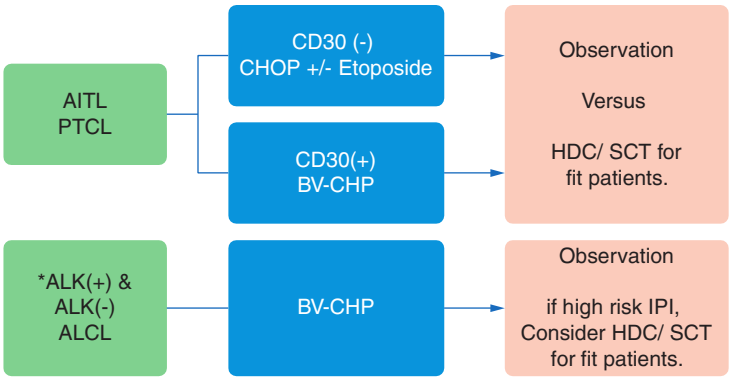


FIGURE 11–4 Frontline treatment algorithm for peripheral T-cell lymphoma (PTCL). AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; BV, brentuximab vedotin; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CHP, cyclophosphamide, doxorubicin, and prednisone; HDC SCT, high-dose chemotherapy with stem-cell transplantation; IPI, International Prognostic Index.
*Universal expression of CD30

In early stage and low IPI group, RT is generally an accepted mode of consolidation based on retrospective analyses and anecdotal experience.[62–64] There are many limitations to these studies, including their small sample size, selection bias of different chemotherapies used, and inclusion of primary refractory disease. The current national guideline- (the NCCN guidelines) recommend consolidative RT in all patients with stage I or II PTCL disease who achieve remission after standard anthracycline-based chemotherapy.

In advance stage with high IPI, studies have supported HDC SCT as a consolidation treatment in patients with all major subtypes of PTCL with noted significant benefit in the first remission compared with subsequent remission (Table 11–3).[65–71] In the ECHELON-2 trial, at the discretion of the investigator, patients underwent consolidative HDC SCT (22% patients in the BV +CHP group and 17% in the CHOP group); however, the study was not designed to look at the effect of transplant.[54] An exploratory analysis was further reported of the patients in CR after BV + CHP who received SCT and those who did not showed a numerical PFS benefit in favor of SCT.[72] The Center for International Blood and Marrow Transplant Research retrospectively evaluated HDC SCT, and the results suggested better outcomes when consolidation was offered earlier in the disease course and limited utility in multiply relapsed disease.[69] Although there is a role for consolidative HDC SCT in the primary treatment of nodal PTCLs, further studies are needed based on clinical and genetic stratification, particularly patients with high-risk features. Allogeneic transplant carries a high transplant-related mortality (TRM) rate and is generally not considered in first remission. Improvements in TRM may permit the role of upfront allogeneic SCT in appropriately designed clinical studies with high-risk characteristics.[73]

TABLE 11–3 Outcome of High-Dose Chemotherapy Autologous Stem-Cell Transplantation in First Remission in Peripheral T-Cell Lymphoma from Landmark Studies

Reference	Patients (*n*)	Frontline Treatment	PFS and EFS	OS
Mercadal et al[66] (2008)	41	High-dose CHOP/standard ESHAP	4-year PFS, 30%	4-year OS, 39%
Corradini et al[68] (2006)	62	(1) 32 patients received APOx2 + DHAPx2 followed by HDT/ASCT (2) 30 patients received MACOP-B for 8 weeks with intensification with a 3-day course of mitoxantrone and ara-C, followed by HDT/ ASCT	ALK-positive lymphomas: 12-year EFS, 54%	ALK-positive lymphomas: 12-year OS, 62%
d'Amore et al[65] (2012)	166	Biweekly CHOEP for six cycles	5-year PFS, 44%	5-year OS, 51%
Reimer et al[68] (2009)	83	CHOP	3-year PFS, 36%	3-year OS, 48%
Rodriquez et al[71] (2007)	74	CHOP-based regimen	5-year PFS, 63%	5-year OS, 68%

ALK, anaplastic lymphoma kinase; APO, doxorubicin, vincristine, prednisone; CHOEP, cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; EFS, event-free survival; ESHAP, etoposide, methylprednisolone (solumedrol), high-dose cytarabine (ara-C), and cisplatin; MACOP-B, methotrexate-doxorubicin-cyclophosphamide-vincristine-prednisone- bleomycin; OS, overall survival; PFS, progression-free survival

RELAPSED OR REFRACTORY DISEASE

A substantial number of patients with nodal PTCL either relapse or fail to achieve remission, as shown in the 153-patient BCCA series, and have poor outcomes with short survival times.[74] For patients who are fit and eligible, intensive salvage chemotherapy options are considered with the intention to consolidate with HDC SCT. The ORR for the various salvage regimens is in the 40% to 50% range; only a few patients manage to achieve CR, and the window to get these patients to HDC SCT is often short. In the BCCA series, the median PFS and OS after the first relapse or disease progression were only 3.1 and 5.5 months, respectively, without HDC SCT. Moreover, the patients who did receive chemotherapy at relapse had longer OS, but the difference was only 3 months compared with those who did not (6.5 vs 3.7 months, respectively).

Multiple studies suggest that outcomes of patients who have chemotherapy-sensitive disease have better outcomes with HDC SCT. However, there is a lack of randomized controlled studies, and most data on the role of HDC SCT and the types (autologous vs allogeneic) come from phase II and retrospective studies, which have inherent bias because of patient selection, heterogenous pathology, and inclusion of patients with more favorable PTCL subtypes. In addition, most studies include patients who went on to receive HDT SCT.[69—72] Patients who achieve a CR with salvage regimens could be consolidated with an HDC autologous SCT, but those with a PR should be considered for allogeneic HCT or additional salvage therapy.

Another major challenge in PTCL is that at the time of relapse, many patients are not eligible for intensive chemotherapies because of age, comorbidities, performance status, or personal preferences. In these patients, many new drugs are being investigated to extend the duration of response. The US FDA has approved four drugs with novel mechanisms of action for the treatment of patients with relapsed or refractory nodal T-cell lymphoma based on ORR. These include pralatrexate, romidepsin, belinostat, and BV.[75—81] Response rates with pralatrexate, romidepsin, and belinostat range from 25% to 54% in relapsed or refractory PTCL populations, and the ORR is as high as 86% (CR, 57%) with BV for patients with ALCL (Table 11–4). The actual impact on survival outcome for the single agents remains unclear. There have been attempts made to incorporate these novel agents into the salvage chemotherapy backbone with the intention of providing higher CR rates without an increase in toxicity. This can in turn facilitate subsequent consolidation with HDC SCT.[82]

The role of these novel agents to improve disease-related outcomes is actively being investigated in the frontline induction, disease salvage, and high-dose consolidation or in a maintenance setting. Mature clinical data are needed to show their impact on survival curves.

EMERGING HORIZONS

Clinical trials remain an integral part of the care of patients with PTCL, and participation is therefore highly encouraged. Understanding of the molecular and epigenomic markers has provided targetable mutations and pathways and has the potential to transform the current treatment landscape to more personalized care for patients. Overall, there is a need for effective treatments for most PTCL subtypes, and this requires increased understanding of the biology of PTCL to improve diagnosis and provide biomarkers for assessment of response or relapse. Several novel therapeutic agents are under investigation in relapsed or refractory PTCL, which has shown to result in deeper responses, potentially improving outcomes; however, this discussion is beyond the scope of this chapter. Using these agents, single-agent therapy for palliative intent or combination therapies followed by HDC SCT consolidation is actively being investigated. These investigational agents include ALK inhibitors (crizotinib and ceritinib), alisertib (selective inhibitor of aurora A kinase), panobinostat (pan-HDAC [histone deacetylase] [class ½/4] inhibitor), bortezomib (proteasome inhibitor), denileukin diftitox (IL-2–diphtheria toxin fusion protein), lenalidomide(immunomodulatory, synthetic thalidomide derivative), alemtuzumab (humanized anti-CD52 monoclonal antibody), mogamulizumab (defucosylated, humanized, monoclonal antibody targeting CC chemokine receptor 4), duvelisib and tenalisib (phosphoinositide-3 kinases δ and γ inhibitors), cyclosporine (immunomodulatory), and Selinexor (oral selective inhibitor of nuclear export).[3] Innovative therapies such as chimeric antigen receptor (CAR) T-cell therapy (an adoptive T-cell therapy approach that uses genetically engineered T cells transduced to express an artificial receptor against a target antigen on the tumor) are among the most promising immunotherapies for cancer. They have produced remarkable response rates in patients with B-lymphoid malignancies and are currently in phase ½ trials in patients with PTCL. These approaches have the potential to move rapidly to the frontline clinical investigation; many of these are currently underway.

TABLE 11–4 Targeted Agents and the Pivotal Trials That Led to Approval for Peripheral T-Cell Lymphoma

Study	Drugs	Mechanism of Action	Patients (*n*)	ORR	CR	PFS or EFS	Median OS
PROPEL	Pralatrexate	Novel selective antifolate agent Competitively inhibits dihydrofolate reductase and thymidylate synthase Thereby disrupts the DNA/RNA synthesis required for lymphoma cell proliferation	109	29% PTCL-NOS: 32 sALCL: 35 AITL: 8	11%	3.5 months	14.4 months
BELIEF	Belinostat	Potent IV (class 1/2/4), epigenetic-modifying HDAC inhibitor	129	25.8% PTCL-NOS: 23% AITL: 46% ALK (-) ALCL: 15%	10.8 AITL: 18%	1.6 months	7.9 months
Phase II	Brentuximab (R/R systemic ALCL after treatment failure of at least one prior therapy)	ADC directed against CD30, a cell-surface antigen	58	86%	57%	20 months	Not reached 1 year: 70% 3 years: 63% 4 years: 64%
Phase II	Romidepsin	Epigenetic-modifying agent that alters chromatin, specifically as a potent IV class 1 HDAC inhibitor Interferes with the acetylation pattern of chromatin on histone lysine residues Prevents gene transcription and disrupts protein function in malignant lymphoma cells	130	25% PTCL-NOS: 29% AITL: 30% ALK (-) ALCL: 24%	15%	4 months	11.3 months

ADC, Antibody-drug Conjugates; AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; Phase II BELIEF (CLN-19) Study; CR, complete remission; EFS, event-free survival; FFS, failure-free survival; HDAC, histone deacetylase; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Phase II, PROPEL; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified; R/R, Relapsed / Refractory; sALCL, systemic anaplastic large-cell lymphoma.

CONCLUSIONS

PTCL is a heterogenous group of rare lymphomas with poor prognoses and a lack of large, randomized trials to dictate treatment options. The immediate goal of therapy is to achieve a rapid and complete response and follow different treatment consolidation strategies to maintain this remission. As the field moves toward individualized therapies, large cooperative efforts are needed to advance the research to understand the different molecular subtypes and develop genome-driven clinical trials. Several new therapies, including CAR T-cell therapies, are likely to make a positive impact on survival outcomes in the next few years.

MD ANDERSON PRACTICE TIPS

- Excisional lymph node tissue biopsy is strongly recommended for the diagnosis of PTCL and is considered the gold standard test. Many centers perform core biopsy to provide pathological diagnosis in clinical presentations with time-sensitive requirements. Fine-needle aspiration is considered suboptimal for establishing the diagnosis.
- The presence of neoplastic T-cell infiltrate is determined based on morphology, aberrant T-cell phenotype (loss of expression of antigens normally expressed by T-cells or expression of antigens normally not associated with normal T-cells). Demonstration of T-cell clonality of PTCL is routinely evaluated with a PCR-based method using genomic DNA; however, the absence of an identifiable T-cell clone does not definitively rule out a diagnosis of PTCL.
- For patients 60 years of age or younger with normal LDH, especially for ALK (+) sALCL, addition of etoposide to CHOP may be more efficacious than CHOP according to the subgroup analysis from large, prospective, randomized clinical trials from The German High-Grade Non-Hodgkin Lymphoma Study Group and the analysis of the Swedish Lymphoma Registry. There was a trend toward improved EFS in favor of CHOEP in the other subsets as well, which was not statistically significant.
- For patients older than 60 years, intensive regimens are associated with increased toxicity without the benefit of improvement in outcomes. There was no benefit of CHOP-14 compared with CHOP-21, and adding etoposide CHOP chemotherapy was more toxic in the older adult group; hence, BV-CHP and CHOP continues to be the standard in older adult patients with CD30(+) and CD30(-) PTCL, respectively.
- Because of the high relapse rates in PTCL, high-dose chemotherapy with autologous SCT should strongly be considered for consolidation after the first remission except in the ALK (+) subtypes.
- The US FDA has approved four drugs with novel mechanisms of action for the treatment of patients with relapsed or refractory PTCL. These include pralatrexate in 2009, romidepsin in 2011, BV (for sALCL) in 2011, and belinostat in 2014.

REFERENCES

1. Morton LM, Wang SS, Devesa SS, et al. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. *Blood*. 2006;107(1):265-276.
2. Pinkus GS, Said JW, Hargreaves H. Malignant lymphoma, T-cell type: a distinct morphologic variant with large multilobated nuclei, with a report of four cases. *Am J Clin Pathol*. 1979;72(4):540-550.
3. Teras LR, DeSantis CE, Cerhan JR, et al. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. *Cancer*. 2016;66(6):443-459.
4. Quintanilla-Martinez L. The 2016 updated WHO classification of lymphoid neoplasias. *Hematol Oncol*. 2017;35:37-45.
5. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127(20):2375-2390.
6. Vose J, Armitage J, Weisenburger D, et al. International TCLP. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. *J Clin Oncol*. 2018;26(25):4124-4130.
7. Laurent C, Baron M, Amara N, et al. Impact of expert pathologic review of lymphoma diagnosis: study of patients from the French Lymphopath Network. *J Clin Oncol*. .2017;35(18):2008-2017.
8. Briski R, Feldman AL, Bailey NG, et al. The role of front-line anthracycline-containing chemotherapy regimens in peripheral T-cell lymphomas. *Blood Cancer J*. 2014;4(5):e214.
9. Federico M, Rudiger T, Bellei M, et al. Clinicopathologic characteristics of angioimmunoblastic T-cell lymphoma: analysis of the international peripheral T-cell lymphoma project. *J Clin Oncol*. 2013;31(2):240.
10. Savage KJ, Harris NL, Vose JM, et al. ALK– anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. *Blood*. 2018;111(12):5496-5504.
11. Delabie J, Holte H, Vose JM, et al. Enteropathy-associated T-cell lymphoma: clinical and histological findings from the international peripheral T-cell lymphoma project. *Blood*. 2011;118(1):148-155.
12. Iqbal J, Shen Y, Liu Y, et al. Genome-wide miRNA profiling of mantle cell lymphoma reveals a distinct subgroup with poor prognosis. *Blood*. 2012;119(21):4939-4948.
13. Iqbal J, Shen Y, Huang X, et al. Global microRNA expression profiling uncovers molecular markers for classification and prognosis in aggressive B-cell lymphoma. *Blood*. 2015;125(7):1137-1145.
14. Bouska A, McKeithan TW, Deffenbacher KE, et al. Genome-wide copy-number analyses reveal genomic abnormalities involved in transformation of follicular lymphoma. *Blood*. 2014;123(11):1681-1690.
15. Cairns RA, Iqbal J, Lemonnier F, et al. IDH2 mutations are frequent in angioimmunoblastic T-cell lymphoma. *Blood*. 2012;119(8):1901-1903.
16. Pizzi M, Margolskee E, Inghirami G. Pathogenesis of peripheral T cell lymphoma. *Ann Rev Pathol*. 2018;13:293-320.
17. Vinuesa CG, Tangye SG, Moser B, et al. Follicular B helper T cells in antibody responses and autoimmunity. *Nat Rev Immunol*. 2005;5(11):853-865.
18. de Leval L, Rickman DS, Thielen C, et al. The gene expression profile of nodal peripheral T-cell lymphoma demonstrates a molecular link between angioimmunoblastic T-cell lymphoma (AITL) and follicular helper T (TFH) cells. *Blood*. 2007;109(11):4952-4963.
19. Nguyen TB, Sakata-Yanagimoto M, Fujisawa M, Chiba S. Targeting T-cell receptor signaling pathway in angioimmunoblastic T-cell lymphoma. *Blood*. 2017;130(suppl 1):572-572.
20. Dupuis J, Boye K, Martin N, et al. Expression of CXCL13 by neoplastic cells in angioimmunoblastic T-cell lymphoma (AITL): a new diagnostic marker providing evidence that AITL derives from follicular helper T cells. *Am J Surg Pathol*. 2006;30(4):490-494.
21. Lunning MA, Vose JM. Angioimmunoblastic T-cell lymphoma: the many-faced lymphoma. *Blood*. 2017;129(9):1095-1102.
22. Attygalle AD, Cabeçadas J, Gaulard P. Peripheral T-cell and NK-cell lymphomas and their mimics; taking a step forward—report on the lymphoma workshop of the XVIth meeting of the European Association for Haematopathology and the Society for Hematopathology. *Histopathology*. 2014;64(2):171-199.
23. Willenbrock K, Roers A, Seidl C, et al. Analysis of T-cell subpopulations in T-cell non-Hodgkin's lymphoma of angioimmunoblastic lymphadenopathy with dysproteinemia type by single target gene amplification of T cell receptor-β gene rearrangements. *Am J Pathol*. 2001;158(5)1851-1817.
24. Iqbal J, Wright G, Wang C, et al. Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma. *Blood*. 2014;123(19):2915-2923.
25. Heavican TB, Bouska A, Yu J, et al. Genetic drivers of oncogenic pathways in molecular subgroups of peripheral T-cell lymphoma. *Blood*. 2019;133(15):1664-1676.
26. Etebari M, Navari M, Agostinelli C, et al. Transcriptional analysis of Lennert lymphoma reveals a unique profile and identifies novel therapeutic targets. *Front Genet*. 2019;10:780.
27. Vasmatzis G, Johnson SH, Knudson RA, et al. Genome-wide analysis reveals recurrent structural abnormalities of TP63 and other p53-related genes in peripheral T-cell lymphomas. *Blood*. 2012;120(11):2280-2289.
28. Morris SW, et al. Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma *Science*. 1994;1281-1284.
29. Chiarle R, Gong JZ, Guasparri I, et al. NPM-ALK transgenic mice spontaneously develop T-cell lymphomas and plasma cell tumors. *Blood*. 2003;101(5):1919-1927.
30. Turner SD, Tooze R, Maclennan K, et al. Vav-promoter regulated oncogenic fusion protein NPM-ALK in transgenic mice causes B-cell lymphomas with hyperactive Jun kinase. *Oncogene*. 2003;22(49):7750-7761.
31. Turner SD, Yeung D, Hadfield K, et al. The NPM-ALK tyrosine kinase mimics TCR signalling pathways, inducing NFAT and AP-1 by RAS-dependent mechanisms. *Cell Signal*. 2007;19(4):740-747.
32. Leventaki V, Drakos E, Medeiros LJ, et al. NPM-ALK oncogenic kinase promotes cell-cycle progression through activation of JNK/cJun signaling in anaplastic large-cell lymphoma. *Blood*. 2007;110(5):1621-1630.
33. Piva R, Pellegrino E, Mattioli M, et al. Functional validation of the anaplastic lymphoma kinase signature identifies CEBPB and BCL2A1 as critical target genes. *J Clin Invest*. 2006;116(12):3171-3182.
34. Matsuyama H, Suzuki HI, Nishimori H, et al. miR-135b mediates NPM-ALK–driven oncogenicity and renders IL-17–producing immunophenotype to anaplastic large cell lymphoma. *Blood*. 2011;118(26):6881-6692.
35. Eckerle S, Brune V, Döring C, et al. Gene expression profiling of isolated tumour cells from anaplastic large cell lymphomas: insights into its cellular origin, pathogenesis and relation to Hodgkin lymphoma. *Leukemia*. 2009;23(11):2129-2138.
36. Turner SD. An exploration into the origins and pathogenesis of anaplastic large cell lymphoma, anaplastic lymphoma kinase (ALK)-positive. *Cancer (Basel)*. 2017;9(10):141.
37. Parrilla Castellar ER, Jaffe ES, Said JW, et al. ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes. *Blood*. 2014;124(9):1473-1480.

38. Bruin PD, Beljaards RC, van Heerde P, et al. Differences in clinical behaviour and immunophenotype between primary cutaneous and primary nodal anaplastic large cell lymphoma of T- cell or null cell phenotype. *Histopathology*. 1993;23(2):127-135.
39. Savage KJ, Chhanabhai M, Gascoyne RD, et al. Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification. *Ann Oncol*. 2004;15(10):1467-1475.
40. Herrera AF, Crosby-Thompson A, Friedberg JW. Comparison of referring and final pathology for patients with T-cell lymphoma in the National Comprehensive Cancer Network. *Cancer*. 2014;120(13):1993-1999.
41. Xie W, Hu K, Xu F, et al. Clinical analysis and prognostic significance of lymphoma-associated hemophagocytosis in peripheral T cell lymphoma. *Ann Hematol*. 2013;92(4):481-486.
42. Sharma P, Shinde SS, Luyun RF. Waxing and waning lymphadenopathy. *Am J Med*. 2013;126(5):e3-e4..
43. Weisenburger DD, Savage KJ, Harris NL, et al. Peripheral T-cell lymphoma, not otherwise specified: a report of 340 cases from the International Peripheral T-cell Lymphoma Project. *Blood*. 2011;117(12):3402-3408.
44. Falini B, Pileri S, Zinzani PL, et al. ALK+ lymphoma: clinicopathological findings and outcome. *Blood*. 1999;93(8):2697-270.
45. Falini B. Anaplastic large cell lymphoma: pathological, molecular and clinical features. *Br J Haematol*. 2001;114(4):741-760.
46. Clemens MW, Horwitz SM. NCCN consensus guidelines for the diagnosis and management of breast implant-associated anaplastic large cell lymphoma. *Aesthet Surg J*. 2017;37(3):285-289.
47. Miranda RN, Aladily TN, Prince HM, et al. Breast implant–associated anaplastic large-cell lymphoma: long-term follow-up of 60 patients. *J Clin Oncol*. 2014;32(2):114.
48. Lechner MG, Megiel C, Church CH, et al. Survival signals and targets for therapy in breast implant–associated ALK– anaplastic large cell lymphoma. *Clin Cancer Res*. 2012;18(17):4549-4559.
49. Brown RA, Fernandez-Pol S, Kim J. Primary cutaneous anaplastic large cell lymphoma. *J Cutan Pathol*. 2017;44(6):570-577.
50. Moodley N, Nombona P, Mosam A. Primary cutaneous anaplastic large-cell lymphoma. *Dermatopathology*. 2019;6(2):163-169.
51. Gallamini A, Stelitano C, Calvi R, et al. Peripheral T-cell lymphoma unspecified (PTCL-U): a new prognostic model from a retrospective multicentric clinical study. *Blood*. 2004;103(7):2474-2479.
52. Zhou Z, Sehn LH, Rademaker AW, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. *Blood*. 2014;123(6):837-842.
53. Pautier P, Devidas A, Delmer A, et al. Angioimmunoblastic-like T-cell non Hodgkin's lymphoma: outcome after chemotherapy in 33 patients and review of the literature. *Leuk Lymphoma*. 1999;32(5-6):545-552.
54. Horwitz S, O'Connor OA, Pro B, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. *Lancet*. 2019;393(10168):229-240.
55. Bossard C, Dobay MP, Parrens M, et al. Immunohistochemistry as a valuable tool to assess CD30 expression in peripheral T-cell lymphomas: high correlation with mRNA levels. *Blood*. 2014;124(19):2983-2986.
56. Sabattini E, Pizzi M, Tabanelli V, et al. CD30 expression in peripheral T-cell lymphomas. *Haematologica*. 2013;98(8):e81-e2.
57. Escalón MP, Liu NS, Yang Y, et al. Prognostic factors and treatment of patients with T- cell non- Hodgkin lymphoma: the MD Anderson Cancer Center experience. *Cancer*. 2005;103(10):2091-2098.
58. Schmitz N, Trümper L, Ziepert M, et al. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. *Blood*. 2010;116(18):3418-3425.
59. Ellin F, Landström J, Jerkeman M, et al. Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry. *Blood*. 2014;124(10):1570-1577.
60. Simon A, Peoch M, Casassus P, et al. Upfront VIP- reinforced- ABVD (VIP- rABVD) is not superior to CHOP/21 in newly diagnosed peripheral T cell lymphoma. Results of the randomized phase III trial GOELAMS- LTP95. *Br J Haematol*. 2010;151(2):159-166.
61. Sibon D, Fournier M, Brière J, et al. Long-term outcome of adults with systemic anaplastic large-cell lymphoma treated within the Groupe d'Etude des Lymphomes de l'Adulte trials. *J Clin Oncol*. 20120;30(32):3939-3946.
62. Lee HK, Wilder RB, Jones D, et al. Outcomes using doxorubicin-based chemotherapy with or without radiotherapy for early-stage peripheral T-cell lymphomas. *Leuk Lymphoma*. 2002;43(9):1769-1775.
63. Huang MJ, Jiang Y, Liu WP, et al. Early or up-front radiotherapy improved survival of localized extranodal NK/T-cell lymphoma, nasal-type in the upper aerodigestive tract. *Int J Radiat Oncol Biol Phys*. 2008;70(1):166-174.
64. Zhang XM, Li YX, Wang WH, et al. Survival advantage with the addition of radiation therapy to chemotherapy in early stage peripheral T-cell lymphoma, not otherwise specified. *Int J Radiat Oncol Biol Phys*. 2013;85(4):1051-1056.
65. d'Amore F, Relander T, Lauritzsen GF, et al. Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. *J Clin Oncol*. 2012;30(25):3093-3099.
66. Mercadal S, Briones J, Xicoy B, et al. Intensive chemotherapy (high-dose CHOP/ESHAP regimen) followed by autologous stem-cell transplantation in previously untreated patients with peripheral T-cell lymphoma. *Ann Oncol*. 2008;19(5):958-963.
67. Reimer P, Rüdiger T, Geissinger E, et al. Autologous stem-cell transplantation as first-line therapy in peripheral T-cell lymphomas: results of a prospective multicenter study. *J Clin Oncol*. 2009;27(1):106-113.
68. Corradini P, Tarella C, Zallio F, et al. Long-term follow-up of patients with peripheral T-cell lymphomas treated up-front with high-dose chemotherapy followed by autologous stem cell transplantation. *Leukemia*. 2006;20(9):1533-1538.
69. Smith SM, Burns LJ, van Besien K, et al. Hematopoietic cell transplantation for systemic mature T-cell non-Hodgkin lymphoma. *J Clin Oncol*. 2013;31(25):3100-3109.
70. Beitinjaneh A, Saliba RM, Medeiros LJ, et al. Comparison of survival in patients with T cell lymphoma after autologous and allogeneic stem cell transplantation as a frontline strategy or in relapsed disease. *Biol Blood Marrow Transplant*. 2015;21(5):855-859.
71. Rodríguez J, Conde E, Gutiérrez A, et al. The results of consolidation with autologous stem-cell transplantation in patients with peripheral T-cell lymphoma (PTCL) in first complete remission: the Spanish Lymphoma and Autologous Transplantation Group experience. *Ann Oncol*. 2007;18(4):652-657.
72. Savage KJ, Horwitz SM, Advani RH, et al. An exploratory analysis of brentuximab vedotin plus CHP (A+ CHP) in the frontline treatment of patients with CD30+ peripheral T-cell lymphomas (ECHELON-2): impact of consolidative stem cell transplant. *Blood*. 2019;134(suppl 1):464.
73. Loirat M, Chevallier P, Leux C, et al. Upfront allogeneic stem-cell transplantation for patients with nonlocalized untreated peripheral T-cell lymphoma: an intention-to-treat analysis from a single center. *Ann Oncol*. 2015;26(2):386-392.
74. Mak V, Hamm J, Chhanabhai M, et al. Survival of patients with peripheral T-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors. *J Clin Oncol*. 2013;31(16):1970-1976.

75. Shimanovsky A, Dasanu CA. Pralatrexate: evaluation of clinical efficacy and toxicity in T-cell lymphoma. *Expert Opin Pharmacother*. 2013;14(4):515-523.
76. Khot A, Dickinson M, Prince HM. Romidepsin for peripheral T-cell lymphoma. *Expert Rev Hematol*. 2013;6(4):351-359.
77. O'Connor OA, Horwitz S, Masszi T, et al. Belinostat in patients with relapsed or refractory peripheral T-cell lymphoma: results of the pivotal phase II BELIEF (CLN-19) study. *J Clin Oncol*. 2015;33(23):2492-2499.
78. Bodiford A, Bodge M, Talbott MS, Reddy NM. Profile of belinostat for the treatment of relapsed or refractory peripheral T-cell lymphoma. *Onco Targets Ther*. 2014;7:1971-1977.
79. Karube K, Aoki R, Nomura Y, et al. Usefulness of flow cytometry for differential diagnosis of precursor and peripheral T-cell and NK- cell lymphomas: analysis of 490 cases. *Pathol Int*. 2008;58(2):89-97.
80. Chen X, Soma LA, Fromm JR. Targeted therapy for Hodgkin lymphoma and systemic anaplastic large cell lymphoma: focus on brentuximab vedotin. *Onco Targets Ther*. 2013;7:45-56.
81. Pro B, Advani R, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *J Clin Oncol*. 2012;30(18):2190-2196.
82. Strati P, Chihara D, Oki Y, et al. A phase I study of romidepsin and ifosfamide, carboplatin, etoposide for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma. *Haematologica*. 2018;103(9):e416-e418.
83. Zinzani PL, Bonthapally V, Huebner D, et al. Panoptic clinical review of the current and future treatment of relapsed/refractory T-cell lymphomas: peripheral T-cell lymphomas. *Crit Rev Oncol Hematol*. 2016;99:214-227.

12 Cutaneous Lymphomas

Auris Huen

KEY CONCEPTS

- Cutaneous lymphomas are a heterogenous group of B- and T-lymphocyte infiltration to the skin with varying clinical behaviors and prognoses.
- Mycosis fungoides (MF) is the most common subtype of cutaneous T-cell lymphoma (CTCL) with typical indolent course, but a subset of patients can progress to more advanced stages involving nodal and blood compartments.
- Sézary syndrome (SS) is a leukemic variant of CTCL with a more aggressive course. In many patients, skin biopsy is nondiagnostic because it does not reveal malignant cells, and diagnosis is made by peripheral blood flow cytometry or Sézary cell count.
- The treatment of patients with CTCL is guided by stage and distribution of the skin involvement. The initial treatment approach to skin-limited disease is embodied by the use of skin-directed treatment modalities.
- Two newly approved treatment options for patients with relapsed refractory MF and SS include brentuximab vedotin and mogamulizumab, which target skin and blood compartments of disease, respectively.
- Primary cutaneous B-cell lymphomas should be distinguished from secondary metastasis of B-cell lymphoma to the skin and are typically associated with an indolent disease course and a favorable prognosis.

Cutaneous lymphoma is an umbrella diagnosis consisting of multiple subtypes involving malignant mature B- or T-lymphocyte infiltration in the skin. It should be distinguished from secondary metastasis of systemic lymphoma to the skin where involvement in the skin is considered advanced stage. Cutaneous T-cell lymphoma (CTCL) is considered a rare entity consisting of approximately 4% of all cases of non-Hodgkin lymphoma.[1] In the majority of patients with CTCL, the disease course is typically indolent; however, in a subset of patients, the prognosis is less favorable, and progression to advanced-stage disease with nodal, blood, and visceral compartments can develop. The cutaneous B-cell lymphomas are less common than their T-cell counterparts, also with a favorable prognosis in the majority of patients.[2,3]

In 2008, the World Health Organization (WHO) established the classification of cutaneous lymphomas. This classification was updated in 2016 and again by the WHO–European Organization for Research and Treatment of Cancer (EORTC) and provides the basis for subcategorization of this disease (Table 12–1).[2] Each subtype carries differing clinical presentation, histopathologic features, prognoses, and treatment approaches. The various subtypes of cutaneous B and T-cell lymphomas can be separated into aggressive and less aggressive forms (Table 12–2). Mycosis fungoides (MF), pagetoid reticulosis, and CD30+ lymphoproliferative disorders are considered relatively indolent diagnoses. For B-cell lymphomas, marginal zone and follicle center cell lymphomas are favorable subtypes. In indolent cutaneous lymphoma, skin lesions can wax and wane for years and sometimes even self-resolve without treatment. In more aggressive subtypes such as Sézary syndrome (SS), primary cutaneous γδ T-cell lymphoma (pcGDL), and primary cutaneous CD8+ epidermotropic cytotoxic T-cell lymphoma, diffuse large-cell lymphoma, eg type (DLBCL leg type), patients characteristically develop rapidly progressive skin lesions and systemic involvement pertaining to a poor prognosis.[4,5] It is critical to determine the patient's subtype to accurately provide prognosis and treatment. Appropriate classification of the patient's disease can prevent overtreatment of indolent forms of disease.

TABLE 12–1 World Health Organization–European Organization for Research and Treatment of Cancer 2018 Classification of Cutaneous Lymphomas

Cutaneous T-Cell Lymphomas	Frequency (%)	5-Year DSS (%)
Mycosis fungoides (MF)	39	88
MF variants		
Folliculotropic MF	5	75
Pagetoid reticulosis	<1	100
Granulomatous slack skin	<1	100
Sézary syndrome	2	36
Adult T-cell leukemia/lymphoma	<1	NDA
Primary cutaneous CD30+ lymphoproliferative disorder		
Primary cutaneous anaplastic large-cell lymphoma	8	95
Lymphomatoid papulosis	12	99
Subcutaneous panniculitis-like T-cell lymphoma	1	87
Extranodal NK/T-cell lymphoma, nasal type	<1	16
Chronic active EBV infection	<1	NDA
Primary cutaneous peripheral T-cell lymphoma, rare subtypes		
Primary cutaneous γ/d T-cell lymphoma	<1	11
Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma	<1	31
Primary cutaneous CD4+ Small/medium pleomorphic T-cell lymphoproliferative disorder (P)	6	100
Primary cutaneous acral CD8+ T-cell lymphoma (P)	<1	100
Primary cutaneous peripheral T-cell lymphoma, NOS	2	15
Primary cutaneous marginal zone lymphoma	9	99
Primary cutaneous follicle center cell lymphoma	12	95
Primary cutaneous diffuse large B-cell lymphoma, leg type	4	56
EBV+ mucocutaneous ulcer (P)	<1	100
Intravascular large B-cell lymphoma	<1	72

DSS, disease-specific survival; EBV, Epstein-Barr virus; MF, mycosis fungoides; NDA, no data available; NOS, not otherwise specified; P, provisional.
Modified with permission from Willemze R, Cerroni L, Kempf W, et al: The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas, *Blood* 2019 Apr 18;133(16):1703-1714.

TABLE 12–2 Lymphoma Subtypes

A. T-Cell Lymphoma Subtypes	
Indolent	Aggressive
Mycosis fungoides	Sézary syndrome
Folliculotropic mycosis fungoides	Primary cutaneous natural killer/T-cell lymphoma, nasal type
Pagetoid reticulosis	Primary cutaneous aggressive CD8+ T-cell lymphoma
Granulomatous slack skin	Primary cutaneous γ/δ T-cell lymphoma
Primary cutaneous anaplastic large-cell lymphoma	Primary cutaneous peripheral T-cell lymphoma, unspecified
Lymphomatoid papulosis	Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
Primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoproliferative disorder	
B. B-Cell Lymphoma Subtypes	
Indolent	Aggressive
Marginal zone	Diffuse large B-Cell Leg type
Follicle center cell	Intravascular lymphoma Other

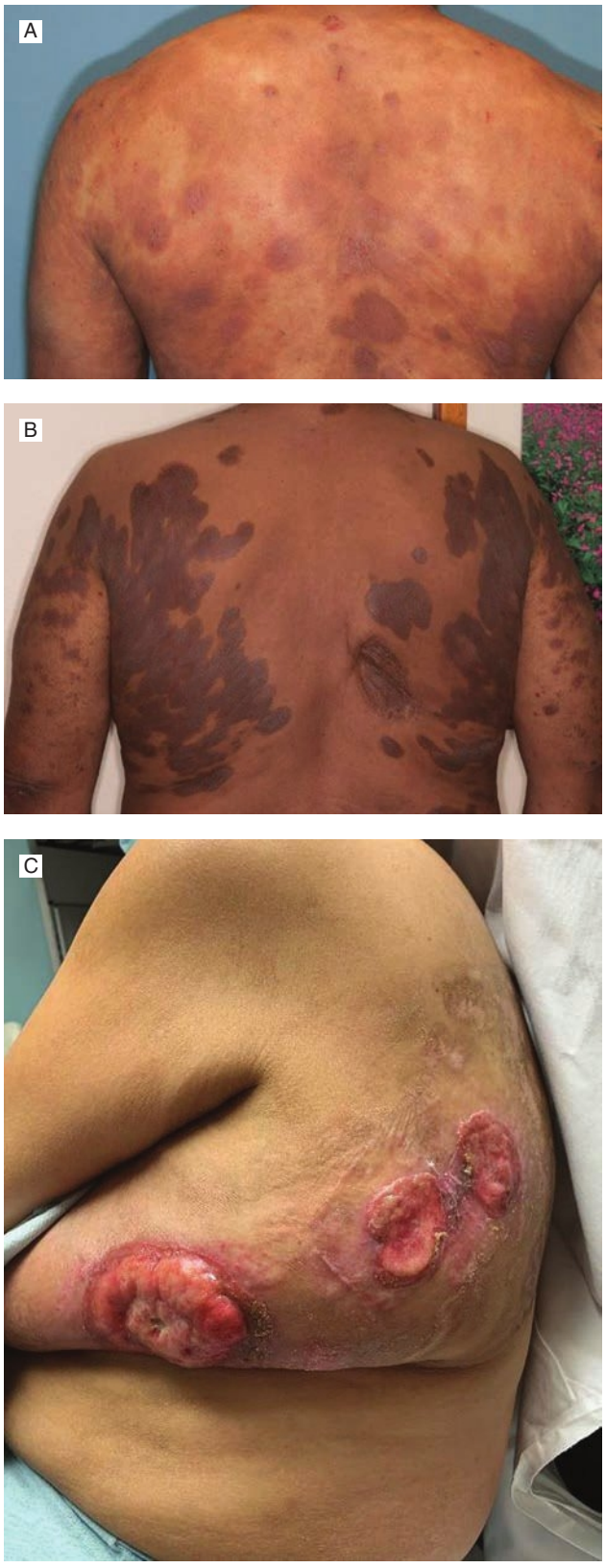


FIGURE 12–1 Patches (A), plaques (B), and tumors (C) of mycosis fungoides.

CUTANEOUS TUMOR TYPES

Patients with cutaneous lymphoma typically present with patches, plaques, and tumors on the skin. Patches are characterized by flat, nonpalpable erythematous involvement in the skin. If lesions become thickened and palpable, they are considered plaques. More advanced stages are associated with tumors in the skin that are more indurated or ulcerated. (Fig. 12–1). Other less common cutaneous findings associated with CTCL include leonine facies, palmar plantar hyperkeratosis (Fig. 12–2), poikiloderma, and

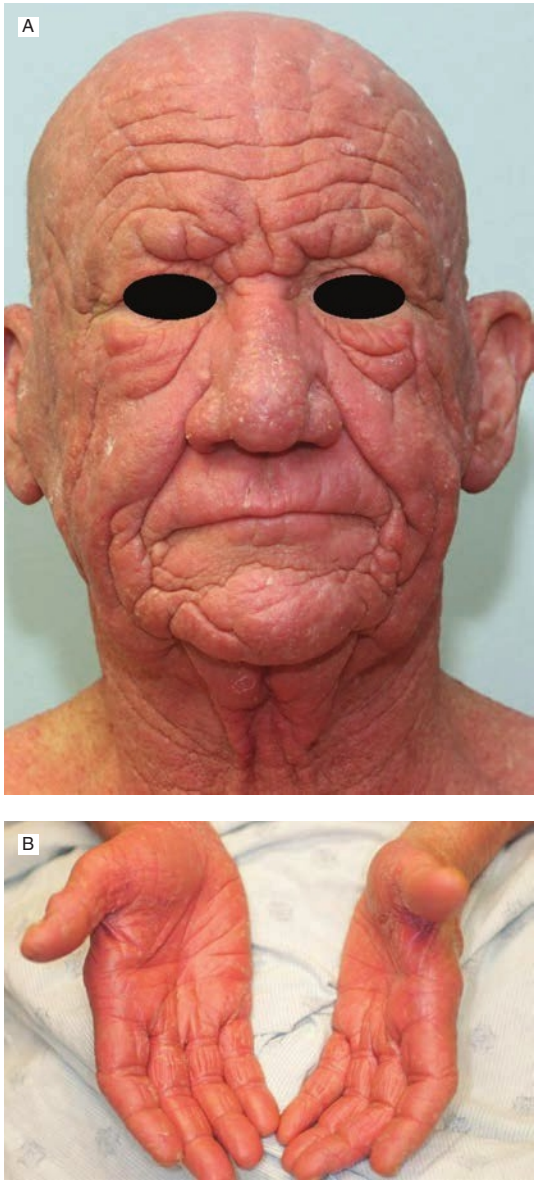


FIGURE 12–2 Leonine facies (A) and palmar plantar keratoderma (B) of Sézary syndrome.



FIGURE 12–3 Hypopigmented mycosis fungoides.

hypopigmentation.[6,7] (Fig. 12–3) These findings are unique to certain subtypes of CTCL and are discussed in individual sections.

EVALUATION OF PATIENTS WITH CUTANEOUS LYMPHOMA

Patients with cutaneous lymphoma are ideally evaluated by a multidisciplinary team with expertise in the disease consisting of dermatologists and oncologists, with support from pathologists and radiation oncologists.[8,9] Patients typically present with skin lesions as the initial presenting sign. Multiple skin biopsies are sometimes needed for the diagnosis of cutaneous lymphoma, especially in patients with thin lesions, often requiring immunohistochemistry markers and clonality studies for diagnosis. Skin lesion examination assessing extent of skin involvement and complete clinical history is vital to aid in classification of disease into subtypes. Quantifying cutaneous involvement of CTCL involves determining body surface area (BSA) and the modified severity-weighted assessment tool (SWAT), which adds the influence of the lesion type. The modified SWAT is the most recognized method of measuring cutaneous involvement with CTCL and is often used clinically and in clinical trials for skin assessment. The patient's hand size is used to estimate about 1% BSA (Table 12–3). Patches are weighted with factor of 1, plaques are weighted with factor of 2, and tumors are weighted with factor of 4 to determine the modified SWAT. This weighted model takes into consideration changes in skin lesions type and more

TABLE 12–3 Sample Form for Body Surface Area (BSA) Calculation and Modified Severity-Weighted Assessment Tool (mSWAT)

Area	BSA for Region (%)	BSA Patch (%)	BSA Plaque (%)	BSA Tumor (T)
Head	7			
Neck	2			
Anterior trunk	13			
Posterior trunk	13			
Buttocks	5			
Genitalia	1			
Upper arms	8			
Forearms	6			
Hands	5			
Thighs	19			
Lower legs	14			
Feet	7			
TOTAL[a]	100			

[a]Total BSA involvement:
Percent BSA patch: ___
Percent BSA plaque: ___
Percent BSA tumor: ___
Total BSA: ___
mSWAT = (% BSA patch × 1) + (% BSA plaque × 2) + (% BSA tumor × 4) = ___
Modified with permission from Olsen EA, Whittaker S, Kim YH, et al: Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer, *J Clin Oncol* 2011 Jun 20;29(18):2598-2607.

accurately reflects the severity of the patient's cutaneous involvement.[10]

Taking a complete medication history for recently started medications and history of recent exposures to viral or infectious organisms can help rule out pseudolymphoma. All patients with B-cell cutaneous lymphoma should undergo screening for systemic disease, including computed tomography (CT) with contrast of the chest, abdomen, and pelvis and blood work with a complete blood count (CBC).[11] In patients with CTCL, laboratory workup should include CBC, comprehensive metabolic profile, lactate dehydrogenase (LDH), and screening for infectious triggers such as syphilis, human immunodeficiency virus(HIV), hepatitis B and C, and in select patients, human T-cell leukemia/lymphoma virus-1 (HTLV-1) if applicable. Flow cytometry for aberrant T-cells in the peripheral blood should also be assessed in all patients with erythrodermic and advanced-stage CTCL.[9] In patients with indolent CTCL such as MF, early-stage disease with patch-only involvement, no imaging or bone marrow studies are typically performed unless the patient reports systemic symptoms or has laboratory abnormalities. In patients with thicker plaques, tumors, and erythroderma, full staging evaluation, including CT or positron emission tomography–CT (PET-CT) should be done.[3] Lymph nodes greater than 1.5 cm by palpation or imaging should be evaluated for potential disease involvement with core or excisional biopsies. Fine-needle aspiration of lymph nodes should be avoided so that the lymph node architecture and effacement of the sample can be evaluated.[12]

CUTANEOUS T-CELL LYMPHOMAS

Mycosis Fungoides

The most common subtype of CTCL is MF, which accounts for approximately 50% to 60% of cases of cutaneous lymphoma and typically carries an indolent course. In the United States, the annual age-adjusted incidence is reported at 7.5 cases per million and is considered a rare diagnosis.[13] Patients present with patches and plaques, which are often mistaken for other dermatoses such as atopic dermatitis or psoriasis for years before the correct diagnosis is made. The median delay in diagnosis of 36 months was recently reported in a large series of patients. This is largely due to challenges in evaluating early-stage disease clinically with mimickers and on histopathologic review.[14]

No definite cause or association leading to the development of MF has been identified. However, it is believed that it is triggered by chronic antigenic stimulation, leading to expansion of clonal skin homing T lymphocytes to the skin.[15] This theory is supported by increased dendritic cell such as antigen-presenting cell (APC) ligands B7 and CD40 and their costimulatory ligands CD28 and CD40L in MF lesions.[14] Other studies show elevated Toll-like receptor (TLR) expression by keratinocytes and expression of human leukocyte antigen class II alleles in patients with MF.[16] Stimulation from *Staphylococcus aureus* enterotoxins may contribute to MF. Studies have found high rates of colonization of the bacteria in erythrodermic patients with MF and SS and improvement in their disease with treatment of infection.[17] Viral etiologies such as Epstein-Barr virus (EBV) and cytomegalovirus (CMV) have been investigated.[18,19] Patients receiving immunosuppressive treatment or in immunocompromised state has been reported to be vulnerable to development of cutaneous lymphoma and have a more aggressive course.[20–24]

Several genetic alterations have been linked to MF, including dysregulation in the nuclear factor κ light chain enhancer of activated B-cells (NF-κB) as well as aberrant gene methylation and histone deacetylation.[25,26] Alterations in p16 and p53 tumor suppressor genes have also been associated with MF tumors.[27,28]

MF can be associated with a composite lymphoma where a second unrelated lymphoma can occur concurrently.[29–32] An increased risk for other cancers has also been linked to MF, which can precede, appear concurrently, or appear subsequent to its diagnosis.[33,34]

Clinical Presentation

Patients are typically adults (median age at diagnosis, ~55–60 years), but it can occur rarely in children.[35,36] They typically present with erythematous patches on the skin, which in some patients progress over years to plaques and tumors. The majority of patients present with early-stage disease with 30% of patients presenting with tumors and erythroderma at diagnosis.[37] The lesions favor a "double-hidden" distribution in non–sun-exposed areas beneath underwear. The patches are often described as finely scaly with "cigarette paper" in appearance because of loss of elastic fibers and atrophy of the epidermis.[3] The plaques are typically dark red in appearance and can have variable amounts of scale. Tumors are often ulcerated and have a variable growth rate. Patients with advanced-stage disease may develop tumors while also having patches and plaques. The stage of disease does not only pertain to the percentage skin involvement but also the lesion type.

Other less common skin findings in patients with MF include unique variants reported in the literature. These include leonine facies, especially in patients with folliculotropic variant of the disease and in SS patients. Alopecia can also be seen in folliculotropic patients.[38] Hypopigmentation on the skin has also been associated with the hypopigmented variant of

MF. Loose floppy skin most prominent in skin folds is associated with granulomatous slack skin variant. Poikiloderma is associated with poikiloderma vasculare et atrophicans.[3,39,40]

Histopathology

The typical aberrant cell in MF is the mature small to medium-sized T lymphocytes. They have a "cerebriform" appearance. There is a hallmark epidermotropic feature with intraepidermal infiltration of these lymphocytes. Clustering of these cells are called Pautrier's microabscesses. The immunophenotype of classic MF is typically characterized by α/β T-helper central memory lymphocytes with CD3+, CD4+, CD8-, CD45Ro+, TIA-1- phenotype.[3] In plaques and tumors, the CD4 to CD8 ratio is greater than 4:1. In many cases, there is loss of CD7 and CD26 on the cell surface.[41] In rare cases, CD8+, CD4-/CD8-, γ/δ, and cytotoxic phenotypes have been reported.[42,43] Detection of monoclonal rearrangement of α/β or γ/δ T-cell receptor (TCR) can be used as a tool to support the diagnosis of MF, which can be challenging in early stages of the disease.[44] A clonal TCR has been reported in 40% to 90% of cases of MF.[14] TCR clonality is most commonly determined using polymerase chain reaction technique, but next-generation sequencing has been found to improve sensitivity in detecting a predominant malignant clone.[45] A scoring system devised by the International Society Cutaneous Lymphoma incorporating clinical, histologic, and molecular biological characteristics to support the diagnosis in early ambiguous cases of MF.[46] (Table 12–4).

In cases in which there are increased large cells exceeding 25% of the infiltrate, MF is considered to have large-cell transformation (LCT) and carries a more aggressive course. In patients with LCT, some can express CD30, which is associated with a better prognosis compared with those who are CD30 negative.[47] LCT should only be considered in a patient with preexisting MF. If no prior disease is known, consideration for alternative diagnosis such as lymphomatoid papulosis or anaplastic large-cell lymphoma should be made.

Variants

There are numerous MF variants reported in the literature. The most common variants include folliculotropic MF, granulomatous slack skin, and hypopigmented MF. Folliculotropic MF is an entity in which the malignant lymphocytes have affinity for the pilosebaceous units. Typically, mucin deposits are also seen, and there is associated follicular mucinosis. Clinically, these patients present with acneiform lesions along with scalp involvement and alopecia. Patients with folliculotropic MF were also found to have increased risk of disease progression and lower overall survival (OS) compared with those with conventional MF (82% vs 91% at 10 years; 41% vs 91% at 15 years).[48] This is likely attributed to decreased response to skin-directed therapy because of disease sanctuary in the follicles.[49]

TABLE 12–4 Algorithm for the Diagnosis of Early Mycosis Fungoides Proposed by the International Society for Cutaneous Lymphoma

Criteria	Scoring System[a]
Clinical basic	2 points for basic plus two additional criteria
Persistent or progressive patches or thin plaques Additional	1 point for basic plus one additional criterion
Non–sun-exposed location Size or shape variation Poikiloderma Histopathologic basic	2 points for basic plus two additional criteria
Superficial lymphoid infiltrate Additional	1 point for basic plus one additional criterion
Epidermotropism without spongiosis Lymphoid atypia Molecular Clonal T-cell receptor gene rearrangement	1 point for clonality
Immunopathologic <50% CD2+, CD3+, and/or CD5+T-cells <10% CD7+T-cells Epidermal/dermal discordance of CD2, CD3, CD5, or CD7	1 point for one or more criteria

[a]A total of 4 points is required for the diagnosis of mycosis fungoides based on any combination of points from the clinical, histopathologic, molecular, and immunopathologic criteria.

Modified with permission from Pimpinelli N, Olsen EA, Santucci M, et al: Defining early mycosis fungoides, *J Am Acad Dermatol* 2005 Dec;53(6):1053-1063.

Granulomatous slack skin is a rare indolent variant of MF in which there are granulomatous T-cell infiltrates in the skin and destruction of elastic fibers, resulting in loose skin folds. Given that the infiltration of malignant cells is typically deep into the dermis and subcutis, localized radiation can be used for local control of the disease. Systemic treatment is needed for advanced-stage disease.[40]

Hypopigmented MF is a unique variant of MF seen in younger patients. The median age of onset is 28 to 35 years with an overall favorable prognosis. This is predominantly a CD8+ phenotype; however, CD4+ variants have been reported. Phototherapy is an effective treatment modality in this variant.[50,51]

Staging

MF is staged using the International Society of Cutaneous Lymphoma (ISCL) and EORTC proposed TNMB system evaluating all compartments of involvement. T refers to tumor and is staged by increasing skin involvement and worsening lesion types (Table 12–5). Patients with tumors and erythroderma are considered to have advanced-stage skin disease. The lymph node stage is determined by N0 to N3 grading corresponding to increasing effacement of the lymph node by the lymphoma cells. The blood staging for patients with MF is similar to that of patients with SS using flow cytometry to evaluate the degree of aberrant cells in the peripheral blood.[12] Using flow cytometry analysis for CD4+/CD7- or CD4+/CD26- cells, the highest B2 stage pertains to those with CD4:CD8 ratio of 10 or greater, CD4+/CD26- of 30% or greater of total lymphocytes or CD4+/CD7- of 40% or greater of total lymphocytes (or ≥1000 aberrant cells).[52] The overall stage can be summarized as stage IA and IB corresponding to skin-limited involvement of less than 10% and 10% or greater of skin patches and plaques, respectively. In patients with tumors on the skin, this relates to stage IIB. Stage III corresponds to erythroderma in the skin defined as more than 80% skin involvement, and stage IV pertains to patients with significant blood and lymph node involvement.

TABLE 12–5 Staging of Mycosis Fungoides and Sézary Syndrome

Stage	T	N	M	B
IA	1	0	0	0 or 1
IB	2	0	0	0 or 1
IIA	1 or 2	1 or 2	0	0 or 1
IIB	3	0–2	0	0 or 1
IIIA	4	0–2	0	0
IIIB	4	0–2	0	1
IVA_1	1–4	0–2	0	2
IVA_2	1–4	3	0	0–2
IVB	1–4	0–3	1	0–2

B, blood; M, metastasis; N, node; T, tumor.

Prognosis

The majority of patients (~70%) present with early-stage disease (stage IA–IIA).[37] In patients with stage IA, similar life expectancy as age, sex, and race-matched control populations are predicted.[53] Patients with plaques have a poorer prognosis than those with patch disease, even in early-stage disease. The degree of skin disease involvement from stage T1 to T4 is associated with decreased OS and progression-free survival with the risk for disease progression at 5 years estimated for T1 disease at 10%, T2 at 22%, T3 at 48%, and T4 at 56%.[54]

Prognostic factors in patients with MF include advanced age at diagnosis, LCT, elevated serum LDH and β2 microglobulin, and folliculotropic disease. Poorer prognosis is also associated with presence of T-cell clonal population in the blood of patients.[55] Other factors considered to pertain to poor prognosis include high Sézary cell count, loss of T-cell markers such as CD5 and CD7, and chromosomal abnormalities in the circulating T-cells.[9,37,54]

The Cutaneous Lymphoma International Prognosis Index (CL-IPI) has been proposed as a prognostic index tool for patients with MF, enabling prediction of OS in early- and late-stage patients. Significant adverse prognostic factors in the early-stage group are male gender, age older than 60 years, presence of plaques, folliculotropic disease, and stage N1/Nx. For the advanced-stage group, adverse prognostic factors are male gender, age older than 60 years, stages B1/B2, N2/N3 and visceral involvement.[56]

Treatment

The goals of treatment for MF are similar to those of other indolent lymphomas in maintaining remission and treating symptoms, but cure of disease is rare. Treatment is guided by patient age and comorbidities, extent and progression rate of skin disease, and involvement of other compartments.[53] Figure 12–4 summarizes the approach to patients with MF separated by stage of disease. In patients with early-stage disease (stage IA to IIA) with skin-limited disease, skin-directed treatment is used frontline. Early aggressive intervention with chemotherapy and radiation for MF has not been shown to improve prognosis compared with topical therapy.[57] Most studies in early-stage disease are retrospective, single-arm studies with few patients, making comparative efficacy challenging.

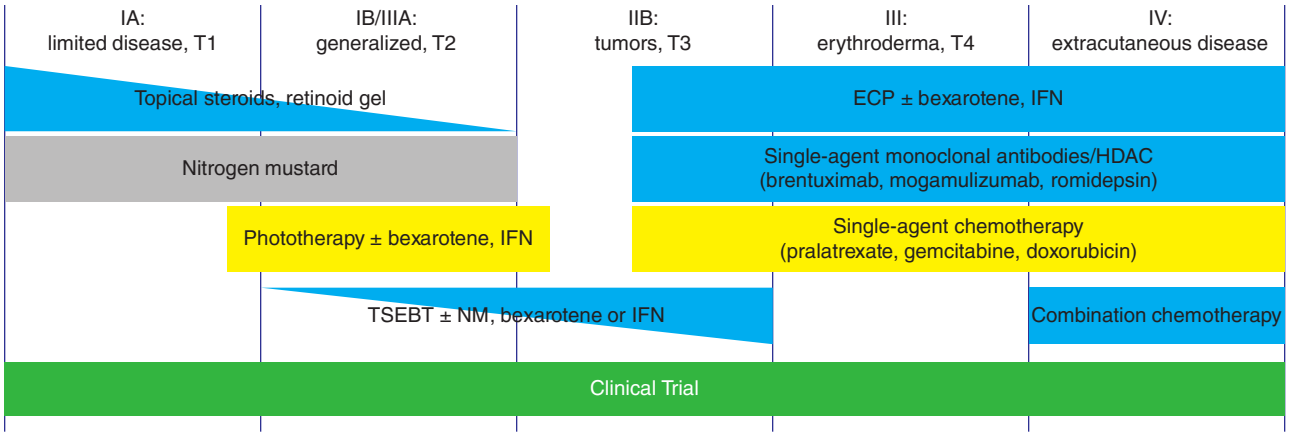


FIGURE 12–4 **Summary of treatment approach in cutaneous T-cell lymphoma. ECP, extracorporeal photopheresis; HDAC, histone deacetylase inhibitor; IFN, interferon; NM, nitrogen mustard; TSEBT, total-skin electron-beam radiation.**

In patients with advanced stages of disease (stage IIB–IVB), the disease is often treatment refractory, and the prognosis is poor. The duration of response for systemic treatment options such as immunotherapy and targeted therapy is relatively short, and in select younger patients, allogeneic stem cell transplantation should be considered when remission is achieved.[58,59] Clinical trials should be considered in patients with relapsed or refractory disease.

Skin-Directed Therapies

Topical Corticosteroids

Topical corticosteroid treatment is often used as frontline treatment in patients with early-stage disease as well as in combination with other treatment modalities.[60] The mechanism of action in cutaneous lymphoma is proposed to be that of apoptosis, interference lymphocyte adhesion to the endothelium, and downregulation of NF-κB with downstream suppression of cytokine and growth factor production.[61,62] Mid- to high-potency steroid creams and ointments have been studied in small series demonstrating effectiveness in the treatment of MF. In a large retrospective review of 163 patients treated with topical corticosteroid monotherapy for MF, 73% of patients responded to treatment with 33% achieving a complete response. Most patients in the study were treated with clobetasol 0.05% cream or ointment along with a lower potency steroid such as hydrocortisone for the skin folds.[63] In a prospective trial of 79 patients treated with mid- to high-potency steroid twice daily for 2 to 3 months, 94% of stage T1 patients and 82% of stage T2 patients achieved a response with complete remission (CR) rate of 63% and 25% in stage T1 and T2, respectively. However, a sustained result for was not maintained upon drug discontinuation. Side effects of topical steroid use include skin atrophy with prolonged use, striae, and possible hypothalamic–pituitary–adrenal axis suppression, which were observed in up to 13% of patients in this study.[64] Additionally, topical steroids also decrease erythema, pruritus, and scale in patients with CTCL.[65] Given the relatively ease of availability of topical steroids, it has become the favored initial treatment modality.

Nitrogen Mustard

Nitrogen mustard (mechlorethamine) is an alkylating chemotherapy agent that directly induces DNA damage to malignant cells. When applied to the skin, an immune-mediated antitumor mechanism or by interruption of Langerhans and epidermal cell interaction has been proposed. A retrospective trial was conducted of 203 patients receiving topical nitrogen mustard as an aqueous solution of 10 to 20 mg/100 mL in an earlier cohort and ointment formulation in similar concentration in a later cohort of patients. Overall response rates (ORRs) and complete response rates were 93% and 65% respectively for T1 stage patients 72% and 34% for stage T2 patients. The median time to complete response was 12 months, and the duration of response was also 12 months, with some patients achieving long-term remission of over 8 years.[66] Nitrogen mustard has been used in the treatment of patients with cutaneous lymphoma for several decades as a compounded medication until the availability of a new gel-based product (Valchlor, mechlorethamine 0.016%), which is commercially available. When evaluated in a multicenter trial in comparison with the ointment formulation, the gel formulation resulted similar response rates of 58.5% versus 47.7% in the ointment formulation. The time to response was superior in the gel formulation, achieving response 16 weeks sooner than the comparator.[67] The main side effects include local skin reactions similar to those seen in an irritant contact dermatitis or allergic contact dermatitis in up to 16% of patients and resulting pruritus, which should be managed by holding the medication

and using topical steroids or antihistamines. There is also reported increased risk for skin cancers in some series.[68,69]

Imiquimod

Imiquimod is a topical imidazoquinolinone immunomodulator with activity as an agonist for the TLR 7 demonstrating antiviral and antitumor effects. When applied topically, the innate immune system is activated inducing production of interferon-α (INF-α) and interleukin (IL)-12 and blocking IL-4 and IL-5.[70] In a small prospective study of six patients, 50% response was observed in patients with MF treated with the 5% imiquimod cream three times weekly for 12 weeks. An initial inflammatory response was observed at the application site only in those responding to treatment and should not be mistaken for disease progression.[71] Other smaller case reports and series have been reported effectiveness of the drug.[72] Application site reaction is the most common adverse effect, with erythema and peeling of skin reported in up to 100% of patients followed by edema, pruritus, and a burning sensation. Flulike symptoms are reported in up to 4% of patients treated with imiquimod. Imiquimod can induce psoriasis or psoriasis-like skin dermatitis in susceptible individuals possibly because of a shift toward the T-helper (Th) 1 pathway and the IL-23 and IL-17 axis and is avoided for CD8+ predominate MF at our institution because of possible risk for worsening disease from stimulation of INFs.[73]

Topical Bexarotene

The topical formulation of bexarotene is a 1% gel also approved for treatment of patients with MF. This topical gel can be applied up to four times daily, but most patients are only able to tolerate twice daily applications due to skin irritation. Patients achieved an ORR of 63% and a clinical complete response rate of 21% and median time to response was 20 weeks.[74]

Phototherapy

Phototherapy is the use of ultraviolet (UV) light for the treatment of cutaneous disorder. Patients are treated at predetermined most effective narrowband wavelength (311 nm) with UVB light and UVA light exposure at 320 to 400 nm. Patients are treated two or three times weekly at increasing time intervals to increase dosing exposure as tolerated to avoid toxicity. Uninvolved sites of the skin are shielded. When remission is achieved, treatment is tapered down or maintained at less frequent intervals. In patients receiving UVA, oral 8-methoxypsoralen is taken 60 to 90 minutes before treatment to sensitize the skin to the UV rays and thus is called PUVA. No sensitizer is needed for narrowband UVB (NB-UVB). PUVA light has been reported to induce tumor apoptosis, suppression of cytokine production, and decreasing Langerhans cells in the skin. Complete response has been reported in up to 71% of patients with early-stage disease, but it is less effective with thicker plaques and tumors. It can be used in combination with other systemic agents such as INF-α or retinoids.[75–77] Side effects associated with PUVA include nausea from the psoralen, erythema, burning, and pruritus, all improve with dose or interval adjustment. Squamous cell carcinomas have been reported in patients treated with PUVA, likely related to cumulative dose.[78]

NB-UVB has been shown to inhibit neoplastic T-cell function and proliferation through APC inhibition and increased production of keratinocyte cytokines. UVB has a shorter wavelength than UVA and therefore does not penetrate the skin as well for thicker lesions. It has greater activity toward skin patches over plaques with one series of 23 patients reporting 100% complete response to treatment for skin patches compared with 60% in patients with plaques. It is an effective modality for treatment of hypopigmented MF.[79] Other studies demonstrate complete response to NB-UVB ranging from 54% to 91%.[80] It is generally well tolerated. Side effects to treatment are related to UV-induced burning, pruritus, and erythema. Cumulative UV-induced skin aging can develop but less than with PUVA. NB-UVB can also be used in combination with retinoids successfully.[81,82]

Radiation

Radiation is one of the most effective treatment modalities for the treatment of patients with MF and other cutaneous lymphomas. Local radiation to tumors and thicker plaques has complete response rates of more than 90%. Typically, using single or two fractions of low-dose radiation (8 Gy) is sufficient to effect complete responses in most patients.[83,84] However, a longer duration of response appears to be associated with higher doses.[85] Total-skin electron-beam therapy (TSEBT) treats the entire surface of the skin radiation and with more penetration than phototherapy. Electrons can be controlled more effectively than photons, which help spare deeper tissues from exposure. TSEBT is typically reserved for patients with skin-limited disease with more significant disease burden involving plaques and tumors. Conventional doses of TSEBT (30–36 Gy delivered over 8–10 weeks) has been reported to have ORRs of 100% and complete response seen in 60% of patients with patches, plaques, and tumors. Higher CR was observed in patients with T2 (patches and plaques; 75%) versus T3 (tumors; 43%).[86] Cumulative toxicity with repeated doses of TSEBT prevent frequent retreatment with this modality. Lower dose TSEBT (10–20 Gy) has been found to be highly effective and results comparable to the conventional doses.[87,88]

Toxicity associated with TSEBT includes erythema, desquamation, xerosis, anhidrosis, skin atrophy or necrosis, alopecia, and nail dystrophy. These effects are dose dependent with significantly fewer side effects associated with low-dose versus conventional doses (5–10 Gy, 16%; 10–20 Gy, 35%; 20–30 Gy, 34%; and >30 Gy, 62%).[88] Risk for radiation dermatitis or recall should be considered in patients receiving radiation-sensitizing medications such as methotrexate, doxorubicin, or gemcitabine.

Systemic Therapies

Retinoids

The retinoids are structural and functional derivatives of vitamin A (retinol). They exert their mechanism of action by control of gene expression, affecting cell proliferation, differentiation, and apoptosis. In the treatment of patients with cancer, retinoids are considered biologic response modifiers, inducing response without immune suppression. In T-cell lymphoma cells, retinoids have been found to induce apoptosis and DNA fragmentation in affected T lymphocytes.[89,90] Several systemic and topical retinoids have been studied for treatment of patients with CTCL. Retinoids bind to two distinct families of nuclear receptors regulating gene expression called retinoic acid receptors (RARs) and retinoic X receptors.[91]

Bexarotene is a synthetic retinoid binding to retinoid X receptor. It is available as an oral capsule and approved for treatment of patients with CTCL in the United States. Patients in the advanced-stage (stage IIB–IVB) group were treated with 300 mg/m^2/day with clinical responses of 45% and 2% complete response.[92] In early-stage patients (stage IA–IIA), responses at 300 mg/m^2/day were ORR of 54% and complete response of 7%.[93] Dose response was observed in the clinical trial with highest response noted in patients receiving more than 300 mg/m^2/day; however, at our institution, most patients are unable to tolerate more than 300 mg/day because of toxicity. Bexarotene has also been studied in small combination trials with systemic chemotherapy, INFs, phototherapy, and radiation and appears to be well tolerated.[94,95]

Unique side effects associated with oral bexarotene include central hypothyroidism and hyperlipidemia occurring in the majority of patients, which should monitored in patients taking the medication. All patients should have baseline thyroid function and lipid panel assessment before starting treatment. All patients are started on an HMG-CoA reductase inhibitor "statin" such as atorvastatin 40 mg/day and levothyroxine 25 to 50 mcg/day at the start of bexarotene treatment. Free serum thyroxine (not thyroid-stimulating hormone) levels should be monitored and used for thyroid supplementation adjustment at follow-up visits. Further adjustments of thyroid and lipid medications should be performed at regular intervals.[91]

Acitretin is a retinoid also evaluated for treatment of patients with CTCL. Unlike bexarotene, it binds to the RAR receptor and therefore has a different side effect profile. In a retrospective review of 32 patients with CTCL, acitretin in varying doses of 10 to 50 mg/day used as monotherapy or combination therapy with second CTCL treatment modality achieved ORR of 59% with one patient achieving CR (although only six patients received treatment as monotherapy). It was noted that many patients who responded to treatment with acitretin also previously responded to treatment with bexarotene. Adverse effects include dyslipidemia, xerosis, alopecia, cheilitis, and depression.[96] In another more recent retrospective review of 128 patients, acitretin alone or in combination with another agent was found to have an 77% ORR with 44% complete responses seen. It was noted that acitretin was more effective as a first-line option compared with use in patients who are more refractory.[97] Isotretinoin, another RAR receptor ligand, has also been studied in patients with CTCL. Dosages ranged from 0.2 to 2 mg/kg/day have demonstrated ORR ranging from 43% to 100%.[91] Its use in patients with CTCL is limited by the burden of the iPLEDGE program's monthly laboratory surveillance requirements to have access to the medications.

Overall, all retinoids appear to have activity in CTCL, but no direct comparative trial has established a definite superior agent in this patient population. A limiting factor for use of this class of medications in younger patients is that significant precaution must be taken to prevent pregnancy while patients are taking these medications to avoid birth defects. At our institution, this class of medications is used in patients progressing through topical therapy, in those with diffuse distribution of cutaneous disease limiting topical application of medications, or for maintenance of response after radiation or chemotherapy in patients with more advanced-stage disease.

Interferons

INF-α and INF-γ are two types of INFs used in the treatment of patients with CTCL. In the human body, INFs are peptides produced by the innate immune system with antiviral and antitumor properties. The malignant T-cells in CTCL are typically skin-homing T-cells releasing IL-4, IL-5, and IL-10 cytokines, along the T-helper 2 (Th2) phenotype. It is observed that this shift toward Th2 activity propagated by the tumor cells allows for immune suppression and blocking of the antitumor response in patients with CTCL. IFN-α and -γ augment CD8+ T-cells and natural killer (NK) cells and suppresses the Th2 activity incited by

lymphoma cells.[98] In patients with CTCL, IFN-α-2b has been studied at varying doses ranging from 2 million units three times per week to 18 million units per day. ORRs noted ranged from 20% to 80% with 0% to up to 67% complete responses noted.[99] Although higher doses have been reported in the literature, IFN-α-2b is typically dosed as 3 to 6 million units given subcutaneously three times per week with titration per tolerance. In a prospectively enrolled study evaluating low (3 million units) versus high (dose escalation up to 36 million units) intramuscular injections of INF-α daily for 10 weeks, several patients in the high-dose arm required dose reduction because of toxicity.[100] A pegylated version of IFN-α-2b is commercially available and allows for weekly dosing. Evidence suggests the pegylated formulation is also effective in patients with CTCL.[98,101] Side effects associated with IFN-α-2b include flulike symptoms (fever, fatigue, chills, myalgias) in the majority of patients. Other adverse effects include anorexia, weight loss, depression, cough, and hair loss.[100]

IFN-γ's activity in T-cell lymphoma is less well understood. Fewer studies have been performed for treatment of patients with CTCL. INF-γ was studied in a phase II prospective trial with 16 patients reporting objective partial response in 31% of patients.[102] In another study from Japan, 15 patients with MF were treated with INF-γ at 2 million units daily for 5 days for 4 weeks. The ORR was 60% with a durable disease response. The median duration of response was not reached at 170 days. The drug was overall well tolerated, and flulike illness was the main adverse effect.[103] Although not formally compared, it is the author's impression that INF-γ appears to be better tolerated than INF-α and may be considered in patients who are intolerant to the α type.

At our institution, nonpegylated INF-α is typically started at lower dosages of 1.5 to 3 million units three times weekly and increased to 6 million units as tolerated. The medication is self-injected at night by the patient with acetaminophen as premedication to attenuate the flulike symptoms associated with the drug. These symptoms typically decrease in severity over time. Patients should have monitoring of the CBC and liver function tests, holding the drug if moderate or severe abnormalities occur. INF-γ is typically given at 50 to 100 μg/m^2 three times weekly. These medications should be used with caution in patients with preexisting autoimmune, mood, or cardiovascular disorders.[98]

Brentuximab Vedotin

Brentuximab vedotin (BV) is an anti-CD30 conjugate monoclonal antibody linked to a toxin monomethyl auristatin E (MMAE). The antitumor effect of the drug is assumed to be targeting CD30 and bringing the MMAE toxin to the malignant cells; however, diffusion of the toxin to the surrounding supportive microenvironment may also play a role in its mechanism of action.[104] The drug was investigated for use in CTCL in a large, randomized, phase III trial of 131 patients comparing BV with physician choice of methotrexate or bexarotene. For treatment of patients with MF, the ORR was 65% with 10% achieving complete response in the BV-treated arm compared with 16% in the bexarotene or methotrexate arm. When combined with all patients in the study, which includes patients with primary cutaneous anaplastic large-cell lymphoma (pcALCL), ORR was 67% compared with 20% in the comparator arm. BV appears to have comparable, if not higher, activity in patients with advanced-stage disease compared with early-stage patients. In the phase III trial, ORR was 69% in the advanced-stage group compared to 53% in the early-stage group. Patients qualified for the trial if their skin biopsies had at least 10% of tumor cells expressing CD3≈0.[105] Two additional phase II open-label studies also demonstrate similar activity in CTCL patients but, unlike the phase III trial, accepted patients with lower CD30 expression[106,107] (Table 12–6). Based on findings of these two studies, it is unclear if any presence of CD30 expression or

TABLE 12–6 Summary of Clinical Trials of Brentuximab Vedotin in Patients with Mycosis Fungoides and Sézary Syndrome

Reference	Phase	Trial Design	Evaluable Patients (n)	CD30 Eligibility	ORR	CR
Duvic et al (2015)	II	Open label, single center	28	CD30+ (no lower limit but expression graded)	15 (54%)	2 (7%)
Kim et al (2015)	II	Open label, investigator initiated, multicenter	30	Negligible to 100% CD30 expression levels	21 (70%)	1 (3%)
Prince et al (2017)	III	Randomized open label, multicenter, international	48	CD30+ (10% tumor cells expressing CD30)	31 (65%)	5 (10%)

CR, complete remission; ORR, overall response rate.
Data from reference 105, 106, 107.

higher expression translates to an increase in BV activity. Anecdotal report of BV activity in a CD30-negative MF patient has been reported.[108]

The dose-limiting toxicity for BV is peripheral sensory neuropathy, which was found in 45% of patients with 5% developing severe grade 3 neuropathy. Other less common side effects include nausea (36%), diarrhea (29%), fatigue (29%), vomiting (17%), alopecia (15%), and pyrexia (17%). Rash was also noted in 11% of patients.[105] Patients should be monitored closely for signs of peripheral neuropathy, and dose modification or suspension should be considered. Lower dose (<1.8 mg/kg) or alternate interval (dosing as needed) strategies have been proposed to improve tolerability of BV in patients with CTCL but have not yet been validated in trials.[109]

Mogamulizumab

Mogamulizumab is a humanized monoclonal antibody against chemokine receptor type 4 (CCR4) approved in the United States for patients with relapsed or refractory MF or SS after at least one prior systemic therapy. The cytokine CCR4 is normally involved in the trafficking of T-cells to the skin.[110] It is expressed by multiple subtypes of malignant T-cells and are most notably found in adult T-cell leukemia/lymphoma. It is also expressed in CTCL and other peripheral T-cell lymphomas, especially in advanced-stage disease with blood involvement.[111] The drug was evaluated in a randomized phase III trial comparing the drug with vorinostat in 372 patients with MF and SS. Mogamulizumab was associated with 28% ORR compared with 5% in the vorinostat arm. Notably, the best response was in the blood compartment, where the response was 68% in the mogamulizumab arm compared with 19% in patients treated with vorinostat. Skin response of 42% was also superior in the mogamulizumab arm compared with 16% for vorinostat.[112]

Mogamulizumab is generally well tolerated with mild infusion-related reaction as the most common toxicity. The drug has also been associated with causing a drug eruption, reported in 20% of patients, which can be confused with disease progression, especially in patients with erythroderma.[113,114] Skin biopsy should be performed in patients who appear to have skin progression despite improvement in other compartments or who initially have response to the drug but develop a flare to help rule out drug hypersensitivity. In patients who have CD4+ CTCL, the presence of significant numbers of CD8+ T-cells in the skin biopsy may suggest reactive dermatitis rather than lymphoma progression. Most drug hypersensitivity associated with mogamulizumab can be managed with topical steroids and holding the drug. After improvement, many patients can tolerate restarting the medication. Photosensitivity has also been reported in the literature related to the drug. Mogamulizumab treatment before allogeneic transplantation has also been associated with increased risk for graft-versus-host disease.[115]

Histone Deacetylase Inhibitors

Two histone deacetylase (HDAC) inhibitors, romidepsin and vorinostat, are approved for the treatment of patients with CTCL. HDACs are enzymes that regulate the cell cycle, apoptosis, and protein folding through acetylation and deacetylation. The equilibrium of this process is dysregulated in cancer cells.[116,117] HDAC inhibitors are small molecules that prevent removal of acetyl groups, blocking the effects of HDACs. HDACs are also implicated in oncogenic pathways by upregulation of signal transducer and activator of transcription (STAT) family of proteins, which has been implicated in the pathogenesis of CTCL and T-cell proliferation.[118] Notably, STAT 5 is important for expression of antiapoptotic proteins such as bcl-2, cell cycle genes such as cyclin-D and c-myc, and oncogenic miR-155 microRNA. STAT 6 is associated with Th2 phenotype seen in CTCL. HDAC inhibitors upregulate STAT 4, which promotes Th1 and suppresses STAT 6, restoring the imbalance.[116]

Vorinostat is an oral HDAC inhibitor that has been shown to have activity in CTCL. ORRs of 30% was noted in a phase IIb multicenter trial. Despite achieving response, the median time to progression was only 4.9 months, which is quite brief. Patients report significant gastrointestinal (GI) toxicity when taking this medication with almost half of treated patients experiencing nausea and diarrhea. Other adverse effects include fatigue (46%) and anorexia (26%). Of note, pulmonary embolism was observed in 5% of patients.[119] The drug was quite effective in improving pruritus in 32% of patients and is often used in lower doses at our institution for this purpose.

Romidepsin is given as an intravenous infusion. In a large phase II trial in patients with CTCL, romidepsin at 14 mg/m^2 weekly for 3 weeks of a 4-week cycle demonstrated an ORR of 34% with 4 of 71 patients achieving complete responses. Unlike vorinostat, the median duration of response was longer at 13.7 months.[120] Romidepsin has been reported to have activity in tumor-stage MF and its folliculotropic variant with 45% and 60% ORR observed in the respective patient groups in a phase II trial.[121] In a second phase II trial, 96 patients were treated, resulting in similar response of 34% and median duration of response of 15 months. Time to response of 8 weeks is also relatively faster than other treatment options.[122] Adverse effects appear similar to those of vorinostat, which include GI symptoms of nausea and vomiting, anorexia, and diarrhea as most common. Fatigue is also a commonly reported side effect of the drug seen in almost 50% of patients. In our institution, romidepsin is considered in patients

with advanced-stage CTCL with blood involvement or tumor-stage disease.

Alemtuzumab

Alemtuzumab is a monoclonal antibody targeting CD52 on the surface of lymphocytes. This depletes the peripheral blood of T- and B-cells, including malignant T-cells.[123] It is effective in patients with MF with blood involvement and in patients with SS. ORRs range from 38% to 100%.[124–126] Low-dose alemtuzumab is also found to be efficacious in patients with CTCL at 10 mg subcutaneously three times per week.[127] The treatment is associated with significant immunosuppression, which requires prophylaxis for opportunistic infections.[128,129]

Chemotherapy

In patients with CTCL, chemotherapy agents are typically reserved for those with aggressive systemic involvement of disease or when other options for treatment are exhausted. As previously mentioned, early aggressive intervention with chemotherapy and radiation for MF has not been shown to improve prognosis when compared with topical therapy.[57] Moreover, chemotherapy has a shorter time to next treatment compared with single-drug treatment with INF-α or HDAC inhibitors. The median time to next treatment for single or multiagent chemotherapy is only 3.9 months, and it can be associated with more toxicity.[58]

Antimetabolites

Methotrexate and pralatrexate are competitive dihydrofolate reductase inhibitors that are cell cycle S–specific chemotherapeutic agents. They exert anti-inflammatory and antitumor effects by blocking the metabolism of folic acid. Recently, methotrexate has been found to block protein and DNA methylation, resulting in control of gene regulation through this mechanism. Increase in Fas death receptor protein expression has also been noted in patients treated with methotrexate.[130]

Oral methotrexate at doses up to 100 mg per week have been reported for treatment of patients with CTCL. Clinical practice is closer to 25 mg per week.[130] Most studies evaluating the use of methotrexate in CTCL are small, and the response criteria are not well defined. One retrospective study of 29 patients report an ORR of 58% in patients with erythrodermic MF with 41% achieving CR.[131] In another review of 69 patients, 33% ORR was seen in patients with plaque MF.[132] Surprisingly, a much lower response was noted in the phase III ALCANZA trial when methotrexate (or bexarotene) was used as a comparator to BV in CD30 positive CTCL patients.[105] Patients receiving low-dose oral methotrexate do not typically require leucovorin rescue at the low doses used, but our practice has been to give patients folic acid on the days of the week they are not receiving methotrexate. Adverse reactions to methotrexate include infections, liver enzyme abnormality, nausea, dyslipidemia, and myelosuppression.[133]

Pralatrexate is a more potent antimetabolite than methotrexate with higher affinity for dihydrofolate reductase.[130,134] In patients with CTCL, lower doses of pralatrexate weekly for 3 weeks in a 4 week cycle was found to be the optimal dose between tolerability and efficacy. At this dose level, the ORR was 45% with two patients achieving complete responses.[135] All patients should receive vitamin B_{12} and folate supplementation while on treatment. In some patients, the addition of leucovorin greatly reduced the incidence of mucositis when treated with pralatrexate.[136]

Gemcitabine

Gemcitabine is a pyrimidine analog that incorporates into DNA causing disruption of DNA replication. In a phase II prospective study of gemcitabine in 30 previous treated patients with MF and 14 patients with peripheral T-cell lymphoma, an ORR of 70% was observed with 11% achieving complete response.[137] Specific to CTCL, gemcitabine at 1000 mg/m^2 as monotherapy achieved an ORR of 68% in 25 patients. Eight percent of patients achieved complete responses.[138] The most common adverse effect of gemcitabine is myelosuppression, which is seen in 56% of patients. Gemcitabine was found to have an ORR of 75% as frontline therapy for patients with CTCL, but the median duration of response was only 10 months.[139] Increase hepatitis transaminases, fatigue, radiation recall, and mucositis was also reported.[138]

Pegylated Liposomal Doxorubicin

Pegylated liposomal doxorubicin is a different formulation of doxorubicin in which the drug is encapsulated in liposomes and stabilized by the attachment of polyethylene glycol to the liposomal surface, resulting in improved accumulation in tumor tissues. In a phase II trial in patients with advanced-stage MF, a 41% ORR was observed. Significant side effects include hand–foot reaction and other skin reactions, hypersensitivity reaction, and GI toxicity.[140] Other studies demonstrating response rates of 56% to 88% have been reported in other trials.[141–143]

Combination Chemotherapy

Combination chemotherapy with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or CHOP-based treatments for CTCL was found to have ORR of 40% with 25% complete response, but the median duration of response is only 5.7 months and with more toxicity.[144]

Other Modalities

Extracorporeal Photopheresis

Extracorporeal photopheresis (ECP) was developed when patients with CTCL were treated with leukapheresis and their blood was treated with PUVA. In early investigative research, evidence of anti-idiotypic response to malignant TCRs were discovered when these cells were exposed to UVA light and 8-methoxsalen, a photosensitizer. Patients receiving ECP first undergo leukapheresis; then the buffy coat is treated with methoxsalen photosensitizer and irradiated with UVA (320- to 400-nm wavelength). The mechanism of action was initially considered to be due to DNA crosslinking and apoptosis. However, upon reinfusion of the treated and likely apoptotic cells, there was conversion of circulating monocytes to immature dendritic cells, presentation of tumor-loaded dendritic cells to cytotoxic T-cells, and expansion of the cytotoxic T-cells against the malignant clone.[145–147] ECP is established as a frontline treatment of patients with blood involvement of CTCL.[145] In a meta-analysis, ECP was found to have a response rate of 55% and CR rate of 18% with higher response seen in patients with lower disease burden.[145,146] Multimodality treatment using ECP in combination with other immunomodulatory treatments may enhance its effects.[148]

Stem Cell Transplantation

Hematopoietic allogeneic stem cell transplantation may induce durable remission in patients with advanced CTCL likely because of the donor T-cell and NK cell graft-versus-tumor effect. Long-term response durations of more than 5 years have been reported after transplant; however, transplant-associated toxicity and mortality can occur in up to 30% of patients because of infections and graft-versus-host disease.[59,149,150] Lower intensity nonmyeloablative conditioning regimens may be associated with less toxicity and still maintain graft-versus-tumor response.[151] In comparison, autologous transplantation is associated with frequent and early relapses.[152]

PAGETOID RETICULOSIS

Sometimes also referred to as Woringer-Kolopp disease, this indolent form of CTCL presents as localized psoriasiform plaques, usually in the extremities, favoring the acral sites. The lesions may clinically be mistaken for warts or other benign lesions of the skin. Histopathologic features include epidermal hyperplasia and typically CD8+ cytotoxic neoplastic cells with marked exocytosis of cells in the epidermis. A CD4- and CD8- case has also been reported in the literature without poor prognosis observed.[153] It is important to differentiate this condition with more aggressive cytotoxic NK or T-cell lymphomas of the skin by history. Treatment is primarily radiation or excision because superficial treatment modalities are insufficient for controlling the deeper extension of the disease in the skin.[3] Successful treatment with phototherapy in combination with INF-α-2b has been reported.[154]

CD30 LYMPHOPROLIFERATIVE DISORDERS

Lymphomatoid papulosis (LyP) and primary cutaneous anaplastic large-cell lymphoma (pcALCL) are two entities on the spectrum of CD30 lymphoproliferative disorders that are associated with good prognoses.[155] On one end of the spectrum is LyP, which are clinically small (<1 cm), red, grouped papules or nodules that spontaneously resolve within 1 to 2 months. This condition is considered to be benign, but in 10% to 20% of patients, it can appear along with another type of lymphoma, most commonly in MF. It is also reported in patients with other hematologic malignancies such as Hodgkin lymphoma or pcALCL.[156,157] Although clinically similar, histopathologic features can be divided into five main subtypes, all with CD30 as prominent feature. Type A is the "conventional" and most common type; it is described as a wedge-shaped infiltrate with large atypical anaplastic cells admixed with histiocytes, eosinophils, and neutrophils. Type B is MF-like and resembles a wedge-shaped infiltrate with CD4+ bandlike epidermotropic cells. Type C is indistinguishable from pcALCL by histopathologic features alone and diagnosis is made by correlation with clinical history. Type D is similar to aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma. Epidermotropism is very prominent as is CD8 and CD30 positivity, but the clinical course is indolent like other LyPs. Type E has angiocentric or angiodestructive features and may be mistaken for vasculitis or NK T-cell lymphoma. Lesions can be monitored for resolution. In patients with widespread involvement, improvement has been reported with phototherapy, methotrexate, or bexarotene.[158–160] More recently, treatment with BV is associated with high response rates.[161]

Primary cutaneous ALCL is often histologically indistinguishable from LyP. Unlike systemic ALCL, pcALCL does not express anaplastic lymphoma kinase and if positive suggests a secondary ALCL in the skin. This condition typically presents as single ulcerated tumor or cluster of tumors. In contrast to LyP, there is rarely spontaneous resolution, but the prognosis is good with the estimated 5-year survival rate at more than 90%.[155] Frontline treatment

for localized disease is radiation. For more extensive disease, systemic treatment with BV has demonstrated superiority over methotrexate or bexarotene in the recent ALCANZA study. Overall response for pcALCL in the BV arm was 75% compared with 33% in the comparator arm.[105]

CD4 SMALL-MEDIUM PLEOMORPHIC LYMPHOPROLIFERATIVE DISORDER

CD4 small-medium pleomorphic lymphoproliferative disorder is an indolent condition previously listed as "CD4 small-medium pleomorphic lymphoma" but downgraded to lymphoproliferative disorder in 2016 by the WHO. It manifests clinically as a solitary lesion on the upper body, face, or neck without systemic involvement. Histologic features include CD4+ lymphocytes with αβ phenotype and absence of CD30 and background of reactive cells. These patients are successfully treated with radiation or surgery. Radiation may be preferred in some sites to avoid excessive scarring from surgery.[162,163]

SÉZARY SYNDROME

SS is a leukemic variant of CTCL in which patients present with new-onset erythroderma, lymphadenopathy, and aberrant cells in the peripheral blood compartment. Unlike patients with erythrodermic MF who progressively develop worsening blood involvement at advanced stages of disease, patients with SS typically do not report a history MF-like lesions preceding the diagnosis. Histopathologic findings on skin biopsy can be nondiagnostic in 30% of patients with known erythrodermic CTCL, and the diagnosis is made by flow cytometry analysis of peripheral blood.[164] A matching T-cell clone in the skin and blood compartment helps support the diagnosis in ambiguous cases. SS is associated with a poor prognosis and aggressive disease course with 5-year survival rate estimated to be 36% in the updated 2018 WHO-EORTC classification of cutaneous lymphomas.[2] Genetic variation in *CDKN2A* and *CDKN2B* genes have been linked to shorter survival periods in patients with SS.[165] The expression of FOX-P3 by SS cells has also been associated with a poor prognosis.[166] Unique clinical features of this variant include hyperkeratosis of the palms and soles, nail dystrophy, and ectropion.

Treatment of patients with SS is similar to the management of patients with advanced-stage MF with blood compartment involvement. Frontline treatment incorporating the use of ECP in the setting of multimodality therapy in combination with retinoid or INF produces high overall responses of 75% with a 30% complete response.[167] Mogamulizumab can also be considered in this group of patients given its high blood compartment response of 68% in the MAVORIC trial.[112] Supportive care is crucial in the care of patients with SS because of the high risk for skin infections and severe pruritus associated with the disease. See the Supportive Care section for review.

γδ T-CELL LYMPHOMA

γδ T-cell Lymphoma (GDTCL) is a rare aggressive primary cutaneous lymphoma presenting as fast-growing nodules and tumors with ulceration. Unlike MF tumors, in which there is a preceding history of lesions that have been present for years, lesions in GDTCL typically develop over weeks to months. The median survival associated time with this condition is 15 months, and it carries a poor response to conventional chemotherapy.[2] Histologic features include CD4-CD8- double-negative phenotype with strong expression of cytotoxic markers granzyme B and TIA-1.[168] Treatment with combination chemotherapy is typically used, but there are insufficient data to dictate a preferred course of management.

A subset of patients demonstrating γδ TCR staining but behaving in a more indolent fashion has also been reported. In one series, average survival from onset of symptoms was 7.3 years. A proposed hypothesis is that expression of CD4, CD30, or βF1 in some of the cases was associated with good prognosis.[169]

PRIMARY CUTANEOUS CD8+ CYTOTOXIC AGGRESSIVE EPIDERMOTROPIC T-CELL LYMPHOMA

Primary cutaneous CD8+ cytotoxic aggressive epidermotropic T-cell lymphoma is a rare cutaneous lymphoma with a poor prognosis; median OS was 12 months with 5-year OS of 32% in one series.[170] Histologic features include CD8+ lymphocyte full-thickness exocytosis into the epidermis in pagetoid pattern. Expression of at least one cytotoxic marker (TIA-1) and granzyme B was noted in almost all biopsies. Clinically, patients present with plaques on the skin with ulceration related to the cytotoxic granules released by the malignant cells. Treatment with standard CTCL treatment is ineffective in most cases, and the scarceness of data on this entity prevents the development of treatment recommendations and management guidelines.

SUBCUTANEOUS PANNICULITIS T-CELL LYMPHOMA

Subcutaneous panniculitis T-cell lymphoma (SPTCL) is a rare form of CTCL presenting as deep painful inflammatory nodules, resulting in atrophic plaques in involved sites. There is usually no surface change to the skin. The median age at diagnosis is in the third or fourth decade of life, occurring in younger female patients. The αβ subtype has an indolent course presenting histologically as a lobular lymphocytic panniculitis with tumor cells rimming around the fat lobules. The malignant lymphocyte is typically CD4-, CD8+, βF1 + and expresses cytotoxic granules. A history of autoimmune disorder was found in 25% of patients, with the most common being systemic lupus erythematosus. Because lupus panniculitis also presents as a lobular panniculitis and difficult to distinguish from SPTCL, patients should be screened for lupus at diagnosis.[171] Patients who develop hemophagocytic lymphohistiocytosis with this condition have a poorer prognosis. A more aggressive course is also seen patients with the γδ phenotype.[172] A variety of treatment options have been reported benefit, but corticosteroids with immunosuppressive therapy are frequently used as the initial treatment. The 5-year disease-specific survival rate is about 85%.[173]

PRIMARY CUTANEOUS B-CELL LYMPHOMAS

Primary Cutaneous Marginal Zone Lymphoma and Primary Cutaneous Follicle Center Lymphoma

The cutaneous B-cell lymphomas are less common than their T-cell counterparts. We will discuss the three most common types in this review. Because they are so rare, all patients should be screened for systemic B-cell lymphoma. Primary cutaneous marginal zone lymphoma (pcMZL) and primary cutaneous follicle center lymphoma (pcFCL) are both indolent subtypes of B-cell lymphoma in the skin associated with an excellent prognosis. The 5-year disease-specific survival rates are 99% for pcMZL and 95% for pcFCL.[2] PcFCL presents as reddish-brown papules and nodules with preference for the head and neck. Histologic features include nodular or diffuse infiltrates of lymphocytes, which are CD20+, Bcl-6 +, with monoclonal rearrangement of Ig genes detected. In contrast, pcMZL prefers the trunk and upper extremities. Histologic features include patch, nodular, or diffuse lymphocytic infiltrates without germinal centers with central nodular dark area of small reactive lymphocytes. The immunohistochemistry profile is CD20+, Bcl-2 +, CD5-, and Bcl-6 -.[3] Monoclonal Ig genes are present in only half of cases. In patients with the lymphoplasmacytic variant of pcMZL, association with *Borrelia burgdorferi* has been reported and should be screened.[174] Although no definitive link has been established between other infections such as *Helicobacter pylori*, hepatitis C virus, or Epstein-Barr virus, we screen all patients to rule out treatable infections. Treatment for pcMZL and pcFCL is similar and entails low-dose radiation, intralesional corticosteroids, intralesional INF, or rituximab. Systemic rituximab or chemotherapy is reserved for widespread or progressive systemic involvement.

Diffuse Large B-Cell Lymphoma, Leg Type

Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBL-LT), is a rare entity of primary cutaneous B-cell lymphoma with more aggressive course, resulting in a relatively lower 5-year disease-specific survival rate of 56%.[2] Despite the name of the condition, PCDLBL-LT can develop outside of the lower extremities and may be associated with improved survival.[175]A unique histologic feature is the predominance of centroblasts staining MUM-1 + along with CD20+, CD3-, and Bcl-2+.[176] Patients are typically treated with combination chemotherapy and radiation, with one review series demonstrating an improved 2-year survival rate in patients treated with rituximab plus anthracycline-based chemotherapy.[175]

SUPPORTIVE CARE

Pruritus

Pruritus is a cause of significant morbidity in patients with cutaneous lymphoma. In a retrospective analysis, a high prevalence of severe pruritus was found in patients with advanced-stage MF (83%) and SS (94%).[177] In patients with CTCL, multiple cytokines such as IL-4 and IL-5 have been upregulated, consequently leading to recruitment of eosinophils. Eosinophils in the blood can drive skin inflammation and pruritus.[178] More recently, IL-31 has been found to be upregulated in patients with CTCL and to correlate with itch.[179] Patients with CTCL-associated pruritus are best treated with treatment of the underlying lymphoma; however, many patients have treatment-refractory disease or are slow to respond to lymphoma treatment. Although pruritus caused by CTCL does not typically respond to antihistamines, multiple other nontraditional treatments for pruritus can be tried. Gabapentin is an anticonvulsant that dampens the release of neurotransmitters, promoting itch. Doses up to 2400 mg in divided doses daily

can be used.[180] Other options, such as aprepitant, naloxone, mirtazapine, and thalidomide, have been suggested.[178,180] In very pruritic patients, phototherapy may be helpful in select patients.

Infections

Patients with cutaneous lymphoma have decreased natural barrier to infection because of the disease and further breakdown from scratching. In addition, host immunosuppression and decrease in cell-mediated immunity put patients at risk for skin infection and colonization with bacteria and herpes virus.[181–183] *S. aureus* infections are common and can promote worsening of disease.[17,184,185] Treatment of skin infections has been reported to improve disease severity.[181,186]

MD ANDERSON PRACTICE TIPS

- Patients with cutaneous lymphoma should be ideally evaluated by a multidisciplinary team consisting of dermatologists, oncologists, radiation oncologists, and pathologists at a referral center with expertise in the disease.
- Imaging using CT or PET-CT should be performed in patients with thicker plaques, tumors, or erythroderma to rule out systemic involvement of CTCL. No imaging is typically needed for patients with early patch-stage disease unless there are systemic symptoms or rapid progression of disease.
- Peripheral blood flow cytometry should be obtained on all erythrodermic patients to rule out SS. Many patients with SS do not have positive skin biopsy results for lymphoma but rather reactive dermatitis on histopathology.
- In patients with skin-limited indolent cutaneous lymphoma, the frontline treatment is skin-directed therapy. Early aggressive intervention with chemotherapy and radiation for MF has not been shown to improve prognosis compared with topical therapy.
- Mogamulizumab is highly effective for blood compartment disease especially, in patients with SS, but has lower response rates in the skin and lymph node compartments.
- BV may be effective for patients with MF with low expression of CD30.

REFERENCES

1. American Cancer Society. Cancer Statistics Center. Accessed August 31, 2020. http://cancerstatisticscenter.cancer.org.
2. Willemze R, Cerroni L, Kempf W, et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. *Blood*. 2019;133(16):1703-1714.
3. Cerroni L. *Skin Lymphoma: The Illustrated Guide*. 4th ed. Markano Print Media Pte Ltd; 2014.
4. Toro JR, Liewehr DJ, Pabby N, et al. Gamma-delta T-cell phenotype is associated with significantly decreased survival in cutaneous T-cell lymphoma. *Blood*. 2003;101(9):3407-3412.
5. Vitiello P, Sica A, Ronchi A, et al. Primary cutaneous B-cell lymphomas: an update. *Front Oncol*. 2020;10:651.
6. Nassem S, Kashyap R, Awasthi NP, et al. Sézary syndrome presenting with "leonine facies." *Australas J Dermatol*. 2009;50(4):285-288.
7. King LE Jr, Dufresne RG Jr, Lovett GL, Rosin MA. Erythroderma: review of 82 cases. *South Med J*. 1986;79(10):1210-1215.
8. Wilcox RA. Cutaneous T-cell lymphoma: 2017 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2017;92(10):1085-1102.
9. Jawed SI, Myskowski PL, Horwitz S, et al. Primary cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome): part II. Prognosis, management, and future directions. *J Am Acad Dermatol*. 2014;70(2):223.e1-17; quiz 40-42.
10. Olsen EA, Whittaker S, Kim YH, et al. Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. *J Clin Oncol*. 2011;29(18):2598-2607.
11. Goyal A, LeBlanc RE, Carter JB. Cutaneous B-cell lymphoma. *Hematol Oncol Clin North Am*. 2019;33(1):149-161.
12. Olsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). *Blood*. 2007;110(6):1713-1722.
13. Korgavkar K, Xiong M, Weinstock M. Changing incidence trends of cutaneous T-cell lymphoma. *JAMA Dermatol*. 2013;149(11):1295-1299.
14. Jawed SI, Myskowski PL, Horwitz S, et al. Primary cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome): part I. Diagnosis: clinical and histopathologic features and new molecular and biologic markers. *J Am Acad Dermatol*. 2014;70(2):205.e1-16; quiz 21-22.
15. Girardi M, Heald PW, Wilson LD. The pathogenesis of mycosis fungoides. *N Engl J Med*. 2004;350(19):1978-1988.
16. Jarrousse V, Quereux G, Marques-Briand S, et al. Toll-like receptors 2, 4 and 9 expression in cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome). *Eur J Dermatol*. 2006;16(6):636-641.
17. Talpur R, Bassett R, Duvic M. Prevalence and treatment of Staphylococcus aureus colonization in patients with mycosis fungoides and Sézary syndrome. *Br J Dermatol*. 2008;159(1):105-112.
18. Herne KL, Talpur R, Breuer-McHam J, et al. Cytomegalovirus seropositivity is significantly associated with mycosis fungoides and Sézary syndrome. *Blood*. 2003;101(6):2132-2136.
19. Shimakage M, Sasagawa T, Kawahara K, et al. Expression of Epstein-Barr virus in cutaneous T-cell lymphoma including mycosis fungoides. *Int J Cancer*. 2001;92(2):226-231.
20. Geskin LJ, Akilov OE, Kwon S, et al. Therapeutic reduction of cell-mediated immunosuppression in mycosis fungoides and Sézary syndrome. *Cancer Immunol Immunother*. 2018;67(3):423-434.
21. Martinez-Escala ME, Posligua AL, Wickless H, et al. Progression of undiagnosed cutaneous lymphoma after anti-tumor necrosis factor-alpha therapy. *J Am Acad Dermatol*. 2018;78(6):1068-1076.
22. Rodríguez-Gil Y, Palencia SI, López-Ríos F, et al. Mycosis fungoides after solid-organ transplantation: report of 2 new cases. *Am J Dermatopathol*. 2008;30(2):150-155.
23. Ravat FE, Spittle MF, Russell-Jones R. Primary cutaneous T-cell lymphoma occurring after organ transplantation. *J Am Acad Dermatol*. 2006;54(4):668-675.
24. Burns MK, Cooper KD. Cutaneous T-cell lymphoma associated with HIV infection. *J Am Acad Dermatol*. 1993;29(3):394-399.
25. Izban KF, Ergin M, Qin JZ, et al. Constitutive expression of NF-kappa B is a characteristic feature of mycosis fungoides: implications for apoptosis resistance and pathogenesis. *Hum Pathol*. 2000;31(12):1482-1490.
26. Ferrara G, Pancione M, Votino C, et al. A specific DNA methylation profile correlates with a high risk of disease progression in stage I classical (Alibert-Bazin type) mycosis fungoides. *Br J Dermatol*. 2014;170(6):1266-1275.
27. Navas IC, Algara P, Mateo M, et al. p16(INK4a) is selectively silenced in the tumoral progression of mycosis fungoides. *Lab Invest*. 2002;82(2):123-132.
28. Marrogi AJ, Khan MA, Vonderheid EC, et al. p53 tumor suppressor gene mutations in transformed cutaneous T-cell lymphoma: a study of 12 cases. *J Cutan Pathol*. 1999;26(8):369-378.
29. Chou YC, Shih IH, Yang CP, et al. Concurrent mycosis fungoides and precursor B cell lymphoblastic lymphoma in a 6-year-old child. *Pediatr Dermatol*. 2005;22(1):23-25.
30. Chen Y, Nong L, Li X, Wang Y. Cutaneous composite lymphoma of mycosis fungoides and Hodgkin lymphoma: response to sequential therapy. *J Cutan Pathol*. 2020;47(9):829-833.
31. Chen S, Boyer D, Hristov AC. Primary cutaneous composite lymphomas. *Arch Pathol Lab Med*. 2018;142(11):1352-1357.
32. Barzilai A, Trau H, David M, et al. Mycosis fungoides associated with B-cell malignancies. *Br J Dermatol*. 2006;155(2):379-386.
33. Sherman S, Kremer N, Dalal A, et al. Melanoma risk is increased in patients with mycosis fungoides compared with patients with psoriasis and the general population. *Acta Derm Venereol*. 2020;100(19):adv00346.
34. Goyal A, O'Leary D, Goyal K, et al. Increased risk of second primary hematologic and solid malignancies in patients with mycosis fungoides: a Surveillance, Epidemiology, and End Results analysis. *J Am Acad Dermatol*. 2020;83(2):404-411.
35. Bradford PT, Devesa SS, Anderson WF, Toro JR. Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases. *Blood*. 2009;113(21):5064-5073.
36. Wu JH, Cohen BA, Sweren RJ. Mycosis fungoides in pediatric patients: clinical features, diagnostic challenges, and advances in therapeutic management. *Pediatr Dermatol*. 2020;37(1):18-28.
37. Talpur R, Singh L, Daulat S, et al. Long-term outcomes of 1,263 patients with mycosis fungoides and Sézary syndrome from 1982 to 2009. *Clin Cancer Res*. 2012;18(18):5051-5060.
38. Kreutzer KM, Effendy I. Cicatricial alopecia related to folliculotropic mycosis fungoides. *Dermatol Ther (Heidelb)*. 2020;10(5):1175-1180.
39. Amorim GM, Niemeyer-Corbellini JP, Quintella DC, et al. Hypopigmented mycosis fungoides: a 20-case retrospective series. *Int J Dermatol*. 2018;57(3):306-312.
40. Shah A, Safaya A. Granulomatous slack skin disease: a review, in comparison with mycosis fungoides. *J Eur Acad Dermatol Venereol*. 2012;26(12):1472-1478.
41. Kim EJ, Hess S, Richardson SK, et al. Immunopathogenesis and therapy of cutaneous T cell lymphoma. *J Clin Invest*. 2005;115(4):798-812.

42. Diwan H, Ivan D. CD8-positive mycosis fungoides and primary cutaneous aggressive epidermotropic CD8-positive cytotoxic T-cell lymphoma. *J Cutan Pathol*. 2009;36(3):390-392.
43. Nikolaou VA, Papadavid E, Katsambas A, et al. Clinical characteristics and course of CD8+ cytotoxic variant of mycosis fungoides: a case series of seven patients. *Br J Dermatol*. 2009;161(4):826-830.
44. Xu C, Wan C, Wang L, et al. Diagnostic significance of TCR gene clonal rearrangement analysis in early mycosis fungoides. *Clin J Cancer*. 2011;30(4):264-272.
45. Kirsch IR, Watanabe R, O'Malley JT, et al. TCR sequencing facilitates diagnosis and identifies mature T cells as the cell of origin in CTCL. *Sci Transl Med*. 2015;7(308):308ra158.
46. Pimpinelli N, Olsen EA, Santucci M, et al. Defining early mycosis fungoides. *J Am Acad Dermatol*. 2005;53(6):1053-1063.
47. Talpur R, Sui D, Gangar P, et al. retrospective analysis of prognostic factors in 187 cases of transformed mycosis fungoides. *Clin Lymphoma Myeloma Leuk*. 2016;16(1):49-56.
48. Wieser I, Wang C, Alberti-Violetti S, et al. Clinical characteristics, risk factors and long-term outcome of 114 patients with folliculotropic mycosis fungoides. *Arch Dermatol Res*. 2017;309(6):453-459.
49. Gerami P, Rosen S, Kuzel T, et al. Folliculotropic mycosis fungoides: an aggressive variant of cutaneous T-cell lymphoma. *Arch Dermatol*. 2008;144(6):738-746.
50. Wongpraparut C, Setabutra P. Phototherapy for hypopigmented mycosis fungoides in Asians. *Photodermatol Photoimmunol Photomed*. 2012;28(4):181-186.
51. Lambroza E, Cohen SR, Phelps R, et al. Hypopigmented variant of mycosis fungoides: demography, histopathology, and treatment of seven cases. *J Am Acad Dermatol*. 1995;32(6):987-993.
52. Scarisbrick JJ, Hodak E, Bagot M, et al. Blood classification and blood response criteria in mycosis fungoides and Sézary syndrome using flow cytometry: recommendations from the EORTC cutaneous lymphoma task force. *Eur J Cancer*. 2018;93:47-56.
53. Horwitz SM, Olsen EA, Duvic M, et al. Review of the treatment of mycosis fungoides and Sézary syndrome: a stage-based approach. *J Natl Compr Canc Netw*. 2008;6(4):436-442.
54. Kim YH, Liu HL, Mraz-Gernhard S, et al. Long-term outcome of 525 patients with mycosis fungoides and Sezary syndrome: clinical prognostic factors and risk for disease progression. *Arch Dermatol*. 2003;139(7):857-866.
55. Fraser-Andrews EA, Woolford AJ, Russell-Jones R, et al. Detection of a peripheral blood T cell clone is an independent prognostic marker in mycosis fungoides. *J Invest Dermatol*. 2000;114(1):117-121.
56. Benton EC, Crichton S, Talpur R, et al. A cutaneous lymphoma international prognostic index (CLIPi) for mycosis fungoides and Sezary syndrome. *Eur J Cancer*. 2013;49(13):2859-2868.
57. Kaye FJ, Bunn PA Jr, Steinberg SM, et al. A randomized trial comparing combination electron-beam radiation and chemotherapy with topical therapy in the initial treatment of mycosis fungoides. *N Engl J Med*. 1989;321(26):1784-1790.
58. Hughes CF, Khot A, McCormack C, et al. Lack of durable disease control with chemotherapy for mycosis fungoides and Sézary syndrome: a comparative study of systemic therapy. *Blood*. 2015;125(1):71-81.
59. Hosing C, Bassett R, Dabaja B, et al. Allogeneic stem-cell transplantation in patients with cutaneous lymphoma: updated results from a single institution. *Ann Oncol*. 2015;26(12):2490-2495.
60. Mehta-Shah N, Horwitz SM, Ansell S, et al. NCCN guidelines insights: primary cutaneous lymphomas, version 2.2020. *J Natl Compr Canc Netw*. 2020;18(5):522-536.
61. Pitzalis C, Pipitone N, Bajocchi G, Hall, et al. Corticosteroids inhibit lymphocyte binding to endothelium and intercellular adhesion: an additional mechanism for their anti-inflammatory and immunosuppressive effect. *J Immunol*. 1997;158(10):5007-5016.
62. Schwartzman RA, Cidlowski JA. Glucocorticoid-induced apoptosis of lymphoid cells. *Int Arch Allergy Immunol*. 1994;105(4):347-354.
63. Kartan S, Shalabi D, O'Donnell M, et al. Response to topical corticosteroid monotherapy in mycosis fungoides. *J Am Acad Dermatol*. 2020.
64. Zackheim HS, Kashani-Sabet M, Amin S. Topical corticosteroids for mycosis fungoides. Experience in 79 patients. *Arch Dermatol*. 1998;134(8):949-954.
65. Berthelot C, Rivera A, Duvic M. Skin directed therapy for mycosis fungoides: a review. *J Drugs Dermatol*. 2008;7(7):655-666.
66. Kim YH, Martinez G, Varghese A, Hoppe RT. Topical nitrogen mustard in the management of mycosis fungoides: update of the Stanford experience. *Arch Dermatol*. 2003;139(2):165-173.
67. Lessin SR, Duvic M, Guitart J, et al. Topical chemotherapy in cutaneous T-cell lymphoma: positive results of a randomized, controlled, multicenter trial testing the efficacy and safety of a novel mechlorethamine, 0.02%, gel in mycosis fungoides. *JAMA Dermatol*. 2013;149(1):25-32.
68. Lee LA, Fritz KA, Golitz L, et al. Second cutaneous malignancies in patients with mycosis fungoides treated with topical nitrogen mustard. *J Am Acad Dermatol*. 1982;7(5):590-598.
69. Du Vivier A, Vonderheid EC, Van Scott EJ, Urbach F. Mycosis fungoides, nitrogen mustard and skin cancer. *Br J Dermatol*. 1978;99(1):61-63.
70. Huen AO, Rook AH. Toll receptor agonist therapy of skin cancer and cutaneous T-cell lymphoma. *Curr Opin Oncol*. 2014;26(2):237-244.
71. Deeths MJ, Chapman JT, Dellavalle RP, et al. Treatment of patch and plaque stage mycosis fungoides with imiquimod 5% cream. *J Am Acad Dermatol*. 2005;52(2):275-280.
72. Lewis DJ, Byekova YA, Emge DA, Duvic M. Complete resolution of mycosis fungoides tumors with imiquimod 5% cream: a case series. *J Dermatolog Treat*. 2017;28(6):567-569.
73. van der Fits L, Mourits S, Voerman JS, et al. Imiquimod-induced psoriasis-like skin inflammation in mice is mediated via the IL-23/IL-17 axis. *J Immunol*. 2009;182(9):5836-5845.
74. Breneman D, Duvic M, Kuzel T, et al. Phase 1 and 2 trial of bexarotene gel for skin-directed treatment of patients with cutaneous T-cell lymphoma. *Arch Dermatol*. 2002;138(3):325-332.
75. Thomsen K, Hammar H, Molin L, Volden G. Retinoids plus PUVA (RePUVA) and PUVA in mycosis fungoides, plaque stage. A report from the Scandinavian Mycosis Fungoides Group. *Acta Derm Venereol*. 1989;69(6):536-538.
76. Kuzel TM, Roenigk HH Jr, Samuelson E, et al. Effectiveness of interferon alfa-2a combined with phototherapy for mycosis fungoides and the Sézary syndrome. *J Clin Oncol*. 1995;13(1):257-263.
77. Marka A, Carter JB. Phototherapy for cutaneous T-cell lymphoma. *Dermatol Clin*. 2020;38(1):127-135.
78. Verdich J. Squamous cell carcinoma. Occurrence in mycosis fungoides treated with psoralens plus long-wave ultraviolet radiation. *Arch Dermatol*. 1979;115(11):1338-1339.
79. Kanokrungsee S, Rajatanavin N, Rutnin S, Vachiramon V. Efficacy of narrowband ultraviolet B twice weekly for hypopigmented mycosis fungoides in Asians. *Clin Exp Dermatol*. 2012;37(2):149-152.
80. Lovgren ML, Scarisbrick JJ. Update on skin directed therapies in mycosis fungoides. Chin Clin Oncol. 2019;8(1):7.
81. Lokitz ML, Wong HK. Bexarotene and narrowband ultraviolet B phototherapy combination treatment for mycosis fungoides. *Photodermatol Photoimmunol Photomed*. 2007;23(6):255-257.
82. D'Acunto C, Gurioli C, Neri I. Plaque stage mycosis fungoides treated with bexarotene at low dosage and UVB-NB. *J Dermatolog Treat*. 2010;21(1):45-48.

83. Neelis KJ, Schimmel EC, Vermeer MH, et al. Low-dose palliative radiotherapy for cutaneous B- and T-cell lymphomas. *Int J Radiat Oncol Biol Phys*. 2009;74(1):154-158.
84. Cotter GW, Baglan RJ, Wasserman TH, Mill W. Palliative radiation treatment of cutaneous mycosis fungoides—a dose response. *Int J Radiat Oncol Biol Phys*. 1983;9(10):1477-1480.
85. Prince HM, Whittaker S, Hoppe RT. How I treat mycosis fungoides and Sézary syndrome. *Blood*. 2009;114(20):4337-4353.
86. Navi D, Riaz N, Levin YS, et al. The Stanford University experience with conventional-dose, total skin electron-beam therapy in the treatment of generalized patch or plaque (T2) and tumor (T3) mycosis fungoides. *Arch Dermatol*. 2011;147(5):561-567.
87. Kamstrup MR, Specht L, Skovgaard GL, Gniadecki R. A prospective, open-label study of low-dose total skin electron beam therapy in mycosis fungoides. *Int J Radiat Oncol Biol Phys*. 2008;71(4):1204-1207.
88. Harrison C, Young J, Navi D, et al. Revisiting low-dose total skin electron beam therapy in mycosis fungoides. *Int J Radiat Oncol Biol Phys*. 2011;81(4):e651-e657.
89. Cheng SX, Kupper T. A new rexinoid for cutaneous T-cell lymphoma. *Arch Dermatol*. 2001;137(5):649-652.
90. Zhang C, Hazarika P, Ni X, et al. Induction of apoptosis by bexarotene in cutaneous T-cell lymphoma cells: relevance to mechanism of therapeutic action. *Clin Cancer Res*. 2002;8(5):1234-1240.
91. Huen AO, Kim EJ. The role of systemic retinoids in the treatment of cutaneous t-cell lymphoma. *Dermatol Clin*. 2015;33(4):715-729.
92. Duvic M, Hymes K, Heald P, et al. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. *J Clin Oncol*. 2001;19(9):2456-2471.
93. Duvic M, Martin AG, Kim Y, et al. Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. *Arch Dermatol*. 2001;137(5):581-593.
94. Straus DJ, Duvic M, Horwitz SM, et al. Final results of phase II trial of doxorubicin HCl liposome injection followed by bexarotene in advanced cutaneous T-cell lymphoma. *Ann Oncol*. 2014;25(1):206-210.
95. Bassuner J, Miranda RN, Emge DA, et al. Mycosis fungoides of the oral cavity: fungating tumor successfully treated with electron beam radiation and maintenance bexarotene. *Case Rep Dermatol Med*. 2016;2016:5857935.
96. Cheeley J, Sahn RE, DeLong LK, Parker SR. Acitretin for the treatment of cutaneous T-cell lymphoma. *J Am Acad Dermatol*. 2013;68(2):247-254.
97. Nikolaou V, Patsatsi A, Sidiropoulou P, et al. Monotherapy and combination therapy with acitretin for mycosis fungoides: results of a retrospective, multicentre study. *J Eur Acad Dermatol Venereol*. 2020.
98. Spaccarelli N, Rook AH. The use of interferons in the treatment of cutaneous T-cell lymphoma. *Dermatol Clin*. 2015;33(4):731-745.
99. Olsen EA, Bunn PA. Interferon in the treatment of cutaneous T-cell lymphoma. *Hematol Oncol Clin North Am*. 1995;9(5):1089-1107.
100. Olsen EA, Rosen ST, Vollmer RT, et al. Interferon alfa-2a in the treatment of cutaneous T cell lymphoma. *J Am Acad Dermatol*. 1989;20(3):395-407.
101. Yanagi T, Shimizu T, Ujiie H, et al. Peginterferon alfa-2b for mycosis fungoides. *Arch Dermatol*. 2006;142(5):649-651.
102. Kaplan EH, Rosen ST, Norris DB, et al. Phase II study of recombinant human interferon gamma for treatment of cutaneous T-cell lymphoma. *J Natl Cancer Inst*. 1990;82(3):208-212.
103. Sugaya M, Tokura Y, Hamada T, et al. Phase II study of i.v. interferon-gamma in Japanese patients with mycosis fungoides. *J Dermatol*. 2014;41(1):50-56.
104. Katz J, Janik JE, Younes A. Brentuximab vedotin (SGN-35). *Clin Cancer Res*. 2011;17(20):6428-6436.
105. Prince HM, Kim YH, Horwitz SM, et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. *Lancet*. 2017;390(10094):555-566.
106. Kim YH, Tavallaee M, Sundram U, et al. Phase II investigator-initiated study of brentuximab vedotin in mycosis fungoides and Sézary syndrome with variable CD30 expression level: a multi-institution collaborative project. *J Clin Oncol*. 2015;33(32):3750-3758.
107. Duvic M, Tetzlaff MT, Gangar P, et al. Results of a phase II trial of brentuximab vedotin for CD30+ cutaneous T-Cell lymphoma and lymphomatoid papulosis. *J Clin Oncol*. 2015;33(32):3759-3765.
108. Zhang C, Chairatchaneeboon M, Haun P, et al. Treatment of CD30-negative refractory mycosis fungoides with brentuximab vedotin. *JAMA Dermatol*. 2018;154(1):109-110.
109. Stranzenbach R, Dippel E, Schlaak M, Stadler R. Brentuximab vedotin in CD30(+) cutaneous lymphoma: how do we treat, how shall we treat? A review of the literature. *Br J Dermatol*. 2017;177(6):1503-1509.
110. Ollila TA, Sahin I, Olszewski AJ. Mogamulizumab: a new tool for management of cutaneous T-cell lymphoma. *Onco Targets Ther*. 2019;12:1085-1094.
111. Moore DC, Elmes JB, Shibu PA, et al. Mogamulizumab: an anti-CC chemokine receptor 4 antibody for T-cell lymphomas. *Ann Pharmacother*. 2020;54(4):371-379.
112. Kim YH, Bagot M, Pinter-Brown L, et al. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. *Lancet Oncol*. 2018;19(9):1192-1204.
113. Wang JY, Hirotsu KE, Neal TM, et al. Histopathologic characterization of mogamulizumab-associated rash. *Am J Surg Pathol*. 2020;44(12):1666-1676.
114. Chen L, Carson KR, Staser KW, et al. Mogamulizumab-associated cutaneous granulomatous drug eruption mimicking mycosis fungoides but possibly indicating durable clinical response. *JAMA Dermatol*. 2019 May 29:e190369. doi: 10.1001/jamadermatol.2019.0369. Epub ahead of print.
115. Fuji S, Inoue Y, Utsunomiya A, et al. pretransplantation anti-ccr4 antibody mogamulizumab against adult T-cell leukemia/lymphoma is associated with significantly increased risks of severe and corticosteroid-refractory graft-versus-host disease, nonrelapse mortality, and overall mortality. *J Clin Oncol*. 2016;34(28):3426-3433.
116. Duvic M. Histone deacetylase inhibitors for cutaneous T-cell lymphoma. *Dermatol Clin*. 2015;33(4):757-764.
117. Lakshmaiah KC, Jacob LA, Aparna S, et al. Epigenetic therapy of cancer with histone deacetylase inhibitors. *J Cancer Res Ther*. 2014;10(3):469-478.
118. Litvinov IV, Cordeiro B, Fredholm S, et al. Analysis of STAT4 expression in cutaneous T-cell lymphoma (CTCL) patients and patient-derived cell lines. *Cell Cycle*. 2014;13(18):2975-2982.
119. Olsen EA, Kim YH, Kuzel TM, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. *J Clin Oncol*. 2007;25(21):3109-3115.
120. Piekarz RL, Frye R, Turner M, et al. Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma. *J Clin Oncol*. 2009;27(32):5410-5417.
121. Foss F, Duvic M, Lerner A, et al. Clinical efficacy of romidepsin in tumor stage and folliculotropic mycosis fungoides. *Clin Lymphoma Myeloma Leuk*. 2016;16(11):637-643.
122. Whittaker SJ, Demierre MF, Kim EJ, et al. Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. *J Clin Oncol*. 2010;28(29):4485-4491.

123. Clark RA, Watanabe R, Teague JE, et al. Skin effector memory T cells do not recirculate and provide immune protection in alemtuzumab-treated CTCL patients. *Sci Transl Med*. 2012;4(117):117ra7.
124. Alinari L, Geskin L, Grady T, et al. Subcutaneous alemtuzumab for Sézary Syndrome in the very elderly. *Leuk Res*. 2008;32(8):1299-1303.
125. Gautschi O, Blumenthal N, Streit M, et al. Successful treatment of chemotherapy-refractory Sézary syndrome with alemtuzumab (Campath-1H). *Eur J Haematol*. 2004;72(1):61-63.
126. Kennedy GA, Seymour JF, Wolf M, et al. Treatment of patients with advanced mycosis fungoides and Sézary syndrome with alemtuzumab. *Eur J Haematol*. 2003;71(4):250-256.
127. Bernengo MG, Quaglino P, Comessatti A, et al. Low-dose intermittent alemtuzumab in the treatment of Sézary syndrome: clinical and immunologic findings in 14 patients. *Haematologica*. 2007;92(6):784-794.
128. Lundin J, Hagberg H, Repp R, et al. Phase 2 study of alemtuzumab (anti-CD52 monoclonal antibody) in patients with advanced mycosis fungoides/Sezary syndrome. *Blood*. 2003;101(11):4267-4272.
129. O'Brien S, Ravandi F, Riehl T, et al. Valganciclovir prevents cytomegalovirus reactivation in patients receiving alemtuzumab-based therapy. *Blood*. 2008;111(4):1816-1819.
130. Wood GS, Wu J. Methotrexate and pralatrexate. *Dermatol Clin*. 2015;33(4):747-755.
131. Zackheim HS, Kashani-Sabet M, Hwang ST. Low-dose methotrexate to treat erythrodermic cutaneous T-cell lymphoma: results in twenty-nine patients. *J Am Acad Dermatol*. 1996;34(4):626-631.
132. Zackheim HS, Kashani-Sabet M, McMillan A. Low-dose methotrexate to treat mycosis fungoides: a retrospective study in 69 patients. *J Am Acad Dermatol*. 2003;49(5):873-878.
133. Olek-Hrab K, Maj J, Chmielowska E, et al. Methotrexate in the treatment of mycosis fungoides—a multicenter observational study in 79 patients. *Eur Rev Med Pharmacol Sci*. 2018;22(11):3586-3594.
134. Lansigan F, Foss FM. Current and emerging treatment strategies for cutaneous T-cell lymphoma. *Drugs*. 2010;70(3):273-286.
135. Horwitz SM, Kim YH, Foss F, et al. Identification of an active, well-tolerated dose of pralatrexate in patients with relapsed or refractory cutaneous T-cell lymphoma. *Blood*. 2012;119(18):4115-4122.
136. Foss FM, Parker TL, Girardi M, Li A. Effect of leucovorin administration on mucositis and skin reactions in patients with peripheral T-cell lymphoma or cutaneous T-cell lymphoma treated with pralatrexate. *Leuk Lymphoma*. 2019;60(12):2927-2930.
137. Zinzani PL, Baliva G, Magagnoli M, et al. Gemcitabine treatment in pretreated cutaneous T-cell lymphoma: experience in 44 patients. *J Clin Oncol*. 2000;18(13):2603-2606.
138. Duvic M, Talpur R, Wen S, et al. Phase II evaluation of gemcitabine monotherapy for cutaneous T-cell lymphoma. *Clin Lymphoma Myeloma*. 2006;7(1):51-58.
139. Marchi E, Alinari L, Tani M, et al. Gemcitabine as frontline treatment for cutaneous T-cell lymphoma: phase II study of 32 patients. *Cancer*. 2005;104(11):2437-2441.
140. Dummer R, Quaglino P, Becker JC, et al. Prospective international multicenter phase II trial of intravenous pegylated liposomal doxorubicin monochemotherapy in patients with stage IIB, IVA, or IVB advanced mycosis fungoides: final results from EORTC 21012. *J Clin Oncol*. 2012;30(33):4091-4097.
141. Wollina U, Graefe T, Karte K. Treatment of relapsing or recalcitrant cutaneous T-cell lymphoma with pegylated liposomal doxorubicin. *J Am Acad Dermatol*. 2000;42(1 Pt 1):40-46.
142. Wollina U, Dummer R, Brockmeyer NH, et al. Multicenter study of pegylated liposomal doxorubicin in patients with cutaneous T-cell lymphoma. *Cancer*. 2003;98(5):993-1001.
143. Quereux G, Marques S, Nguyen JM, et al. Prospective multicenter study of pegylated liposomal doxorubicin treatment in patients with advanced or refractory mycosis fungoides or Sézary syndrome. *Arch Dermatol*. 2008;144(6):727-733.
144. Fierro MT, Quaglino P, Savoia P, et al. Systemic polychemotherapy in the treatment of primary cutaneous lymphomas: a clinical follow-up study of 81 patients treated with COP or CHOP. *Leuk Lymphoma*. 1998;31(5-6):583-588.
145. Cho A, Jantschitsch C, Knobler R. Extracorporeal photopheresis—an overview. Front Med (Lausanne). 2018;5:236.
146. Edelson R, Berger C, Gasparro F, et al. Treatment of cutaneous T-cell lymphoma by extracorporeal photochemotherapy. Preliminary results. *N Engl J Med*. 1987;316(6):297-303.
147. Zic JA. Extracorporeal photopheresis in the treatment of mycosis fungoides and Sézary syndrome. *Dermatol Clin*. 2015;33(4):765-776.
148. Quaglino P, Knobler R, Fierro MT, et al. Extracorporeal photopheresis for the treatment of erythrodermic cutaneous T-cell lymphoma: a single center clinical experience with long-term follow-up data and a brief overview of the literature. *Int J Dermatol*. 2013;52(11):1308-1318.
149. Polansky M, Talpur R, Daulat S, et al. Long-term complete responses to combination therapies and allogeneic stem cell transplants in patients with Sézary syndrome. *Clin Lymphoma Myeloma Leuk*. 2015;15(5):e83-e93.
150. Duarte RF, Canals C, Onida F, et al. Allogeneic hematopoietic cell transplantation for patients with mycosis fungoides and Sézary syndrome: a retrospective analysis of the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. *J Clin Oncol*. 2010;28(29):4492-4499.
151. Duvic M, Donato M, Dabaja B, et al. Total skin electron beam and non-myeloablative allogeneic hematopoietic stem-cell transplantation in advanced mycosis fungoides and Sezary syndrome. *J Clin Oncol*. 2010;28(14):2365-2372.
152. Wu PA, Kim YH, Lavori PW, et al. A meta-analysis of patients receiving allogeneic or autologous hematopoietic stem cell transplant in mycosis fungoides and Sézary syndrome. *Biol Blood Marrow Transplant*. 2009;15(8):982-990.
153. Mourtzinos N, Puri PK, Wang G, Liu ML. CD4/CD8 double negative pagetoid reticulosis: a case report and literature review. *J Cutan Pathol*. 2010;37(4):491-496.
154. Wang T, Liu YH, Zheng HY. Localized pagetoid reticulosis (Woringer-Kolopp disease) completely response to NB-UVB combined with IFN. *Dermatol Ther*. 2014;27(4):227-229.
155. Kempf W, Pfaltz K, Vermeer MH, et al. EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. *Blood*. 2011;118(15):4024-4035.
156. Kaudewitz P, Stein H, Plewig G, et al. Hodgkin's disease followed by lymphomatoid papulosis. Immunophenotypic evidence for a close relationship between lymphomatoid papulosis and Hodgkin's disease. *J Am Acad Dermatol*. 1990;22(6 Pt 1):999-1006.
157. Wieser I, Oh CW, Talpur R, Duvic M. Lymphomatoid papulosis: treatment response and associated lymphomas in a study of 180 patients. *J Am Acad Dermatol*. 2016;74(1):59-67.
158. Fernández-de-Misa R, Hernández-Machín B, Servitje O, et al. First-line treatment in lymphomatoid papulosis: a retrospective multicentre study. *Clin Exp Dermatol*. 2018;43(2):137-143.
159. Newland KM, McCormack CJ, Twigger R, et al. The efficacy of methotrexate for lymphomatoid papulosis. *J Am Acad Dermatol*. 2015;72(6):1088-1090.
160. Fujimura T, Furudate S, Tanita K, et al. Successful control of phototherapy-resistant lymphomatoid papulosis with oral bexarotene. *J Dermatol*. 2018;45(2):e37-e38.

161. Lewis DJ, Talpur R, Huen AO, et al. Brentuximab vedotin for patients with refractory lymphomatoid papulosis: an analysis of phase 2 results. *JAMA Dermatol*. 2017;153(12):1302-1306.
162. James E, Sokhn JG, Gibson JF, et al. CD4 + primary cutaneous small/medium-sized pleomorphic T-cell lymphoma: a retrospective case series and review of literature. *Leuk Lymphoma*. 2015;56(4):951-957.
163. Kim EJ, Aria AB, Wilmas K, et al. Primary cutaneous CD4+ small- to medium-sized pleomorphic T-cell lymphoproliferative disorder in a pediatric patient successfully treated with low-dose radiation. *Pediatr Dermatol*. 2019;36(1):e23-e26.
164. Moriarty B, Whittaker S. Diagnosis, prognosis and management of erythrodermic cutaneous T-cell lymphoma. *Expert Rev Hematol*. 2015;8(2):159-171.
165. Laharanne E, Chevret E, Idrissi Y, et al. CDKN2A-CDKN2B deletion defines an aggressive subset of cutaneous T-cell lymphoma. *Mod Pathol*. 2010;23(4):547-558.
166. Capriotti E, Vonderheid EC, Thoburn CJ, et al. Expression of T-plastin, FoxP3 and other tumor-associated markers by leukemic T-cells of cutaneous T-cell lymphoma. *Leuk Lymphoma*. 2008;49(6):1190-1201.
167. Raphael BA, Shin DB, Suchin KR, et al. High clinical response rate of Sezary syndrome to immunomodulatory therapies: prognostic markers of response. *Arch Dermatol*. 2011;147(12):1410-1415.
168. Guitart J, Weisenburger DD, Subtil A, et al. Cutaneous γδ T-cell lymphomas: a spectrum of presentations with overlap with other cytotoxic lymphomas. *Am J Surg Pathol*. 2012;36(11):1656-1665.
169. Vin H, Talpur R, Tetzlaff MT, Duvic M. T-cell receptor-γ in gamma-delta phenotype cutaneous T-cell lymphoma can be accompanied by atypical expression of CD30, CD4, or TCRβF1 and an indolent clinical course. *Clin Lymphoma Myeloma Leuk*. 2014;14(6):e195-e200.
170. Guitart J, Martinez-Escala ME, Subtil A, et al. Primary cutaneous aggressive epidermotropic cytotoxic T-cell lymphomas: reappraisal of a provisional entity in the 2016 WHO classification of cutaneous lymphomas. *Mod Pathol*. 2017;30(5):761-772.
171. Bosisio F, Boi S, Caputo V, et al. Lobular panniculitic infiltrates with overlapping histopathologic features of lupus panniculitis (lupus profundus) and subcutaneous T-cell lymphoma: a conceptual and practical dilemma. *Am J Surg Pathol*. 2015;39(2):206-211.
172. Kao GF, Resh B, McMahon C, et al. Fatal subcutaneous panniculitis-like T-cell lymphoma gamma/delta subtype (cutaneous gamma/delta T-cell lymphoma): report of a case and review of the literature. *Am J Dermatopathol*. 2008;30(6):593-599.
173. López-Lerma I, Peñate Y, Gallardo F, et al. Subcutaneous panniculitis-like T-cell lymphoma: clinical features, therapeutic approach, and outcome in a case series of 16 patients. *J Am Acad Dermatol*. 2018;79(5):892-898.
174. Cerroni L, Zöchling N, Pütz B, Kerl H. Infection by Borrelia burgdorferi and cutaneous B-cell lymphoma. *J Cutan Pathol*. 1997;24(8):457-461.
175. Grange F, Beylot-Barry M, Courville P, et al. Primary cutaneous diffuse large B-cell lymphoma, leg type: clinicopathologic features and prognostic analysis in 60 cases. *Arch Dermatol*. 2007;143(9):1144-1150.
176. Hallermann C, Niermann C, Fischer RJ, Schulze HJ. New prognostic relevant factors in primary cutaneous diffuse large B-cell lymphomas. *J Am Acad Dermatol*. 2007;56(4):588-597.
177. Vij A, Duvic M. Prevalence and severity of pruritus in cutaneous T cell lymphoma. *Int J Dermatol*. 2012;51(8):930-934.
178. Ahern K, Gilmore ES, Poligone B. Pruritus in cutaneous T-cell lymphoma: a review. *J Am Acad Dermatol*. 2012;67(4):760-768.
179. Nattkemper LA, Martinez-Escala ME, Gelman AB, et al. Cutaneous T-cell lymphoma and pruritus: the expression of IL-31 and its receptors in the skin. *Acta Derm Venereol*. 2016;96(7):894-898.
180. Demierre MF, Taverna J. Mirtazapine and gabapentin for reducing pruritus in cutaneous T-cell lymphoma. *J Am Acad Dermatol*. 2006;55(3):543-544.
181. Emge DA, Bassett RL, Duvic M, Huen AO. Methicillin-resistant Staphylococcus aureus (MRSA) is an important pathogen in erythrodermic cutaneous T-cell lymphoma (CTCL) patients. *Arch Dermatol Res*. 2020;312(4):283-288.
182. Segal RJ, Watson W. Kaposi's varicelliform eruption in mycosis fungoides. *Arch Dermatol*. 1978;114(7):1067-1069.
183. Mallo-García S, Coto-Segura P, Suárez-Casado H, et al. Fatal outcome due to bacterial superinfection of eczema herpeticum in a patient with mycosis fungoides. *Dermatol Online J*. 2008;14(6):21.
184. Krejsgaard T, Willerslev-Olsen A, Lindahl LM, et al. Staphylococcal enterotoxins stimulate lymphoma-associated immune dysregulation. *Blood*. 2014;124(5):761-770.
185. Jackow CM, Cather JC, Hearne V, et al. Association of erythrodermic cutaneous T-cell lymphoma, superantigen-positive Staphylococcus aureus, and oligoclonal T-cell receptor V beta gene expansion. *Blood*. 1997;89(1):32-40.
186. Lewis DJ, Holder BB, Duvic M. The "Duvic regimen" for erythrodermic flares secondary to Staphylococcus aureus in mycosis fungoides and Sézary syndrome. *Int J Dermatol*. 2018;57(1):123-124.

13 Hodgkin Lymphoma

Collin K. Chin
L. Jeffrey Medeiros
Fredrick B. Hagemeister
Hun J. Lee

KEY CONCEPTS

- Nodular lymphocyte–predominant Hodgkin lymphoma (HL) usually presents in early stages. Therapy depends on disease extent, but localized radiotherapy is the usual choice for early-stage disease. Rituximab is also an effective agent, but it should be given in combination with chemotherapy.
- Staging by positron emission tomography is standard, and marrow biopsy is generally unnecessary. Response after two cycles of therapy is a standard to assess response, and the Lugano (Deauville score) response criteria should be followed. Patients with DS 1 or 2 should be considered as having a metabolic complete response. Those with DS 4 or 5 should be considered to have likely had failure of therapy, and those with persistent positivity after four cycles of therapy are at a high risk of failure. German Hodgkin Lymphoma Study Group criteria and the International Prognostic Score should be calculated for all patients to assess outcomes of therapy.
- Standard of care for favorable early-stage classical HL is two cycles of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) and 20-Gy involved site radiation therapy (ISRT). For unfavorable early-stage disease, it is four cycles of ABVD and 30 Gy ISRT. The ABVD regimen remains the preferred regimen for most patients with advanced disease treated in the United States even though BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) has proven to be a better regimen for unfavorable early-stage and advanced-stage disease. BEACOPP is associated with a higher risk of neutropenia and hospitalization and in the United States is administered to only selected patients.
- Brentuximab vedotin (BV) has been studied as adjuvant therapy for early-stage disease, as a single agent and in combinations for relapsed and refractory disease, as prophylaxis after autologous stem cell transplant (ASCT), and in combinations for initial treatment of classical Hodgkin disease. The drug causes some peripheral neuropathy but is generally tolerable, and the A (BV)-AVD regimen provides better progression-free survival results for most patients with advanced disease than ABVD.
- PD-1 (programmed death-1) inhibitors (nivolumab, pembrolizumab) are also effective single agents for relapsed disease and in combinations improve responses for relapsed and untreated disease even in patients who have previously received BV. The most effective combinations using this and other targets are still under investigation.
- High-dose therapy followed by ASCT remains the standard of care for patients with relapsed HL. However, proof of adequate response, usually by PET and in most patients by biopsy, is necessary before this therapy. Patients with refractory disease should be offered alternate therapies, and novel agents and therapies, including T-cell and other immunotherapy, are under investigation for this small group of patients.

Hodgkin lymphoma (HL) was recognized in the first half of the 19th century by Thomas Hodgkin and Samuel Wilks.[1] HL usually arises in lymph nodes, preferentially in the cervical area, and the majority of HLs manifest clinically in young adults in their third and fourth decades of life. In 2018, 79,990 new cases of the disease were described, and 34,984 persons were reported to have died of the illness worldwide from 185 countries.[2] In a recent report, the incidence of HL was 3.0 per 100,000 person-years in the United States; it is higher in Western countries than in Asian countries.[3] Biological and clinical studies have shown that HLs include two disease entities: nodular lymphocyte–predominant HL (NLPHL) and classical HL (cHL). The two entities differ in their clinical features and behaviors. Within cHL, four subtypes have been described:

nodular sclerosis (NS), mixed cellularity, lymphocyte rich, and lymphocyte depleted. These four subtypes differ in their clinical features, growth pattern, presence of fibrosis, and frequency of Epstein-Barr virus (EBV) infection but share the immunophenotype of tumor cells.

In 2019, it was estimated that 8110 Americans would be diagnosed with HL, and as of January1, 2019, there were 234,890 survivors of the disease.[4] HL has been traditionally defined as a hematopoietic neoplasm composed of diagnostic Hodgkin and Reed-Sternberg (HRS) cells within a reactive cell background. An HRS cell is large, 30 to 60 μm, containing a bilobed vesicular nucleus, with each lobe containing a prominent round eosinophilic nucleolus surrounded by a clear zone or halo; it also has abundant cytoplasm. However, HRS cells often comprise less than 1% of the involved tumor tissue and are absent in NLPHL. HRS cells are believed to be derived from germinal center (GC) B cells that have unfavorable immunoglobulin V gene mutations, whereas lymphocyte-predominant (LP) cells, which were previously termed lymphocytic and histiocytic (LH) cells, are thought to originate from antigen-selected GC B cells.[5]

IMMUNOPHENOTYPIC FINDINGS IN HODGKIN LYMPHOMAS

NLPHL is immunophenotypically distinct from other types of HL. LP cells usually express leukocyte common antigen (LCA; CD45), immunoglobulin J chain, B-cell antigens (CD19, CD20, CD22, CD79A, and BCL-6), and epithelial membrane antigen (EMA) and are negative for CD15 and CD30 (Figs. 13–1C and D). These results suggest that the LP cells are B cells that arise from the GC. LP cells are negative for T-cell antigens but are often surrounded by a rosette of small, reactive T cells that may be positive for pan-T-cell antigens and CD57 (Fig. 13–1E). EBV is almost always absent in the LP cells of NLPHL.

Immunophenotypic findings in classical HL differ from those observed in NLPHL. Overall, the mature B-cell origin of the HRS cells is not readily apparent because HRS cells have a very unusual phenotype and have expression of genes that are seen on many hematopoietic cell types. The neoplastic cells are positive for CD15 and CD30 and negative for LCA (CD45) (Fig. 13–2) and EMA.[1] B-cell antigens, such as CD20, CD79A, PAX-5/BSAP, and MUM1/IRF4, are expressed in a subset of cases. CD20 expression is often weak. T-cell antigens are usually not expressed by the neoplastic cells. BCL-2 is positive in up to half of cases and has been correlated with poorer prognosis.[6] EBV is relatively common in cHL, but its frequency varies greatly among different types.

The management of patients with HL continues to evolve. Before the widespread use of modern polychemotherapy, large-field radiation therapy (RT) was able to cure patients with cHL. However, reliance on radiation alone required extensive radiation portals to treat nearly the entire lymphatic system with radiation doses up to 44 Gy. With long-term follow-up, many patients developed cardiac toxicity and second malignancies. Therefore, efforts have been made to reduce the long-term toxicities of treatment for HL while maintaining excellent cure rates. With modern chemotherapy, multiple randomized studies have shown that radiation portals can be safely reduced from extended-field radiation therapy (EFRT) to involved-field radiation therapy (IFRT) and, now, even smaller fields of radiation, including involved-node radiation.

Currently, the treatment of patients with cHL is stratified by risk groups—early-stage favorable, early-stage unfavorable, and advanced-stage disease—according to the clinical stage and the presence or absence of adverse clinical features. This chapter reviews advances in the management of HL, including recent publications about strategies of management of patients with the rarer diagnosis of NLPHL.

CLINICAL SUBTYPES OF HODGKIN LYMPHOMA

Over the past decade, investigators have made significant progress in the diagnosis, classification, staging, prognosis, and treatment of HL. In past years, the true lineage of the neoplastic cells in HL was unknown; hence, the term *Hodgkin disease* was used. It is now recognized that almost all cases of HL are of B-cell lineage; hence, the name was changed to HL. However, the classification of HL has remained relatively stable over the past 40 years, and the World Health Organization (WHO) classification of lymphoid neoplasms was updated in 2016 (Table 13–1).[1] The current WHO classification recognizes that NLPHL is distinct from the other types that can be grouped together under the rubric of cHL.[1]

Nodular Lymphocyte–Predominant Hodgkin Lymphoma

Clinical Features

Approximately 5% of patients with HL have NLPHL. This disease is usually localized and most often involves cervical or axillary lymph nodes.[1,7] The disease affects patients of all ages, males more often than females, and is clinically indolent (Table 13–2). Systemic symptoms such as fever, weight loss, and nights sweats (also known as B symptoms) are infrequent. Patients with

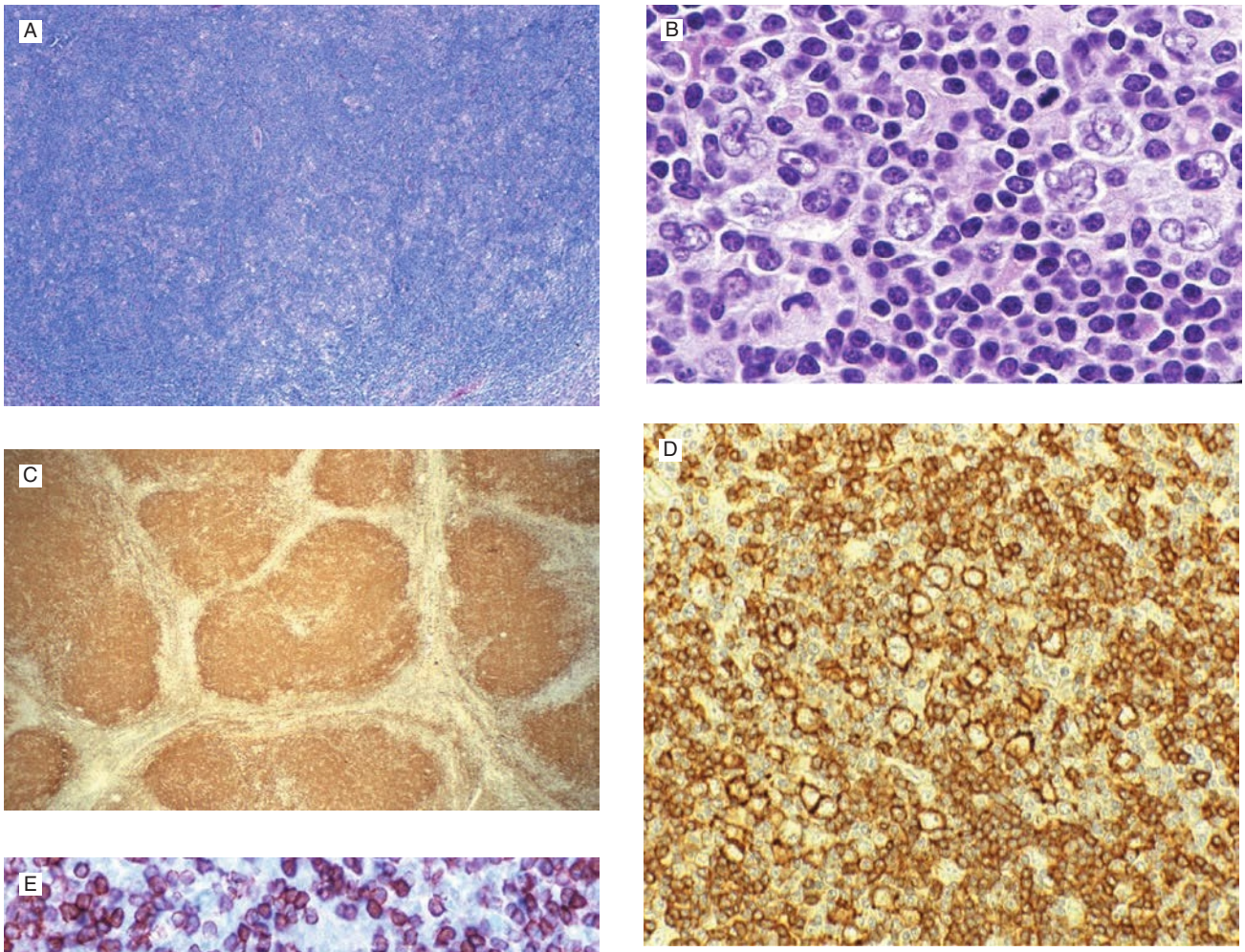


FIGURE 13–1 **Nodular lymphocyte–predominant Hodgkin lymphoma. A. At low-power magnification, the neoplasm is vaguely nodular. B. At high-power magnification, large lymphocytic and histiocytic (LH) cells, resembling popped kernels of corn, are identified in a background of reactive lymphocytes and histiocytes. C and D. Immunohistochemical stain for CD20. C. At low-power magnification, this immunostain highlights the nodular pattern and shows numerous B cells in the nodules. D. At high-power magnification, large LH cells and small reactive B cells are positive for CD20. E. Immunohistochemical stain for CD3. Scattered small reactive T cells are present and focally surround the LH cells (so-called rosetting).**

NLPHL are characterized as having a more indolent course with delayed relapse compared with those with cHL, analogous to low-grade non-HLs.[7] Patients with NLPHL are at a 5% to 6% risk of developing diffuse large B-cell lymphomas (DLBCLs) or T-cell/histiocyte-rich large B-cell lymphomas.[1]

The German Hodgkin Lymphoma Study Group (GHSG) has reported a large retrospective study of 394 patients with NLPHL. Patients were predominantly men (75%), only 9% had B symptoms, and 79% had early-stage disease.[8] With a median follow-up of period 50 months, tumor control (freedom from treatment failure [FFTF]) and overall survival (OS) were 88% and 96%, respectively, slightly better than in cHL (82% and 92%, respectively).

Histologic Features

NLPHL is characterized by effacement of nodal architecture by variably sized, vague nodules composed of numerous small lymphocytes, histiocytes, and characteristic neoplastic LP cells (see Fig. 13–1A).[1,9] These cells are typically large, with pale cytoplasms and polyploid vesicular nuclei containing inconspicuous

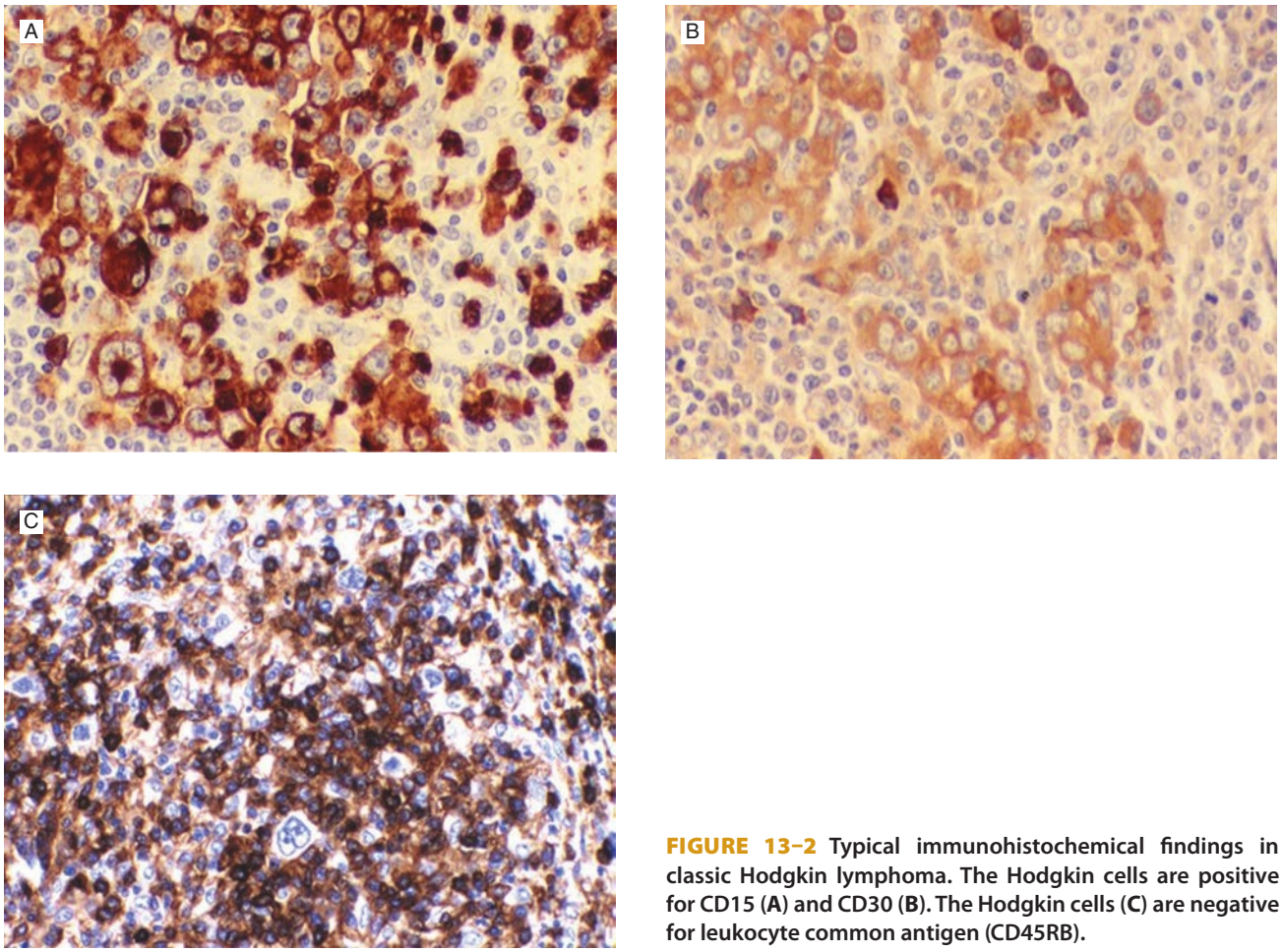


FIGURE 13–2 Typical immunohistochemical findings in classic Hodgkin lymphoma. The Hodgkin cells are positive for CD15 (**A**) and CD30 (**B**). The Hodgkin cells (**C**) are negative for leukocyte common antigen (CD45RB).

TABLE 13–1 World Health Organization Classification of Hodgkin Lymphoma

Nodular lymphocyte predominant
Classical Hodgkin lymphoma - Nodular sclerosis - Lymphocyte rich - Mixed cellularity - Lymphocyte deplete

nucleoli resembling kernels of popped corn—hence the nickname popcorn cells (see Fig. 13–1B). However, LP cells can exhibit a range of cytologic appearances. These cells can be round or have relatively prominent nucleoli. Eosinophils, neutrophils, and plasma cells are usually absent in NLPHL, and there is no associated necrosis or fibrosis.

Cases of NLPHL can also have diffuse areas. When diffuse areas are large, their presence often correlates with more aggressive disease. To reflect this change in clinical behavior, many pathologists

TABLE 13–2 Comparison of Clinical Features of Nodular Lymphocyte–Predominant (NLPHL) and Classical Hodgkin Lymphoma (HL)

Clinical Feature	NLPHL	Classical HL
Frequency	5%	95%
Age distribution	Unimodal: equal in children and adults	Bimodal: peak in second and third decades of life
Male (%)	70	50
Sites involved	Lymph nodes with sparing mediastinum	Mediastinum, cervical lymph nodes
Stage at diagnosis[a]	I	II or III
B symptoms (%)	<20	40
Clinical course	Indolent, late relapses	Aggressive, curable

[a]Most common stage at time of diagnosis.

diagnose such cases as NLPHL with progression to T-cell/histiocyte-rich large B-cell lymphoma, also described as T-cell–rich B-cell lymphoma (TCRBCL). Other pathologists use the term *NLPHL with large diffuse areas* and suggest that the diffuse areas may represent the beginning stages of progression to DLBCL. The boundary between NLPHL with diffuse areas and TCRBCL remains blurred. Most cases previously designated as diffuse LPHL, as defined previously, are now classified differently.[10] With appropriate workup, these cases are usually classified as NLPHL with large diffuse areas, lymphocyte-rich cHL, or TCRBCL.

Gene expression profiling of NLPHL to determine the origin and pathogenesis of LP cells found significant similarities between NLPHL, TCRBCL, and cHL.[11] Overall, LP cells are thought to derive from antigen-selected GC B cells.[5] LP cells also demonstrate deregulation of numerous apoptosis regulators and putative oncogenes and a partial loss of their B-cell phenotype. In addition, there is constitutive activation of nuclear factor-κB (NF-κB), the Janus kinases/signal transducers and activator of transcription (JAK/STAT) pathway, and aberrant extracellular-regulated kinase signaling.

Lymphocyte-Rich Classical Hodgkin Lymphoma

Lymphocyte-rich cHLs (LRHLs) have been recognized that resemble NLPHL histologically but are cHL immunophenotypically.[1,7] In a study of NLPHL by the European Task Force on Lymphoma, a large number of tumors that had been classified as NLPHL were reviewed; the diagnosis was confirmed in only half of these cases. Most of those excluded were reclassified as LRHL.[9] The frequency of this type of HL is not well known but is most likely low (<5%). Clinically, patients with LRHL have disease that is similar to that seen in patients with other subtypes of cHL or have clinical findings intermediate between NLPHL and cHL. Unlike patients with NLPHL, late relapse is uncommon in patients with LRHL.

Histologically, these tumors are rich in small lymphocytes and histiocytes. Granulocytes and plasma cells are usually infrequent. Necrosis is usually not present. Lymphocyte-rich cHL may be either nodular or diffuse. The nodular type closely resembles NLPHL. Vague nodules of numerous small lymphocytes are present, and the nodules may have a small, compressed GC (Figs. 13–3A and B). The neoplastic cells are present in the mantle zones of the nodules. These neoplastic cells usually resemble Reed-Sternberg and typical mononuclear variant cells (so-called Hodgkin cells) rather than LP cells. The cell composition is similar in diffuse cases of LRHL, but nodularity is minimal or absent. Immunohistochemical studies of LRHL show that the large neoplastic cells have an immunophenotype similar to that of all cHL cases, positive for CD15 and CD30 and negative for LCA (CD45) (Figs. 13–3C–E).

Nodular Sclerosis Hodgkin Lymphoma

Clinical Features

NS is the most common form of cHL, representing 60% to 70% of all cases in Western countries; it is also the most common type of cHL in patients younger than 50 years of age. Whites are affected more often than others, and nodular sclerosis HL (NSHL) is much less frequent in Asian countries.[2,3] The age-adjusted incidence rate of NSHL has been stable since 1993 to 2008 in the United States according to the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) data.[2] The male-to-female ratio is approximately equal. NSHL has a marked predilection for involving mediastinal, supraclavicular, and cervical lymph nodes. A mediastinal mass is very common, and the thymus may be involved.

Histologic Features

NSHL is characterized by a triad of findings: (1) a nodular pattern, (2) broad bands of fibrosis that outline the nodules, and (3) characteristic mononuclear cell variants known as lacunar cells (Fig. 13–4). A lacunar cell has abundant clear cytoplasm with a sharply demarcated cell membrane. In formalin-fixed tissue, a characteristic artifact occurs. The cell cytoplasm retracts, leaving a clear space or lacuna surrounding the cell, hence the origin of the name. The typical lacunar cell has a polylobate nucleus with one or multiple small nucleoli. However, lacunar cells can show great morphologic variability and can be round with prominent nucleoli, or they may resemble large noncleaved cells. A heterogeneous mixture of reactive cells may be seen in HL, including small lymphocytes, histiocytes, eosinophils, neutrophils, and plasma cells in variable numbers.

NSHL has been graded as 1 or 2 by the British National Lymphoma Investigation (BNLI) group according to numbers of neoplastic cells and reactive cells present; this grading system has been adopted in the WHO classification.[1,12] Grade 2 cases of NSHL show numerous neoplastic (lacunar) cells and depletion of reactive lymphocytes. Lymphocyte-depleted and syncytial variants (Fig. 13–5) of NSHL have been described; these cases are the outermost examples of grade 2 NSHL. This syncytial variant of NSHL is composed of sheets of neoplastic cells and necrosis.

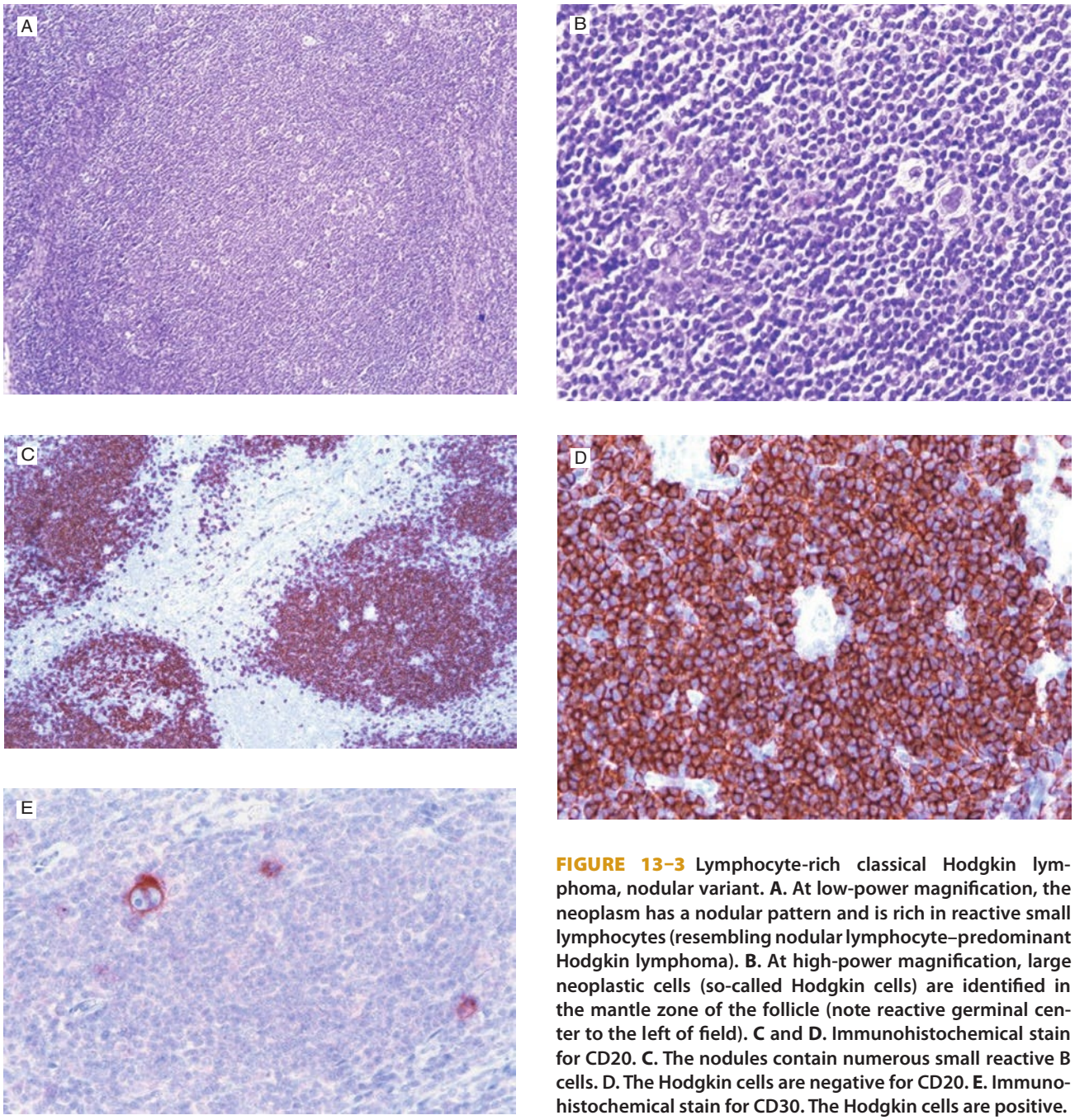


FIGURE 13–3 **Lymphocyte-rich classical Hodgkin lymphoma, nodular variant. A. At low-power magnification, the neoplasm has a nodular pattern and is rich in reactive small lymphocytes (resembling nodular lymphocyte–predominant Hodgkin lymphoma). B. At high-power magnification, large neoplastic cells (so-called Hodgkin cells) are identified in the mantle zone of the follicle (note reactive germinal center to the left of field). C and D. Immunohistochemical stain for CD20. C. The nodules contain numerous small reactive B cells. D. The Hodgkin cells are negative for CD20. E. Immunohistochemical stain for CD30. The Hodgkin cells are positive.**

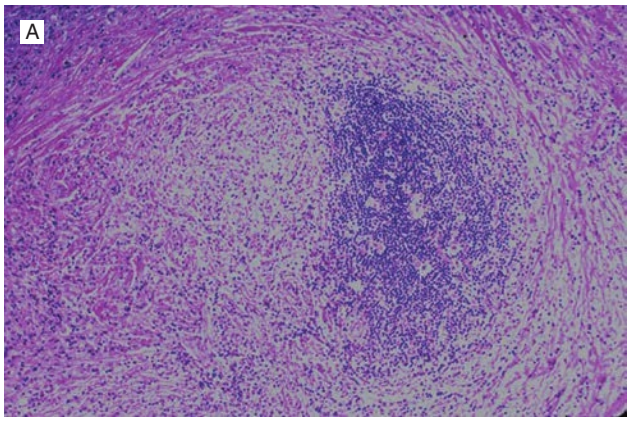
Mixed-Cellularity Hodgkin Lymphoma

Clinical Features

The mixed-cellularity variant of HL (MCHL), the second most common type, affects 15% to 25% of all patients with the disease and is the most common form in patients older than 50 years of age.[1,13] Men are affected more often than women. According to NCI SEER data, MCHL is relatively more common in African Americans and Hispanic Americans than in whites in the United States. A substantial percentage of patients with MCHL have clinical stage III or stage IV disease and B symptoms.

Histologic Features

Mixed-cellularity HL is characterized by a large number of Reed-Sternberg cells and Hodgkin cells in a background of numerous eosinophils, plasma cells, histiocytes, and granulocytes in varying proportions (Fig. 13–6).[1] The lymph node architecture is usually diffusely replaced. Partially involved lymph nodes show



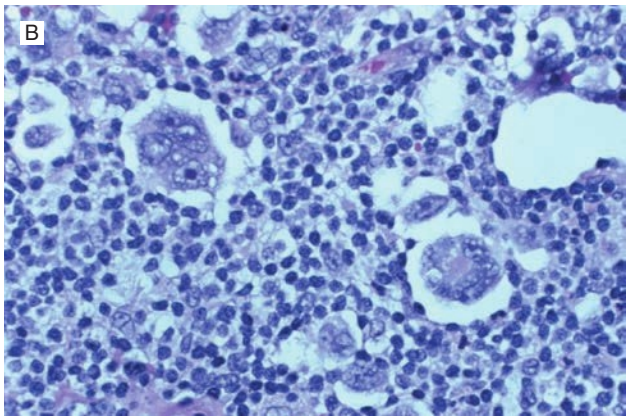
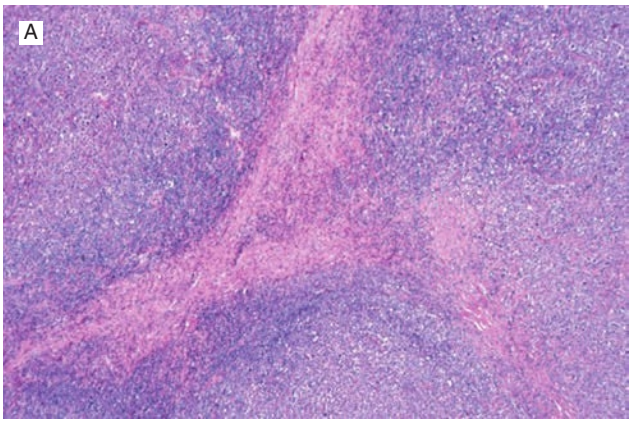


FIGURE 13–4 Nodular sclerosis Hodgkin lymphoma. **A.** The neoplasm is nodular, and the nodules are surrounded by dense fibrous bands. **B.** The large neoplastic cells (lacunar cells) lie within lacunar spaces, and many are multinucleated in this field. Reactive cells are present in the background.



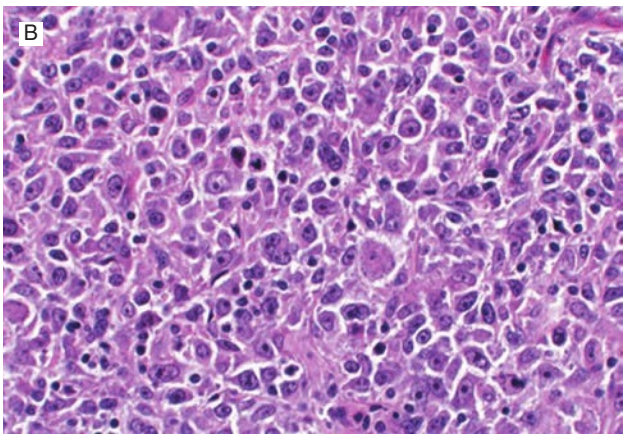
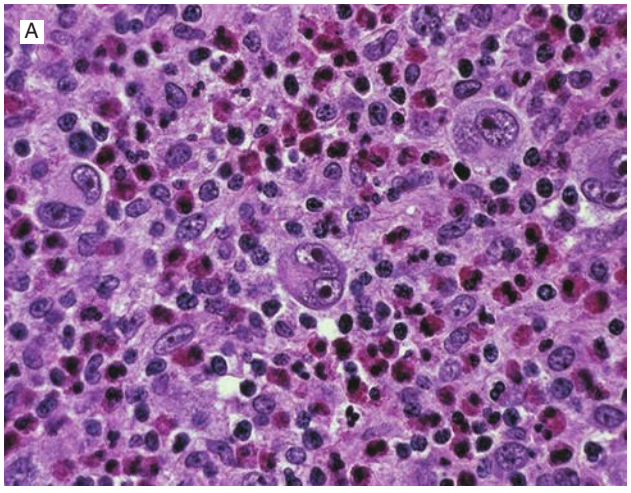


FIGURE 13–5 Syncytial variant of nodular sclerosis Hodgkin lymphoma. **A.** Nodularity and a fibrous bond can be appreciated in this field. B. The nodules are composed of many neoplastic cells with depletion of small lymphocytes.



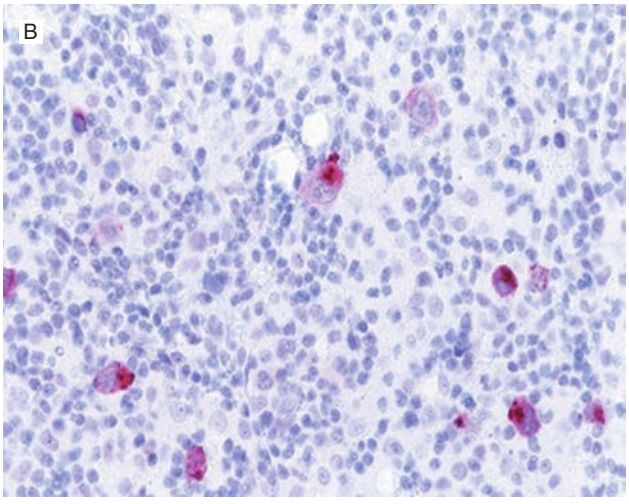


FIGURE 13–6 Mixed-cellularity Hodgkin lymphoma. **A.** Classic Reed-Sternberg cell (center of field) and mononuclear Hodgkin cells can be appreciated in a background of reactive lymphocytes, histiocytes, and eosinophils. **B.** Immunostain for Epstein-Barr virus latent membrane protein type 1. The neoplastic cells are positive.

selective paracortical infiltration. Disorderly fibrosis may be seen, but the broad fibrous bands and capsular fibrosis characteristic of NSHL are absent.

Two variants of MCHL can be relatively more difficult to diagnose. In the interfollicular variant, which most likely represents partial involvement of lymph nodes by HL, the tumor is located in the interfollicular region and is often associated with reactive follicular hyperplasia and marked plasmacytosis. In the epithelioid histiocyte-rich variant, numerous epithelioid histiocytes and granulomas are present; these can be so numerous as to obscure the neoplastic cells. The importance of these variants of MCHL lies in their unusual histologic findings.

Lymphocyte-Depleted Hodgkin Lymphoma

Clinical Features

Lymphocyte-depleted HL (LDHL) is the least common type, representing 1% of all cases.[13] In the NCI SEER study, it was shown that the age-adjusted incidence rate for LDHL has decreased. This decrease is most likely explained by the recognition by pathologists that many tumors previously classified as LDHL are, in fact, non-HLs (eg, anaplastic large-cell lymphoma). Improved classification is the result of application of immunohistochemical and molecular methods to the study of these tumors.

Patients with LDHL are usually older, and LDHL is rare in individuals younger than 40 years of age. There is a slight male predominance. Whites and African Americans are equally affected. Most patients have advanced clinical stage and B symptoms. Patients commonly have a large contiguous mass of matted lymph nodes or diffuse visceral involvement. The diffuse fibrosis type of LDHL commonly has a subdiaphragmatic distribution. Lymphocyte-depleted HL has the poorest prognosis of all types of HL.

Histologic Features

The LDHL category includes two variants originally recognized by Lukes and Butler: diffuse fibrosis and reticular (Fig. 13–7). The diffuse fibrosis variant of LDHL is characterized by an extensive proliferation of disordered, hypocellular fibrosis. Diagnostic HRS cells can be difficult to find and may be spindled within dense collagen. Reactive inflammatory cells are relatively few. The reticular variant of LDHL has numerous HRS cells and bizarre variants that have been termed *pleomorphic variants*. These cells may exhibit marked variations in nuclear number and shape, often with giant nucleoli. Normal small lymphocytes are infrequent compared with the other subtypes of HL. Necrosis is common and may be extensive. The HRS cells and pleomorphic variants may be found in sheets. Mitotic figures are usually numerous.

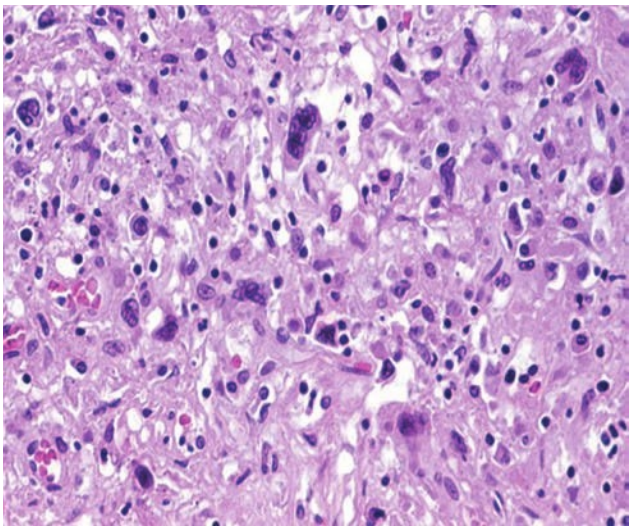


FIGURE 13–7 Lymphocyte-depleted Hodgkin lymphoma. Large neoplastic cells in the background of loose, nonpolarized fibrosis and lymphocyte depletion.

CLINICAL EVALUATION

Staging of Patients

The Ann Arbor system for staging patients with HL at the time of initial presentation forms the basis for the treatment of disease and has allowed comparison of results achieved by different investigations for more than two decades. Important modifications of the Ann Arbor system were developed at the Cotswold Conference in 1989 (Table 13–3).[14] Since then, the staging evaluation has been in evolution. A recent recommendation for the staging procedure in lymphoma described the importance of positron emission tomography (PET)–computed tomography (CT) scan for fluorodeoxyglucose (FDG)-avid lymphomas, of which HL is one example.[15] For HL and other FDG-avid lymphomas, PET-CT improves the accuracy of staging compared with CT scans for nodal and extranodal sites.[16] PET-CT leads to change in stage in 10% to 30% of patients, more often upstaging, although alteration in treatment occurs in fewer patients with no demonstrated impact on overall outcome. However, PET-CT is critical as a baseline measurement before therapy to increase the accuracy of subsequent response assessment.[17] In addition, contrast-enhanced CT should be included for a more accurate measurement of nodal size if required for clinical trials. The University of Texas MD Anderson Cancer Center (MDACC) diagnostic and treatment algorithms for HL are shown in Figure 13–8.

TABLE 13–3 Ann Arbor Staging System with Cotswold Modifications for Hodgkin Lymphoma

Stage I	Involvement of a single lymph node region or lymphoid structure (eg, spleen, thymus, Waldeyer ring) or a single extralymphatic site
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm; localized contiguous involvement of only one extralymphatic organ or site and lymph node region on the same side of the diaphragm (IIE); the number of anatomic regions involved should be indicated by a subscript (eg, II_3)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by spleen involvement (IIIS) or by localized contiguous involvement of only one extralymphatic organ or site (IIIE) or both (IIISE)
Stage IV	Diffuse or disseminated involvement of one or more extranodal organs or tissues, with or without associated lymph node involvement
Modifying Features	
A	No symptoms
B	Fever (>38°C), drenching night sweats, unexplained weight loss of >10% body weight within the preceding 6 months
X	Bulky disease: greater than one third widening of the mediastinum, >10 cm maximum diameter of a nodal mass
E	Involvement of a single extranodal site that is contiguous or proximal to the known nodal site
CS	Clinical stage
PS	Pathologic stage (as determined by laparotomy)

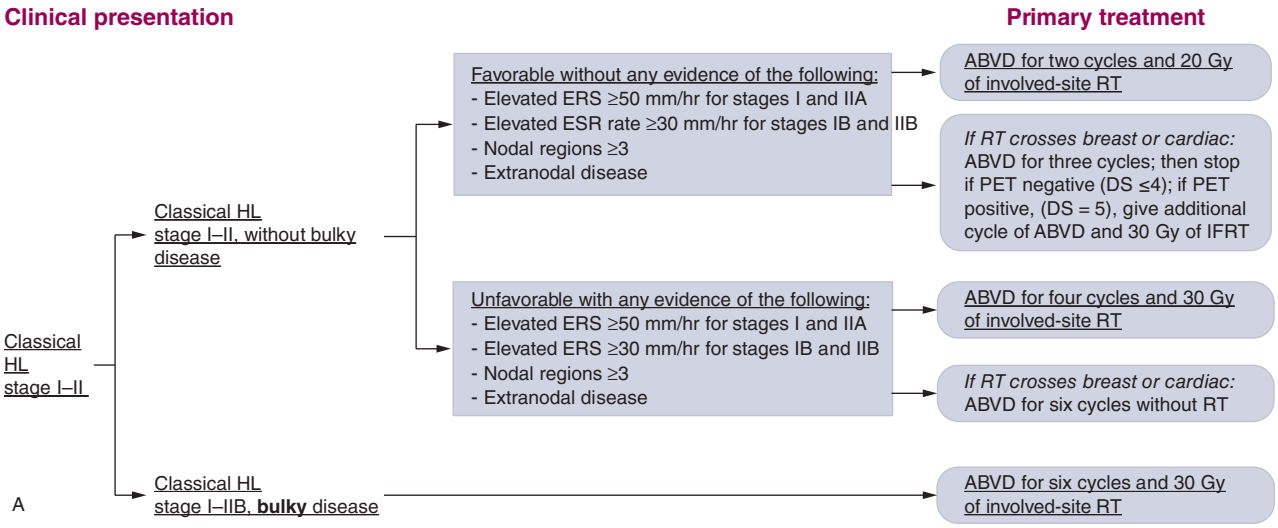


FIGURE 13–8 MD Anderson Cancer Center treatment algorithms for Hodgkin lymphoma (HL). **A.** Therapy for stage I-II HL. **B.** Therapy for advanced stage IIB and stage III-IV classical HL and lymphocyte-predominant HL. **C.** End-of-therapy response assessment and management of classical HL and lymphocyte-predominant HL. **D.** Therapy for relapsed or refractory HL. A + AVD, brentuximab vedotin, Adriamycin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ASCT, autologous stem cell transplantation; AVD, Adriamycin, vinblastine, and dacarbazine; BV, brentuximab vedotin; DHAP, high-dose cytarabine, cisplatin, and dexamethasone; DS, Deauville score; ESR, erythrocyte sedimentation rate; GND, gemcitabine, Navelbine, and Doxil; ICE, ifosfamide, carboplatin, and etoposide; IPS, International Prognostic Score; IFRT, involved-field radiotherapy; IGEV, ifosfamide, gemcitabine, vinorelbine, and prednisone; PD-1, programmed death-1; PET-2, positron emission tomography assessment after two cycles of therapy; R-ABVD, rituximab, doxorubicin, bleomycin, vinblastine, and dacarbazine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; RT, radiation therapy.

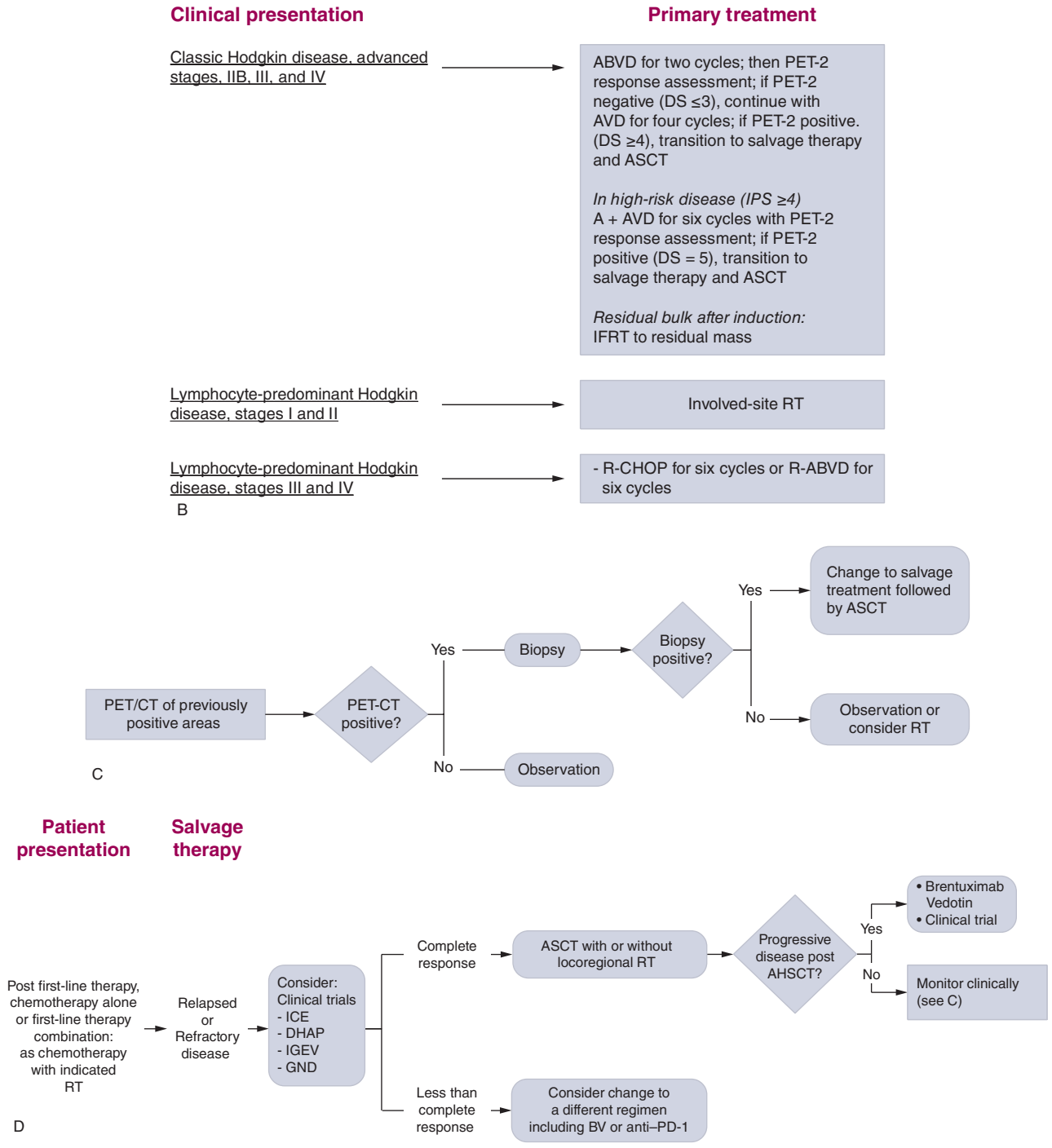


FIGURE 13–8 (Continued)

Patient Evaluation

The initial evaluation of patients with HL has both prognostic and therapeutic significance (see Figure 13–8). Routine studies that should be performed include a complete blood cell count with differential; electrolytes; blood urea nitrogen; creatinine; liver function tests; lactate dehydrogenase; albumin; pregnancy tests in women of childbearing age; erythrocyte sedimentation rate (ESR); pulmonary function testing with carbon monoxide diffusing capacity; evaluation of cardiac ejection fraction; chest radiography; CT of the neck, chest, abdomen, and pelvis; and PET-CT (Table 13–4).

Bone-marrow biopsy has been a standard test for lymphoma staging. However, the high sensitivity of PET-CT for bone-marrow involvement has recently led to questioning the use of bone-marrow biopsy as

TABLE 13–4 Recommended Procedures for Staging of Hodgkin Lymphoma

History and Examination	Identification of B Symptoms
Radiologic and other assessments	- Chest radiograph - CT scans, including the neck, chest, abdomen, and pelvis whole-body PET scan - Echocardiogram or MUGA scan - Pulmonary function tests - HIV serology - Pregnancy test in women of childbearing age
Hematologic procedures	- CBC with differential - ESR
Biochemical procedures	- Liver function tests - Serum albumin - Lactate dehydrogenase
Procedures for use under special circumstances	- Ultrasound scanning - MRI

CBC, complete blood count; CT, computed tomography; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; MUGA, multigated acquisition; PET, positron emission tomography.

a staging procedure in several common histologies, including HL.[15] In one study of patients with HL, 18% had focal skeletal lesion on PET-CT, but only 6% had positive bone-marrow biopsies, all with advanced-stage disease on PET-CT.[18] Patients with early-stage disease rarely have marrow involvement in the absence of a suggestive PET finding, and those with advanced-stage disease rarely have marrow involvement in the absence of disease-related symptoms. Although the issue is controversial and some institutions perform bone-marrow biopsy for initial staging evaluation of HL, almost all patients would not have been allocated to another treatment based on bone-marrow biopsy results. Thus, bone-marrow biopsy is no longer indicated for the routine staging of patients with cHL. Magnetic resonance imaging has also not superseded CT scanning of the chest and abdomen in the evaluation of HL. It is largely restricted to the assessment of specific situations such as bony involvement and spinal cord compression and in lieu of CT scans in pregnant patients.

Prognostic Factors

For clinically early-stage (CS) disease (CS I or CS II), several prognostic factors have been identified through retrospective studies of patients with HLs, largely based on patients treated with radiotherapy alone. Adverse features include (1) advanced age, which correlates with the presence of occult abdominal disease and with poor results of salvage therapy; (2) male gender; (3) MC histologic type, which is associated with the presence of occult abdominal disease; (4) B symptoms, also associated with the presence of occult abdominal disease; (5) large mediastinal mass, defined as a mass measuring greater than one-third of the chest diameter on a standard chest radiograph; (6) a larger number of involved nodal regions; (7) elevated ESR; (8) anemia; and (9) low serum albumin level.[19,20]

International organizations have defined various systems that calculate the risk of recurrence of disease or, in some cases, death, after treatment for HL. The European Organization for the Research and Treatment of Cancer (EORTC) has defined CS I and CS II patients as having an unfavorable risk of development of recurrence if any of the following factors apply: (1) age older than 50 years, (2) no B symptoms present with an ESR greater than 50 mm/hr or B symptoms with ESR greater than 30 mm/hr, (3) a large mediastinal mass, (4) stage II, or (5) at least four nodal regions involved.[21] The GHSG has assigned CS I and CS II patients to the category of unfavorable disease with any of the following adverse factors: (1) large mediastinal mass, (2) at least three nodal regions involved, (3) no symptoms present with ESR greater than 50 mm/hr or B symptoms with ESR greater than 30 mm/hr, or (4) localized extranodal infiltration (so-called E lesions) (Table 13–5).[22] In advanced disease, the International Prognostic Score (IPS) was developed on the basis of an analysis of 5141 patients, most of whom were initially treated with an anthracycline-containing chemotherapy regimen. Seven factors were identified, as shown in Table 13–6.[23]

Response Assessment

Before 1999, the criteria used to assess response to therapy were not routinely standardized. The International Working Group formulated guidelines for the assessment of response to therapy in 1999.[24] The criteria were based on CT scan and gained international recognition. However, with the introduction of the PET scan, the guideline has been updated twice, in 2007 and

TABLE 13–5 Prognostic Classification of the European Organization for the Research and Treatment of Cancer (EORTC) and German Hodgkin Lymphoma Study Group (GHSG) Groups for Clinical Stage I/II Hodgkin Lymphoma

	Unfavorable (presence of *any* of the following)
EORTC	- Age 50 years or younger - ESR >50 mm/hr without B symptoms; ESR >30mm/hr with B symptoms - Four or fewer nodal sites of involvement - Bulky mediastinal mass
	Unfavorable (presence of *any* of the following)
GHSG	- ESR >50 mm/hr without B symptoms; ESR >30 mm/hr with B symptoms - Three or fewer nodal sites of involvement - Bulky mediastinal mass - Extranodal involvement

ESR, erythrocyte sedimentation rate.

TABLE 13–6 International Prognostic Score for Hodgkin Lymphoma

Hemoglobin <10.5 g/dL
Age 45 years or younger
Male sex
Lymphocyte count <600/mL or <8% of WBC count
Serum albumin <4g/dL
WBC count ≤ 15,000/mL
Stage IV disease (Ann Arbor system)

WBC, white blood cell.
Data from Moccia AA, Donaldson J, Chhanabhai M, et al: International Prognostic Score in advanced-stage Hodgkin's lymphoma: altered utility in the modern era, *J Clin Oncol*. 2012 Sep 20;30(27):3383-3388.

TABLE 13–7 Five-Point Deauville Criteria

Score 1: no uptake
Score 2: uptake ≤ mediastinum
Score 3: uptake > mediastinum but ≤ liver
Score 4: moderately increased uptake > liver
Score 5: markedly increased uptake > liver or new lesions related to lymphoma
Score X: new areas of uptake unlikely to be related to lymphoma

in 2014.[15,25] Based on the high negative predictive value (95%–100%) and positive predictive value (>90%) of PET scan in the response evaluation for HL, current recommendations for response evaluation clearly state that PET-CT is more accurate than CT for end-of-treatment (EOT) assessment.[26] Previous guidelines for reviewing PET scans were based on somewhat imprecise visual interpretation as to whether a scan was positive or negative and whether it was intended for EOT evaluation using mediastinal blood pool as the comparator.[27] More recent guidelines recommend using a 5-point scale assessment (Deauville criteria; Table 13–7) for clinical trials including interim analysis and EOT assessment. A score of 1 or 2 is considered to represent complete metabolic response (CMR). A score of 4 or 5 is considered to be treatment failure at the EOT evaluation. Inherent are difficulties in the interpretation of a score of 3, in which the uptake is higher than mediastinal but less than or equivalent to liver uptake. Recent data suggest that patients with a score of 3 at the EOT have a good prognosis and should be considered as having CMRs.[28,29] However, in response-adapted trials exploring treatment deescalation, a more cautious approach may be preferred.

TREATMENT

Nodular Lymphocyte–Predominant Hodgkin Lymphoma

Because of the rarity of this disease, it is difficult to perform randomized prospective clinical trials. However, several well-designed single-arm phase II trials and large retrospective analyses have been recently reported.

Early-Stage Disease

Although radiation as a single modality for treatment would be considered inferior treatment for patients with early-stage cHL, multiple studies have observed excellent outcomes using RT for early-stage NLPHL. In a retrospective review of results for early-staged NLPHL from the HD-4 and HD-7 trials performed by the GHSG, the 2-year FFTF and OS rates after treatment with IFRT were 92% and 100%, respectively, compared with 100% and 94%, respectively, for EFRT.[30] Investigators from our center (MDACC) also reported excellent outcomes with RT alone for stage IA and IIA

patients.[31] With a median follow-up of 8.8 years, only one of 20 patients who received limited-field RT experienced relapse. The best outcome was noted in stage IA patients, who had a 5-year relapse-free survival rate of 95%. The Harvard study group reported a retrospective analysis of long-term outcomes of 113 patients with early-stage NLPHL.[32] Ten-year progression-free survival (PFS) and OS rates were 64% and 100%, respectively, with limited-field RT, and 81% and 95%, respectively, with EFRT. Of note, 86% of patients who received chemotherapy alone had relapse of disease.

These observations suggest that (1) chemotherapy alone is not indicated for patients with NLPHL, (2) RT alone should be the standard of care for patients with early-stage NLPHL without bulky disease or B symptoms, and (3) limited-field RT is appropriate to reduce toxicity and mortality after more extensive RT. In these retrospective analyses, no improvement was seen with combined-modality treatment (chemotherapy and RT) compared with RT alone. However, review of data from therapy of early-stage NLPHL at the British Columbia Cancer Agency (BCCA) have suggested a potential improvement in the outcomes by adding a brief course of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) before RT.[33] Ten-year PFS and OS rates were 65% and 84%, respectively, after RT alone, and 91% and 93%, respectively, for combined-modality treatment. As with retrospective studies, cautious interpretation is needed because of possible selection bias, variable staging procedures, availability of supportive care, and differences in duration of follow-up for these different treatments.

Because of high CD20 expression in NLPHL, rituximab monotherapy was evaluated for the treatment of patients with early-stage NLPHL. The GHSG and Stanford groups have reported analyses of prospective studies of therapy of patients with NLPHL with this drug.[34,35] Overall response rates (ORRs) were high (100% in both studies); however, responses were not durable. Currently, National Comprehensive Cancer Network (NCCN) guidelines recommend IFRT alone for early-stage NLPHL without B symptoms. B symptoms and bulky disease are uncommon presentations for NLPHL and should be treated with combined-modality treatment as for cHL.

Advanced-Stage Disease

Because at least 70% to 80% of patients with NLPHL are diagnosed with early-stage disease, defining the optimal treatment regimen for advanced-stage disease is challenging. However, chemotherapy is the mainstay of treatment for those with stage II or IV disease.

The GHSG recently compared the outcomes of patients with NLPHL and cHL enrolled in prospective trials.[7] There was no significant difference in FFTF results between those with NLPHL and cHL, with 50-month FFTF rates of 77% and 75%, respectively. Chemotherapy regimens used in the GHSG trials were COPP (cyclophosphamide, vincristine, procarbazine, and prednisone), COPP/ABVD, and BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone), combinations that contain higher doses of alkylating agents than ABVD. The BCCA also reported a matched-control analysis of patients with NLPHL and cHL treated with ABVD or ABVD-like chemotherapy.[36] Although not statistically significant, there was a trend toward an inferior PFS for patients with NLPHL compared with that for cHL (44% and 77% at 15 years, respectively; $P = .096$). These studies have suggested that alkylating agents may provide some therapeutic advantage for this disease. We have reported the results of R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) in therapy of patients with advanced-stage NLPHL.[37] Five- and 10-year PFS rates for patients treated with R-CHOP were 88% and 59%, respectively. With a median follow-up period of 6.7 years, no transformation to DLBCL or TCRBL has been observed. Currently, NCCN guidelines list therapeutic options including CVP (cyclophosphamide, vincristine, and prednisone), CHOP, and ABVD with or without rituximab for patients with advanced disease.

Relapsed and Transformed Disease

Patients with NLPHL may have late relapse or develop transformation to B-cell lymphoma, for which standard treatment has to be yet defined. However, rituximab has been evaluated for treatment of patients with relapsed NLPHL. In a study of 14 patients reported by the GHSG, rituximab therapy induced an ORR of 100%, a complete response (CR) rate of 57% and a median time to progression of 33 months.[38] The Stanford group examined the benefit of limited versus extended rituximab therapy in frontline and relapsed settings.[34] Eighteen patients with relapsed NLPHL were enrolled in this study; the ORR with rituximab monotherapy was 100%, and the 5-year PFS was 71.4% with rituximab maintenance therapy, consisting of four weekly infusions every 6 months for 2 years. These results suggest that rituximab monotherapy is effective in relapsed NLPHL.

Transformation at time of relapse can be a challenging disorder. In a retrospective study by the BCCA, 95 patients with NLPHL were seen over a 40-year time period.[39] Median time of follow-up was 6.5 years, and 14% of patients experienced transformation. The median time to transformation was 8.1 years, with a 4:1 ratio of DLBCL to TCRBCL. In the 10 patients with transformed lymphoma, the 10-year PFS and OS rates were 52% and 62%, respectively.

The rarity of the disease makes it difficult to prospectively evaluate the role of autologous stem cell transplantation (ASCT) for patients with relapsed or refractory NLPHL. However, patients who relapse with transformation should be managed according to algorithms for DLBCL. An MDACC retrospective study reviewed the outcomes for 26 patients who underwent ASCT. At the time of transplantation, many had transformation to TCRBCL. At the time of ASCT, 85% were in remission, with 25% in CR. At a median follow-up period of 50 months, the event-free survival (EFS) rate was 69%.[40]

MD Anderson Approach to Therapy for NLPHL: Summary

We treat patients with stage IA and IIA NLPHL with IFRT. It is rare for stage I or II patients to present with B symptoms, but if a patient does, we administer combined-modality therapy with an anthracycline-containing chemotherapy regimen followed by IFRT, particularly for stage IIB. Our preferred regimen is R-CHOP, and patients with advanced-stage disease receive six cycles of this regimen. Patients who experience relapse are considered for extended rituximab therapy. For patients with evidence of transformation to DLBCL or TCRBCL, if anthracycline-containing chemotherapy was already given, we use salvage chemotherapy with regimens such as rituximab plus ICE (ifosfamide, carboplatin, and etoposide) followed by ASCT.

Classical Hodgkin Lymphoma

The common practice for treatment and participation in clinical trials is to divide patients with cHL into three treatment groups: early-stage favorable, early-stage unfavorable, and advanced stage.

Favorable Early-Stage Classical Hodgkin Lymphoma

Treatment of patients with early-stage HL is evolving. Historically, wide-field RT or EFRT without chemotherapy was the standard of care.[41] Extended-field RT produced superior disease-free survival (DFS) results compared with IFRT.[42] More than 90% of patients achieved CR with this approach; however, the relapse rate was unacceptably high (≥30%). In addition, EFRT had considerable long-term side effects. In a large prospective analysis of over 15,000 HL patients, the actuarial risk of developing a solid tumor was 21.9% at 25 years after HL diagnosis, with the absolute risk being nearly 50%. Female breast and lung cancers were common secondary malignancies.[43]

In an attempt to improve these results, the GHSG and EORTC conducted key studies comparing RT alone with combined-modality strategies. In the GHSG HD-7 trial, patients were randomly assigned to receive either 30 Gy of EFRT alone or two cycles of ABVD followed by the same RT.[44] Although response rates did not differ between the two treatment arms, the 7-year FFTF rate was significantly better in the combined-modality arm (88% vs 67%). The results of the randomized EORTC H8F trial were similar. In this trial, treatment arms consisted of three cycles of MOPP (mechlorethamine, vincristine, procarbazine, prednisone)/ABV (doxorubicin, bleomycin, vinblastine) followed by IFRT or subtotal nodal irradiation (STNI) alone.[45] Patients receiving combined-modality treatment had a significantly superior 5-year EFS (98% vs 74%) and better 1-year OS estimates (97% vs 92%). As a result of these two large randomized controlled trials and the recognition of notable long-term side effects and high relapse rates, EFRT monotherapy has now been abandoned in favor of combined-modality therapy, which is now the standard treatment for early-stage HL.

Combined-modality therapy has evolved based on the finding that this approach results in high freedom from recurrence in early-stage HL and that efficacy can be maintained using less toxic chemotherapy and RT regimens. At MDACC, investigators performed a retrospective analysis of 286 patients with early-stage HL treated with chemotherapy followed by IFRT or EFRT with a median dose of 40 Gy.[46] Five-year relapse-free survival (RFS) and OS rates were 88% and 93%, respectively. The type and number of chemotherapy cycles used did not significantly affect RFS and OS. However, the 5-, 10-, and 15-year cumulative risks of developing solid tumors in patients treated with chemotherapy and IFRT were 0%, 6.9% and 11.4%, respectively. These results were strikingly more favorable than those of chemotherapy plus EFRT (2.7%, 11.1%, and 28.7%, respectively).

There are many completed and ongoing trials addressing issues of the best modality, best RT field, optimal dose of RT, optimal combination of drugs, number of cycles, and optimal timing of chemotherapy, with the goals being to maintain efficacy and minimize toxicities (Table 13–8).[22,47–51] The key study in combined-modality therapy for the current standard treatment is the HD-10 trial by the GHSG.[22] This study had four arms testing two versus four cycles of ABVD followed by 20 versus 30 Gy of IFRT in patients with favorable early-stage HL. This trial addressed both the optimal dose of RT and the optimal number of cycles of chemotherapy. The ABVD two- and four-cycle arms both had CR rates of 97%. The 20- and 30-Gy IFRT groups had CR rates of 97% and 98%, respectively. With a median follow-up period of 7.5 years, there were no differences among the four groups with respect to PFS, FFTF, and OS. However, the four-cycle

ABVD and 30-Gy IFRT treatment groups induced more toxicity than the less intensive treatment groups. Based on these data, the least toxic regimen, two cycles of ABVD and 20 Gy of IFRT, is the current preferred approach for patients with favorable early-stage HL.

In an attempt to further reduce toxicity, the GHSG conducted the HD-13 trial, a study that was designed to determine whether bleomycin or dacarbazine can be omitted from the ABVD regimen.[48] This four-arm trial investigated ABVD, AVD (doxorubicin, vinblastine, dacarbazine), ABV, and AV (doxorubicin, vinblastine) plus 30 Gy of IFRT. In this trial, the ABV and AV plus IFRT arms were closed because of concern for higher relapse rates. Five-year FFTF rates were 93%, 81%, 89%, and 77% with ABVD, ABV, AVD, and AV, respectively. Based on results from this trial, both dacarbazine and bleomycin cannot be omitted from this regimen for favorable early-stage disease without a substantial loss of efficacy, and the standard treatment remains ABVD followed by IFRT.

TABLE 13–8 Key Trials for Patients with Favorable Early-Stage Hodgkin Lymphoma

Trial	Trial Design
Milan 1990 to 1997	ABVD × 4 → STLI ABVD × 4 → IFRT
Stanford	Stanford V × 8 weeks → IFRT
EORTC/GELA H9F	EBVP × 6 → IFRT 20 Gy EBVP × 6 → IFRT 30 Gy EBVP × 6 → alone
GHSG HD-10	ABVD × 2 → IFRT 2 Gy ABVD × 4 → IFRT 20Gy ABVD × 2 → IFRT 30 Gy ABVD × 4 → IFRT 30 Gy
GHSG HD-13	ABVD × 2 → IFRT 30 Gy ABV × 2 → IFRT 30 Gy AVD × 2 → IFRT 30 Gy AV × 2 → IFRT 30 Gy
EORTC/LYSA/FIL H10F	ABVD × 3 → INRT 30 Gy (+6 Gy) ABVD × 2 → then PET scan – If PET negative → ABVD × 2 – If PET positive → BEACOPP escalated × 2 → INRT 30 Gy (+ 6 Gy)
GHSG HD-16	ABVD x 2 → IFRT 20 Gy ABVD x 2 → then PET scan – If PET negative → stop treatment – If PET positive → IFRT 20 Gy
UK RAPID	ABVD × 3 → then PET scan – If PET negative (DS ≤4) → stop treatment – If PET positive → ABVD × 1 + 30 Gy IFRT

ABV, doxorubicin, bleomycin, vinblastine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AV, doxorubicin, vinblastine; AVD, doxorubicin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; EBVP, epirubicin, bleomycin, vinblastine, prednisone; EORTC, European Organization for Research and Treatment of Cancer; FIL, Fondazione Italiana Linfomi; GELA, Groupe d'Etude des Lymphomes de l'Adulte; GHSG, German Hodgkin Lymphoma Study Group; IFRT, involved-field radiotherapy; INRT, involved-node radiotherapy; LYSA, Lymphoma Study Association; PET, positron emission tomography; Stanford V, mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, prednisolone; STLI, subtotal lymphoid irradiation.

Several studies have evaluated the utility of interim PET imaging for treatment stratification. The EORTC/Lymphoma Study Association (LYSA)/Fondazione Italiana Linfomi (FIL) H10 trial was conducted to assess whether involved-node radiotherapy (INRT) could be omitted without compromising PFS in patients attaining a negative early PET scan after two cycles (PET-2) of ABVD as compared with standard combined-modality treatment.[47] Patients were randomized to receive standard therapy with INRT or an experimental arm that omitted RT if the PET was interpreted as negative (Deauville score [DS] 1 or 2) after two cycles of ABVD. Patients with a positive interim PET (DS ≥3) continued treatment with two cycles of escalated BEACOPP. The chemotherapy-only arm was closed because of an increased number of events, and all patients with a negative PET findings received additional RT. Five-year PFS was significantly lower in the experimental arm than the standard arm (87% and 99%, respectively).[52] In contrast, the UK RAPID trial showed noninferior outcomes for patients who omitted RT after negative PET scan (DS 1 or 2).[53] Patients were randomized to IFRT or no further treatment if the PET result was negative after three cycles of ABVD. Three-year PFS rates were 93.8% and 90.7%, and 3-year OS rates in an intent-to-treat analysis were 97.0% and 99.5% in patients who received IFRT and no further treatment, respectively. Thus, there was a nonsignificant trend toward improved PFS for patients who received IFRT. In a post-hoc analysis of this trial, investigators reported that only patients with a PET DS score of 5 had inferior PFS compared with patients with a DS score of 4 or less, thereby warranting treatment escalation only for patients with a DS score of 5.[28]

In a similar study, the GHSG HD-16 trial randomized patients with favorable early-stage cHL to two cycles of ABVD and 20 Gy IFRT or to an experimental arm of two cycles of ABVD with PET-guided treatment, omitting IFRT if the PET-2 was negative (DS <3). With a median follow-up period of 45 months, the 5-year PFS rates were 93.4% in the standard therapy arm and 86.1% in the experimental arm. Of the patients who received IFRT, 5-year PFS rates were significantly different in the PET-2–negative and PET-2–positive patients (93.2% and 88.4%, respectively; $P = .047$), which was more pronounced when using the more common liver cut-off for PET scoring, DS less than 4 (5-year PFS rates 93.1% and 80.9%, respectively; $P = .0011$), suggesting that IFRT cannot be safely omitted

in PET-2–negative patients without significant loss of local tumor control.[54] The question of whether treatment can be further reduced based on the results of the PET scan is the subject of ongoing clinical trials. The GHSG HD-17 trial is investigating the potential equivalence of IFRT and INRT. Small phase II studies are investigating the option of using novel agents such as nivolumab or brentuximab vedotin (BV) to replace RT and bleomycin with favorable early results.[55,56]

The MD Anderson Approach for Favorable Early-Stage Classical Hodgkin Lymphoma

The treatment for favorable early-stage HL is still evolving. Patients are screened for clinical protocol options if available. As standard therapy, we use two cycles of ABVD plus 20 Gy of IFRT for this group of patients. In patients in whom the radiotherapy field crosses vital tissues, including breast tissue and coronary arteries, we use three cycles of ABVD followed by interim PET imaging. If PET negative (DS ≤4), no further treatment is given; if PET positive (DS = 5), one additional cycle of ABVD is given with 30 Gy of IFRT.

Unfavorable Early-Stage Hodgkin Lymphoma

Combined-modality approaches consisting of four cycles of chemotherapy followed by IFRT represent the standard of care for patients with unfavorable early-stage HL. Multiple trials have shown that reduction of radiation field does not lead to inferior clinical outcomes. In a retrospective analysis conducted at MDACC, 286 patients (1980–1995) with early-stage HL received chemotherapy followed by IFRT or EFRT. The type and number of chemotherapy regimens used did not significantly affect RFS and OS. There was a trend toward a higher risk of secondary tumors in the EFRT group.[46] Given the relapse rates with ABVD, there is interest in evaluating alternative more intensive regimens (Table 13–9).[47,57–60]

To address whether ABVD or the Stanford V regimen (mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, prednisone) would be the best approach for patients with bulky unfavorable early-stage HL, the SWOG and Eastern Cooperative Oncology Group (ECOG) conducted the intergroup 2496 trial.[57] In this study, patients with bulky unfavorable early-stage disease (patients with advanced-stage disease were also enrolled in this trial) received six cycles of ABVD followed by IFRT, 36 Gy to bulky disease greater than 5 cm, or 12 weeks of Stanford V followed by the same IFRT plan of care. In this study, there were no differences between ABVD and Stanford V with respect to ORR and FFS.

In another study of therapy more intensive than ABVD for unfavorable early-stage cHL, the GHSG HD-11 trial randomized patients to four arms of therapy: four cycles of ABVD followed by 30 versus 20 Gy of IFRT or four cycles of BEACOPP baseline followed by 30 versus 20 Gy of IFRT. FFTF results were better with BEACOPP than with ABVD for patients who received 20 Gy of IFRT, whereas there were no differences between the BEACOPP and ABVD arms for patients who received 30 Gy of IFRT. OS did not differ significantly between the four treatment arms. BEACOPP also induced more toxicity in comparison with ABVD; therefore, four cycles of ABVD remained the standard for these patients with unfavorable early-stage HL.[59] However, in a follow-up study, in an attempt to reduce the toxicity observed with BEACOPP, the

TABLE 13–9 Key Trials for Patients with Unfavorable Early-Stage Hodgkin Lymphoma

Trial	Trial Design
	ABVD × 6 → IFRT 36 Gy to >5 cm disease
	Stanford V × 12 weeks → IFRT 36 Gy to >5 cm disease
EORTC/GELA H9U	ABVD × 6 → IFRT (36–40 Gy)
	ABVD × 4 → IFRT (36–40 Gy)
	BEACOPP × 4 → IFRT (36–40 Gy)
GHSG HD11	ABVD × 4 → IFRT 30 Gy
	ABVD × 4 → IFRT 20 Gy
	BEACOPP baseline × 4 → IFRT 30 Gy
	BEACOPP baseline × 4 → IFRT 20 Gy
GHSG HD-14	ABVD × 4 → IFRT 30 Gy
	BEACOPP escalated + ABVD × 2 → IFRT 30 Gy
EORTC/LYSA/FIL H10U	ABVD × 4 → INRT 30Gy (+ 6 Gy)
	ABVD × 2 → then PET scan
	If PET negative → ABVD × 4
	If PET positive → BEACOPP escalated × 2 → INRT 30 Gy (+ 6 Gy)
GHSG HD-17	BEACOPP escalated + ABVD × 2 → IFRT 30 Gy
	BEACOPP escalated + ABVD × 2 → then PET scan
	If PET negative → stop treatment
	If PET positive → INRT 30 Gy

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; FIL, Fondazione Italiana Linfomi; GELA, Groupe d'Etude des Lymphomes de l'Adulte; GHSG, German Hodgkin Lymphoma Study Group; IFRT, involved-field radiotherapy; INRT, involved-node radiotherapy; LYSA, Lymphoma Study Association; PET, positron emission tomography; Stanford V, mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, prednisone; SWOG, Southwest Oncology Group.

GHSG HD-14 trial evaluated four cycles of ABVD followed by 30 Gy of IFRT versus two cycles of BEACOPP escalated followed by two cycles of ABVD (2 + 2) followed by 30-Gy IFRT for this same group of patients.[58] At a median follow-up period of 43 months, there was better tumor control (5-year FFTF estimate of 94.8%) with the 2 + 2 protocol compared with the ABVD arm (5-year FFTF of 87.7%), although there was no significant difference in OS between the two arms because of more toxic deaths in the 2 + 2 arm.

Using a similar rationale, the EORTC designed the H9U trial, comparing three different less versus more intensive therapies.[60] Patients received either four or six cycles of ABVD followed by IFRT or four cycles of BEACOPP followed by IFRT. Patients in CR/Cru (CR unconfirmed) after chemotherapy received 30 Gy of IFRT with those in partial remission (PR) receiving 36 Gy in total. Four cycles of ABVD followed by IFRT was noninferior to six cycles of ABVD or four cycles of BEACOPP with IFRT (5-year EFS, 86%, 89%, and 90%, respectively) with no differences in 5-year OS rates and fewer toxic events compared with BEACOPP. Based on these two trials, four cycles of ABVD chemotherapy remains the standard comparator for patients with unfavorable early-stage HL.

Similar to favorable early-stage HL, current trials for patients with unfavorable early-stage HL, such as the EORTC/Groupe d'Etude des Lymphomes de l'Adulte H10U and GHSG HD-17, are evaluating treatment stratification according to the result of an interim PET scan. The standard arm in the EORTC/LYSA/FIL H10U trial consisted of four cycles of ABVD followed by 30 Gy of INRT irrespective of the result of an interim PET scan performed after the second cycle of ABVD. In the experimental arm, patients with negative PET results received a total of six cycles of ABVD without consolidation RT, whereas patients with positive PET results continued treatment with two cycles of escalated BEACOPP before receiving INRT. However, as for patients with early-stage favorable HL, the chemotherapy-only arm (six cycles of ABVD) was closed because of an increased number of events, so that all patients with negative PET results received additional RT. There was no difference in the 1-year PFS between the standard and experimental arms (97.3% and 94.7%, respectively). In the GHSG HD-17 trial, all patients received chemotherapy according to the 2 + 2 regimen before a PET scan was performed. In the standard arm, patients received an additional 30 Gy of IFRT irrespective of the results of the PET scan. In the experimental arm, patients with negative PET scan results stopped treatment, whereas patients with positive PET scan results received 30 Gy of INRT. This ongoing trial plans to evaluate whether it is possible to spare RT in patients with a negative PET scan after intensive escalated BEACOPP.

A trial conducted by the National Cancer Institute of Canada and the ECOG indicated that chemotherapy-only approaches appear possible in patients with unfavorable early-stage cHL, at least in patients with nonbulky disease.[61] The trial randomized patients with unfavorable early-stage disease to receive either four to six cycles of ABVD or two cycles of ABVD followed by STNI. At a median follow-up period of 11.3 years, freedom from disease progression was better in patients who received combined-modality treatment; however, OS was better for patients treated with chemotherapy alone. This was mainly caused by the increased number of deaths from secondary neoplasia among patients who had received combined-modality treatment. Because of results of this study and others previously mentioned, STNI fields have been abandoned in favor of limited fields after ABVD or variants. Chemotherapy alone may still be an option for selected patients with nonbulky unfavorable early-stage HL, given similar excellent OS results with and without RT, but the combined-modality therapy approach remains a standard of care.

The MD Anderson Approach to Unfavorable Early-Stage Classical Hodgkin Lymphoma

Treatment with four cycles of ABVD plus 30 Gy of IFRT is our standard-of-care option for unfavorable early-stage HL. We screen patients for any available clinical protocols. If patients have elevated short- or long-term risks associated with RT, such as young female patients who might need significant breast tissue irradiation because of bulky masses at diagnosis, six cycles of ABVD without RT is an acceptable alternative, especially if the PET-2 result is interpreted as negative for active disease.

Advanced-Stage Hodgkin Lymphoma

Treatment of patients with advanced-stage HL usually consists of six to eight cycles of chemotherapy. The ABVD regimen was shown to be effective and less toxic than MOPP and MOPP/ABVD in a randomized clinical trial by the Cancer and Leukemia Group B (CALGB).[62] With ABVD, MOPP, and MOPP/ABVD, 5-year failure-free survival rates were 61%, 50%, and 65%, and 5-year OS rates were 73%, 66%, and 75%, respectively. Based on this trial, the chemotherapy regimen most often used in the United States became ABVD. However, the GHSG subsequently reported that escalated BEACOPP induced better PFS results would ABVD for advanced-stage HL. Many trials are addressing whether one regimen may be more suitable for the treatment of advanced HL than another, and the issue has been the subject of ongoing debate for more than decade (Table 13–10).[26,62–66]

TABLE 13–10 Key Trials for Advanced-Stage Hodgkin Lymphoma

Trials	Design
CALGB	ABVD × 6 to 8
	ABVD/MOPP × 12
	MOPP × 6 to 8
GHSG HD-9	COPP/ABVD × 8
	BEACOPP baseline × 8
	BEACOPP escalated × 8
GHSG HD-12	BEACOPP escalated × 8 → IFRT to bulk/residual mass
	BEACOPP escalated × 8
	BEACOPP escalated × 4 + BEACOPP baseline × 4 → IFRT to bulk or residual mass
	BEACOPP escalated × 4 + BEACOPP baseline × 4
GHSG HD-15	BEACOPP escalated × 8 → IFRT to PET-positive residual masses ≤2.5 cm
	BEACOPP escalated × 6 → IFRT to PET-positive residual masses ≤2.5 cm
	BEACOPP-14 × 8 → IFRT to PET-positive residual masses ≤2.5 cm
LYSA H34	ABVD × 8
	BEACOPP escalated × 4 + BEACOPP baseline × 4
GITIL	ABVD × 6 to 8 depends on the response after four cycles
	BEACOPP escalated × 4 + BEACOPP baseline × 4
	HDCT is planned by protocol at the time of progression or relapse
GHSG HD-18	BEACOPP escalated × 2 → then PET scan
	If PET negative
	Additional BEACOPP escalated × 4
	Additional BEACOPP escalated × 2
	If PET positive
	Additional BEACOPP escalated × 4
	Additional BEACOPP escalated × 4 + rituximab
CALGB	ABVD × 6 to 8
	ABVD/MOPP × 12
SWOG S0816	ABVD × 2 → then PET scan - If PET negative (DS≤3), then ABVD × 4 - If PET positive (DS≥4), then BEACOPP × 6
RATHL	ABVD × 2 → then PET scan - If PET negative (DS≤3), then ABVD × 4 or AVD × 4 - If PET positive (DS ≥4), then BEACOPP × 4 or eBEACOPP × 4
ECHELON-1	A+AVD × 2 → then PET scan - If PET negative (DS ≤4), then A+AVD × 4 - If PET positive (DS = 5), then alternative frontline therapy

A + AVD, brentuximab vedotin, doxorubicin, vinblastine, dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AVD, doxorubicin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; CALGB, Cancer and Leukemia Group B; COPP, cyclophosphamide, vincristine, procarbazine, prednisone; GHSG, German Hodgkin Lymphoma Study Group; GITIL, Gruppo Italiano Terapie Innovative nei Linfomie; HDCT, high-dose chemotherapy; IFRT, involved-field radiotherapy; LYSA, Lymphoma Study Association; MOPP, mechlorethamine, vincristine, procarbazine, prednisone; PET, positron emission tomography; SWOG, South West Oncology Group; RATHL, Response adapted therapy for Hodgkin Lymphoma.

In the original BEACOPP study for advanced cHL, the GHSG HD-9 trial, a three-arm randomized trial evaluated four cycles of COPP/ABVD versus eight cycles of BEACOPP baseline versus eight cycles of BEACOPP escalated.[66,67] The BEACOPP escalated arm provided significantly a better survival rate than the other two arms. With BEACOPP escalated, COPP/ABVD, and BEACOPP baseline, 5-year FFTF rates were 87%, 69%, and 76%, respectively. Five-year OS rates were 91%, 83%, and 88%, respectively. Because of concerns of toxicity with escalated BEACOPP, the GHSG HD-12 trial investigated whether the number of cycles of

BEACOPP escalated could be deescalated by evaluating eight cycles of BEACOPP escalated versus four cycles of BEACOPP escalated plus four cycles of BEACOPP baseline (4 + 4), along with the effect of consolidation RT for sites of initial bulk or residual disease.[65] Severe toxicity and therapy-related death rates were similar in both arms, and the survival outcome was slightly inferior in the 4 + 4 regimen. Thus, the trial could not address how to decrease the toxicity while maintaining the efficacy of eight cycles of BEACOPP escalated. Their next trial (HD15) also aimed to reduce treatment toxicity without compromising efficacy.[26] The trial evaluated the role of response evaluation based on PET scan in assessing the need for IFRT. Chemotherapy consisted of eight cycles of BEACOPP escalated, six cycles of BEACOPP escalated, or eight cycles of BEACOPP-14, a time-dense variant of the BEACOPP baseline protocol. Additional localized RT was only applied to patients who had PET-positive residual lymphoma larger than 2.5 cm at the end of chemotherapy. With eight cycles of BEACOPP escalated, six cycles of BEACOPP escalated, and eight cycles of BEACOPP-14, the 5-year FFTF rates were 85%, 89%, and 85%, respectively, and the 5-year OS rates were 92%, 95%, and 95%, respectively. The negative predictive value of the post chemotherapy PET scan was very high (94.1% at 12 months), allowing omission of PET negative residua. The superiority of six cycles of BEACOPP escalated was mainly attributed to the lower rate of treatment-related adverse events (AEs) and fewer deaths caused by secondary neoplasia compared with those observed with the more intensive regimens.

The GHSG HD-18 trial further evaluated the utility of the interim PET scan after two cycles of eBEACOPP to adapt treatment intensity.[68] Patients with a positive PET after two cycles of eBEACOPP were randomized to six additional cycles of eBEACOPP or eBEACOPP with rituximab (this was amended to four additional cycles in June 2011 based on the GHSG HD-15 results). Patients with negative PET-2 results were randomized to six additional cycles of eBEACOPP or two additional cycles. RT was recommended for lesions of 2.5 cm or larger in the largest diameter with residual FDG uptake after chemotherapy. Of the PET-2–positive patients, there was no survival benefit with the addition of rituximab. However, survival was similar in the PET-2–negative patients who received six additional cycles of eBEACOPP compared with two additional cycles (5-year PFS 90.8% and 92.2%, respectively) with fewer severe infections and organ toxicities in patients only receiving two additional cycles of eBEACOPP. Therefore, for patients with a negative PET-2 results, the standard of care became four cycles of eBEACOPP.

Using a different approach that escalated therapy for PET-2–positive disease, investigators of the SWOG S0816 trial studied results of therapy for patients with stage III or IV disease.[69] All patients underwent staging by PET followed by two cycles of ABVD and a repeat PET scan (PET-2). If the PET-2 result was negative, the patient received four additional cycles of ABVD. If the PET-2 scan result was positive, treatment was changed and intensified to BEACOPP escalated for six cycles for patients who were seronegative for human immunodeficiency virus (HIV); BEACOPP standard for six cycles was given to those who were seropositive). This trial was also the first American study to use centralized real-time intergroup review (SWOG, ECOG, CALGB) of the PET scan results for treatment decisions. The 5-year PFS of PET-2–positive patients with PET-2–positive disease was still lower than that reported for those who had PET-2–negative disease (66% and 76% respectively) even though they received six more cycles of BEACOPP escalated after PET-2.[70]

The Gruppo Italiano Terapie Innovative nei Linfomi (GITIL) conducted a similar trial.[71] In the GITIL HD0607, all patients received two cycles of ABVD and then underwent PET-2. If the results were negative, they received another four cycles of ABVD with or without RT. If the PET-2 results were positive, the patient received four cycles of BEACOPP escalated and two cycles of BEACOPP baseline. The 3-year PFS rates of patients with positive and negative PET-2 scans were 60% and 87%, respectively.[72] In patients with both interim and post-ABVD-negative PET who had a large nodal mass 5 cm or larger at diagnosis, the addition of radiotherapy did not improve PFS (3 year PFS 97% and 93%, respectively, $P = .29$), adding to earlier suggestions that PET negativity at PET-2 and the end of therapy (PET-EOT) may allow deletion of RT altogether. However, those with PET-2 positivity after two cycles of ABVD had inferior results, and further improvements are needed with this approach.

The Response-Adapted Therapy for Advanced Hodgkin Lymphoma (RATHL) trial also used a PET-2 adapted strategy to assess the impact of treatment deescalation in the PET-2–negative population by omitting bleomycin. All patients received two cycles of ABVD followed by PET imaging. Patients with negative PET-2 results were randomized to either four further cycles of ABVD or AVD. Patients with positive PET-2 results proceeded with either BEACOPP-14 or eBEACOPP in a nonrandomized fashion. In the PET-2–negative patients, the regimen without bleomycin just fell short of the specified noninferiority margin (3-year PFS, 85.7% and 84.4%, respectively) with higher rates of respiratory AEs in the ABVD group than the AVD group.[73] The 3-year PFS rates for patients with PET-2–positive and PET-2–negative scans were 67% and 85%, respectively. Although not strictly meeting the specified noninferiority margin, many clinicians in the United States have adopted the practice of dropping

bleomycin in patients with negative PET-2 results after two cycles of ABVD with minimal impact on PFS. The relatively poor results with escalation to BEACOPP after a positive PET-2 result in this trial were similar to those previously reported in other studies.

Even with the results of the GHSG HD-9 trial, initial chemotherapy for advanced-stage HL is still a matter of debate. The standard arm used in the HD-9 trial was COPP/ABVD, not ABVD alone. Three randomized trials have been conducted to address this issue. An Italian group conducted the HD2000 trial and LYSA conducted the H34 trial to compare the outcomes of randomized therapy with BEACOPP and ABVD.[63,74,75] In the HD2000 trial, patients were randomly assigned to receive six cycles of ABVD, four cycles of BEACOPP escalated plus two cycles of BEACOPP baseline, or six courses of CEC (cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epidoxorubicin, vincristine, procarbazine, vinblastine, and bleomycin). Patients who received BEACOPP had higher PFS and OS rates than patients who received ABVD (5-year PFS, 81% and 68%; 5-year OS, 92% and 84%, respectively). In the H34 trial, patients were randomly assigned to receive eight cycles of ABVD or four cycles of BEACOPP escalated plus four cycles of BEACOPP baseline. Both PFS and OS were higher in the BEACOPP arm than the ABVD arm (5-year PFS, 93% and 75%; 5-year OS, 99% and 92%, respectively), results similar to those reported from the HD2000 study. Therefore, in GHSG trials, BEACOPP has been a standard of care for younger patients with advanced-stage cHL. Unfortunately, for patients older than 65 years of age, standard-dose BEACOPP was toxic in the HD9 study, a randomized study of the regimen versus COPP–ABVD, causing 21% early deaths in this older population.[76]

Regardless of these excellent results in younger patients by the GHSG, the GITIL has reported that ABVD has a similar efficacy to BEACOPP if high-dose chemotherapy (HDCT) is planned at the time of relapse or refractory disease.[64] In the GITIL trial, patients were randomly assigned to either four cycles of BEACOPP escalated plus four cycles of BEACOPP baseline or to six to eight cycles of ABVD, each followed by local RT when indicated. Patients with residual or progressive disease after the initial therapy were to be treated with high-dose salvage therapy with ASCT. The 7-year FFTF was significantly better with BEACOPP than ABVD (85% vs 73%); however, there was no significant difference in the 7-year OS between arms after completion of the overall planned treatment (89% vs 84%). Although two of these three randomized trials showed some benefit in survival with BEACOPP, longer follow-up periods are essential to confirm the conclusion because toxicities, including secondary malignancies, are issues for long-term survival in these young patients. Most of the institutes in the United States are still using ABVD as the first-line chemotherapy backbone of treatment for patients with HL, mostly because of its high efficacy, high tolerability, and lower toxicity rates compared with BEACOPP escalated.[75]

After the introduction of BV for patients with relapsed or refractory cHL, investigators conducted a phase III randomized study (ECHELON-1) to incorporate this novel agent into initial therapy of advanced-stage cHL.[77] Because of significant pulmonary toxicity associated with concomitant administration of this agent and bleomycin, this anti-CD30 antibody–drug conjugate was substituted for bleomycin in the ABVD regimen (A + AVD); patients with advanced cHL received six cycles of A+AVD or six cycles of ABVD. All patients underwent PET-2 restaging, and those with a DS score of 5 had the option of switching to alternative frontline therapy. At a median follow-up period of 2 years, modified PFS rates were superior in the A +AVD group compared with the ABVD group (82% vs 77%) with lower rates of pulmonary toxicity. However, higher rates of neutropenia and peripheral neuropathy (all grades) were reported in the A + AVD group. At a 3-year update, results remained superior for those receiving A + AVD.[78] In the North American subgroup, patients with a high-risk IPS (≥4) appeared to have a statistically significant PFS benefit with A + AVD compared with ABVD, with a hazard ratio (HR) of 0.396.[79] Two-year PFS and OS results for this NA subgroup overall were 88% and 76.4%, and 97% and 93.2%, respectively ($P = .094$). Based on these differences at 2 years between the A + AVD and ABVD groups, a number of US centers now administer A + AVD as initial therapy for advanced-stage cHL, especially for patients with high IPS or preexisting lung disease; granulocyte colony-stimulating factor support and careful monitoring of peripheral neuropathy and hepatic function are mandatory with this regimen.

In one phase 2 study, BV was given as initial therapy to patients with cHL 60 years of age or older who were considered ineligible for standard chemotherapy.[80] Ninety-one percent of the patients responded, with a 73% CR rate. Unfortunately, the median PFS result with BV alone was only 10.5 months. Brentuximab has also been studied in combination with other drugs (nivolumab, dacarbazine, bendamustine) in another small study of older patients with cHL who were not considered eligible to receive chemotherapy.[81] Responses were good for all of the regimens in this trial; unfortunately, results with BV appeared inferior compared with results after the combination of this drug with either nivolumab or DTIC. The combination of brentuximab with bendamustine was considered more toxic than the other combinations. Another

small phase II trial has shown early promising activity of the anti-PD1 antibody, nivolumab, as an alternative to bleomycin in combination with AVD, and results of the randomized phase III SWOG S1826 trial comparing N-AVD and A-AVD are awaited.[82]

Predictors of Outcomes for Advanced-Stage Classical Hodgkin Lymphoma

The Value of Positron Emission Tomography in Hodgkin Lymphoma

Staging by PET scan is proven as a standard of care, but PET is also a valuable tool for evaluation of response and prediction of outcomes in patients with HL. In one study, an interim PET scan obtained after two cycles of therapy (PET-2) was a stronger prediction of outcome than the IPS, with 2-year PFS results for patients with positive PET-2 results of 13% compared with 95% for those with negative PET-2 results.[83] The PET-2 also strongly predicts treatment failure.[84] In a meta-analysis, a positive PET-2 result in low-intermediate–risk advanced HL patients was a reliable predictor of poor response.[85] Interim PET scans are now routinely incorporated into clinical trial designs, can stratify high and low risk patients, and guide treatment escalation or deescalation strategies. However, the role of interim PET imaging after two cycles of either ABVD or escalated BEACOPP remains controversial in practice for the individual patient despite integration in numerous upfront studies in advanced cHL. Historical studies that demonstrated that positive PET imaging following two cycles of ABVD were associated with poor outcomes were inherently flawed because treatment failure was determined by imaging with histologic confirmation of relapse rarely performed.[86–88] Given a historically high false-positive rate for FDG-PET imaging in patients with cHL, this may have overestimated the positive predictive value of PET-2 imaging after ABVD therapy. In addition, there are no large studies documenting concordance of PET positivity and histologic findings for cHL. Given the disease biology of cHL, comprising a minority of Reed-Sternberg cells surrounded by an inflammatory infiltrate, a false-positive PET-2 result may be possible. Therefore, other markers are needed as alternative methods to identify poor responders with truly chemorefractory disease.[88]

Other Predictors of Response and Outcomes for Classical Hodgkin Lymphoma

Investigators have demonstrated that tumor burden, as assessed with biochemical markers or by CT imaging, is prognostic for outcomes. A retrospective analysis of patients with early-stage cHL from the HD10 and HD11 trials showed that elevated ESR and large tumor burden (assessed by CT) were predictive of inferior outcomes.[89] With PET imaging, the total metabolic tumor volume (TMTV) measures both tumor size and activity of the tumor and the microenvironment. A prospective analysis of 294 patients with early-stage cHL from the H10 trial found high initial TMTV (>147 cm^3) to be highly prognostic for inferior PFS (5-year rates of 71% and 92%, respectively; P <.0001) and OS (83% and 98%, respectively; P = .0001).[90] However, TMTV was not predictive of PFS or OS results for advanced HL in the PET-adapted HD18 trial cohort, possibly because of a low number of progression events with eBEACOPP.[91]

Investigators have reported that circulating tumor DNA (ctDNA) can predict outcomes of therapy for cHL. A study of 112 patients with newly diagnosed and refractory cHL identified nonsynonymous somatic mutations in ctDNA samples, evaluating previously described *TNFAIP3, ITPKB, GNA13,* and *B2M* genes. *STAT6* was the most frequently mutated gene in 40% of cases.[92] Genotyping of the tumor from HRS cell–enriched samples identified 96 somatic mutations compared with no mutations from the tumor sample from areas devoid of HRS cells. Genotyping of plasma ctDNA identified 106 somatic mutations with a sensitivity of 87.5%, with the additional mutations in the plasma ctDNA thought to be caused by subclonal or anatomic heterogeneity of the tumor. A 2-log-fold drop of ctDNA was associated with superior PFS despite interim PET positivity likely because of the notion that FDG avidity reflects the metabolic activity of the inflammatory component of the mass, whereas ctDNA more accurately reflects tumor burden. Further studies incorporating ctDNA monitoring and PET imaging are needed to establish the role of ctDNA in predicting clinical outcomes.

The MD Anderson Approach to Management of Advanced-Stage Classical Hodgkin Lymphoma

We screen patients for available protocols for initial treatment of advanced-stage disease. As a standard of care, we treat these patients a PET-2–adapted approach. For patients with high-risk disease (IPS ≥4), we use six cycles of A + AVD with interim response assessment using PET-2 imaging. If the PET-2 is interpreted as DS 4 or less, we recommend completing six cycles in total of A + AVD. If the disease is PET-2–positive (DS 5), we transition to non–BEACOPP-based salvage therapy such as ICE or clinical trials using anti-PD1 agents followed by ASCT. In patients with non-high-risk disease (IPS <4) or with contraindications to BV such as preexisting neuropathy or liver disease, we use a RATHL-style approach with two cycles of ABVD followed by interim PET-2 imaging. If PET-2 negative in this situation (DS ≤3), we delete bleomycin and complete four

additional cycles of AVD. If PET-2–positive (DS 4 or 5), we transition to non–BEACOPP-based salvage therapy followed by ASCT if the patient is transplant eligible. We reserve IFRT for patients who have presented with an initial bulky mass with residual bulk at the end of therapy. Based on phase II data, we favor the following regimens in specific patient cohorts. Older patients (older than 65 years) receive two lead-in doses of single-agent BV (1.8 mg/kg once every 3 weeks), then six cycles of AVD, then four consolidative doses of single-agent BV in responding patients.[93] HIV-positive patients receive six cycles of A + AVD with careful medication review to avoid interactions with strong CYP3A4 inhibitors to minimize toxicity.[94]

REFRACTORY OR RELAPSED HODGKIN LYMPHOMA

Although many patients with HL are cured with frontline therapy, 10% to 15% of patients with early-stage disease with unfavorable risk factors and 40% of patients with advanced-stage disease with high-risk factors can develop relapse or refractory disease. Relapsed HL can be divided into three subgroups: early relapse within 12 months of CR after first-line chemotherapy, late relapse after CR more than 12 months after first-line chemotherapy, and primary refractory HL (patients who never achieve a CR). Moskowitz and colleagues[95] identified the following three prognostic factors associated with EFS in patients receiving ICE followed by HDCT and ASCT: CR less than 1 year, extranodal disease, and presence of B symptoms. The 5-year EFS rate was 83% in patients with zero to one factor compared with 10% if all three factors were present.[95]

Standard Therapy for Relapsed or Refractory Classical Hodgkin Lymphoma

For patients with relapsed or refractory disease after standard frontline management, additional salvage chemotherapy followed by HDCT plus ASCT is the standard approach. One of the key goals of salvage chemotherapy is to achieve CR before ASCT. The response rates of multiple salvage regimens are listed in Table 13–11. It is difficult to directly compare these regimens because they have not been evaluated in randomized clinical trials.

Although all patients at relapse should undergo screening for protocol therapy, the most common salvage chemotherapies outside clinical trials are the platinum-containing regimens such as ICE or DHAP (cisplatin, cytarabine, dexamethasone). With ICE, the ORR was 88%, and the CR rate was 26%.[95] Using variations of this this regimen, patients with PET negativity before ASCT had an EFS of greater than 80%.[96] The DHAP regimen provided similar results, with ORR of 89% and CR rate of 21%.[97] Gemcitabine-containing regimens are also effective in therapy of patients with relapsed or refractory cHL. A phase II study of single-agent gemcitabine, 200 mg/m^2 given on days 1, 8, and 15 of a 28-day schedule, produced an ORR of 43% with a CR rate of 14%.[98] The GVD regimen (gemcitabine, vinorelbine, and pegylated liposomal doxorubicin) was evaluated by the CALGB in 91 patients with relapsed or refractory HL. The ORR was 70%, with a CR rate of 19%.[99] The 4-year PFS and OS rates for transplant-naïve patients treated with GVD followed by ASCT were 52% and 70%, respectively. In patients in whom prior transplant had failed, the 4-year DFS and OS rates were 10% and 34%, respectively. The GDP regimen produced similar results, with an ORR of 62% and a CR rate of 10%.[100] A combination regimen named IGEV (ifosfamide, gemcitabine, vinorelbine) was evaluated in 91 patients and produced an ORR of 81% with a high CR rate of 54%; 60% of patients with primary refractory disease responded to IGEV.[101]

TABLE 13-11 Salvage Chemotherapy Regimens for Hodgkin Lymphoma

Regimen	ORR (%)	CR (%)
DHAP	88	21
ASHAP	70	34
ESHAP	73	41
MINE	73	34
ICE	85	26
IGEV	81	54
GND	70	19
GDP	62	10
Nivolumab (+/- ICE if not in CR)[90]	94	91

ASHAP, doxorubicin, methylprednisolone, cytarabine, cisplatin; CR, complete response; DHAP, dexamethasone, cytarabine, cisplatin; ESHAP, etoposide, methylprednisolone, cytarabine, cisplatin; GDP, gemcitabine, dexamethasone, cisplatin; GND, gemcitabine, vinorelbine, pegylated liposomal doxorubicin; ICE, ifosfamide, carboplatin, etoposide; IGEV, ifosfamide, gemcitabine, vinorelbine; MINE, mitoguazone, ifosfamide, vinorelbine, etoposide; ORR, overall response rate.

High-Dose Chemotherapy with Autologous Stem Cell Transplantation for Relapsed Hodgkin Lymphoma

For patients with chemotherapy-sensitive disease, the treatment of choice after relapse is HDCT followed by ASCT. This recommendation is based on reports from two historically important, randomized clinical trials.[102,103] In the BNLI study, patients with relapsed or refractory HL received BEAM (carmustine, etoposide,

Table 13-12 Initial Management of the Patient with HL Establishing the Diagnosis

Diagnosis	Workup

- FNA alone is insufficient
- Hematopathology review of all slides with at least one tumor paraffin block; rebiopsy if consult material is nondiagnostic
- Core-needle biopsy may be adequate if diagnostic, but an excisional or nodal biopsy is recommended
- Recommend staining for CD15, CD30, T and B panels, CD20, PAX5
- Adequate immunophenotype to confirm diagnosis
  ○ Paraffin panel for HL including NLPHL:
  ○ CD20, PAX-5, CD30, CD3, CD15 and CD45 (LCA)
  ○ EBER
- EBV proteins (ie, LMP1) recommended for NS grade 2 or anaplastic variants
Of use in certain circumstances:
- Immunohistochemical studies:
  ○ LMP1
  ○ BOB1, OCT2, and CD79a (differential diagnosis with B-cell lymphoma, unclassifiable with features intermediate between classical HL and DLBCL and primary mediastinal large B-cell lymphoma).
  ○ CD21, CD23, or CD35 (follicular dendritic cell markers), CD57, BCL6, and IgD in cases of NLPHL (may help with T-cell/histiocyte-rich large B-cell lymphoma)
  ○ CD2, CD43, ALK, and EMA (differential diagnosis with anaplastic large-cell lymphoma)
Strongly recommend:
- Core biopsy for tissue banking by protocol
	- History and physical examination, including:
	  ○ B symptoms (fever, sweats, weight loss)
	  ○ ETOH intolerance
	  ○ Pruritus
	  ○ Fatigue
	  ○ Performance status
	  ○ Examination of nodes
	  ○ Spleen, liver
	- CBC, differential, platelets
	- LDH; LFTs, including alkaline phosphatase, AST, ALT, and albumin, BUN, creatinine
	- ESR
	- Screening for HIV-1, HIV-2, hepatitis B and C (HBcAb, HBsAg, HCVAb)
	- Chest radiography
	- CT of the neck, chest, abdomen, and pelvis
	- PET-CT
	- MUGA or ECG
	- Counseling: fertility, psychosocial if clinically indicated
	Useful in selected cases:
	- Pregnancy test: women of childbearing potential
	- Discuss fertility issues and sperm banking for patients of childbearing potential
	- Semen cryopreservation if chemotherapy or pelvic RT is contemplated

ALK, anaplastic lymphoma kinase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood count; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; EBER, Epstein-Barr virus-encoded small RNA; ECG, echocardiography; EBV, Epstein-Barr virus; EMA, epithelial membrane antigen; ESR, erythrocyte sedimentation rate; ETOH, alcohol; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody; HIV, human immunodeficiency syndrome; HL, Hodgkin lymphoma; LDH, lactated dehydrogenase; LFT, liver function test; MUGA, multigated acquisition; NLPHL, nodular lymphocyte–predominant Hodgkin lymphoma; NS, nodular sclerosis; PET, positron emission tomography; RT, radiation therapy.

cytarabine, and melphalan) at high doses followed by an ASCT or at lower doses (mini-BEAM) without an ASCT. The 3-year freedom from second treatment failure was significantly better for patients who received HDCT (53% and 10%, respectively). The GHSG/European Group for Blood and Marrow Transplantation (EBMT) randomized trial compared four cycles of Dexa-BEAM (dexamethasone plus BEAM) versus two cycles of Dexa-BEAM followed by ASCT for patients with relapsed cHL. At 3 years, the FFTF in the high-dose therapy group was 55% compared with 34% after four cycles of chemotherapy. These studies were performed before development of the PET and anti-CD30 therapy.

Multiple investigators have reported that response to salvage chemotherapy is a strong predictor of long-term outcome after ASCT. In one study, the 5-year OS for patients who were in CR at the time of ASCT was 79% compared with 59% for those in PR and 17% for those with resistant disease at the time of ASCT.[104] Studies have shown the impact of pre-ASCT PET scan results on EFS; those with negative pre-ASCT PET scan results have significantly higher EFS and failure-free survival rates compared to patients with positive pre-ASCT PET scan results.[105–107] In another trial, a European intergroup study evaluated a dose-intensified regimen before ASCT.[108] Patients were randomly assigned after two cycles of DHAP to ASCT or sequential cyclophosphamide, methotrexate, and etoposide before ASCT. There were no significant differences between the two treatment arms in terms of mortality, FFTF, and OS. Thus, the less toxic approach consisting of two cycles of DHAP (or other salvage regimen such as ICE) followed by HDCT and ASCT remained the standard of care for patients with relapsed HL. Achievement of PET negativity is also an established goal for these patients before ASCT, but the role of anti-CD30 antibody therapy remained unclear before the development of BV.

Patients with disease progression after ASCT uniformly have a poor outcome. In a study of patients with HL who failed ASCT, the median time to progression after the next therapy was only 3.8 months, and the median survival after ASCT failure was 26

months.[9] An international multicenter retrospective study showed that the survival of patients who relapsed after an ASCT did not improve from 1981 to 2007.[109,110] However, there has been a major advance in the treatment of relapsed or refractory cHL in the past 10 years: development of novel agents for the disease.

Immunotherapeutic Agents for Relapsed or Refractory Classical Hodgkin Lymphoma

Brentuximab Vedotin

CD30 was considered an ideal target for monoclonal antibody therapy for HL because its expression is highly restricted to HRS cells. BV (SGN-35) is an intravenously administered antibody–drug conjugate that consists of the CD30-specific monoclonal antibody conjugated with monomethyl auristatin E (MMAE) by linker peptide. Binding of the antibody–drug conjugate to CD30 on the cell surface causes internalization of the drug by endocytosis, and the drug subsequently travels to the lysosome, where proteases cleave the linker and release MMAE to the cytosol.[111] Released MMAE binds to tubulin and disrupts the microtubule polymerization, resulting in cell cycle arrest and apoptotic death of CD30-expressing cells. After reports of efficacy in a phase I trial in 45 patients with relapsed or refractory CD30-positive hematologic malignancies, investigators conducted a pivotal phase II trial of 102 patients with HL with relapse using this drug alone following HDCT and ASCT.[112,113] Patients received BV 1.8 mg/kg every 3 weeks up to a maximum of 16 cycles. The ORR was 75%, with a CR rate of 34%. These data led to the first drug approval by the US Food and Drug Administration (FDA) for the treatment of patients with HL in more than 30 years. Durable remission was reported with a longer follow-up period, and the median OS and PFS were 40.5 months and 9.3 months, respectively.[114] The 3-year PFS rate of patients who achieved CR with BV was 58%. This survival outcome is notable considering that the patients enrolled in this trial had disease progression after ASCT.

Achieving CR before ASCT is the key to better outcomes in patients with relapsed or refractory HL. Therefore, BV is often used as a third-line therapy in patients who have not achieved CR after second-line salvage chemotherapy such as ICE. The Seattle group retrospectively evaluated the efficacy of BV in patients who had disease refractory to platinum-based salvage chemotherapy.[6] Fifteen patients who had PET-positive disease after platinum-based salvage therapy received a median of four cycles of BV. PET scan negativity occurred in eight (53%) of 15 patients but was only observed in patients who had achieved partial remission or stable disease after salvage therapy. This suggests that BV can achieve CR by PET in a considerable subset of patients with platinum-refractory HL before ASCT.

Maintenance therapy with BV after ASCT was evaluated in a placebo-controlled randomized phase III study (AETHERA).[115,116] Patients were enrolled in this study if they had (1) disease considered refractory to frontline therapy, (2) relapse less than 12 months after frontline therapy, or (3) relapse 12 months or more after frontline therapy with extranodal disease. At 5 years of follow-up, PFS rates were superior in the BV compared with placebo cohorts (59% and 41%, respectively) with 90% of patients who received BV reporting significant improvement or resolution of associated peripheral neuropathy.[117] Patients with high-risk disease, defined as the presence of two or more risk factors (relapse <12 months or refractory to frontline therapy, best response of PR or stable disease to most recent salvage therapy, extranodal disease at pretransplant relapse, B symptoms at pretransplant relapse, two or more prior salvage therapies) demonstrated more pronounced benefit (5-year PFS HR, 0.42) with BV maintenance therapy. Therefore, BV consolidation should be offered to high-risk patients who develop relapse after first-line chemotherapy.

In an attempt to improve responses before ASCT, investigators performed a phase II study of BV in combination with ICE chemotherapy as salvage therapy before ASCT. Patients received two cycles of BV-ICE before evaluation, and patients in CMR received an additional dose of BV only rather than a third cycle of BV-ICE. Of the 39 patients in the efficacy analysis, 69% achieved a CMR, and 26% achieved a partial (P) MR, with a 1-year PFS of 69% post ASCT.[118] In another phase II study of 66 patients who received BV in combination with ESHAP chemotherapy before ASCT, the pretransplant CMR was 80%, with a PMR of 7%, and a projected 1-year PFS of 87% after ASCT.[119] BV was also studied in a phase II trial that combined this drug with bendamustine before ASCT; the pretransplant CMR and PMR rates were 79% and 5%, respectively, with projected 3-year PFS and OS rates of 67% and 88%, respectively.[120] No significant excess in toxicity was reported in the trials evaluating BV in combination with chemotherapy before ASCT; however, a longer follow-up period is required to evaluate whether improved pretransplant responses translate to improved survival outcomes.

Bendamustine is a bifunctional alkylating agent derived from 2-chloroethylamine that had been a standard chemotherapy for patients with indolent lymphoma (follicular lymphoma and mantle cell lymphoma).[121,122] The Memorial Sloan-Kettering Cancer Center conducted a phase II trial of bendamustine in patients with HL who had relapse after ASCT or were

not eligible for ASCT.[123] Patients received bendamustine 120 mg/m^2 on days 1 and 2 of a 28-day cycle for six planned cycles. The ORR was 53%, with a 33% CR rate; the median PFS was 5.2 months. Preliminary data of a phase I/II study for the combination of bendamustine and BV for relapsed or refractory transplant-naïve patients produced an ORR of 94%, with a CR rate of 82%.[124] At the time of report, 20 of 34 patients who had a response to this combination had undergone ASCT.

BV also appears effective in therapy of patients with relapse after allogeneic stem cell transplantation (allo-SCT). In one retrospective analysis of 184 patients with relapsed cHL after allo-SCT, 88 had received BV salvage therapy, and 104 did not. Of the patients who received BV, 29% achieved a CR and 45% PR with significantly more patients alive at last follow-up compared with patients who did not (34% and 18%, respectively; $P = .003$).[125] However, salvage BV did not affect the incidence of chronic graft-versus-host disease, and 1-year OS rates post recurrence after allo-SCT were similar (76% and 67%, respectively).

Programmed Death-1 Inhibitors

PD-1 ligand is overexpressed on malignant Reed-Sternberg cells in HL, facilitating immune evasion from antitumor cells. Nivolumab is a PD-1 immune checkpoint inhibitor antibody that selectively blocks the interaction between PD-1 and its ligands PD-L1 and PD-L2. By inhibiting PD-1 interaction, nivolumab can enhance T-cell function, which results in antitumor activity. Nivolumab has been evaluated in a multicenter phase II trial for patients with relapsed or refractory cHL with or without prior exposure to BV or prior ASCT. Of 243 treated patients, the ORR was 69% with a median PFS of 14.7 months.[126] Based on promising single-agent activity, nivolumab has gained FDA approval for relapsed or refractory HL after ASCT.

PD-1 inhibition with nivolumab has been explored in a phase II study as salvage therapy at first relapse in relapsed or refractory cHL.[127] Thirty-nine patients with relapsed or refractory cHL received 3 mg/kg of nivolumab every 2 weeks for six cycles followed by interim PET imaging. If patients were in CR, they proceeded to ASCT, whereas seven patients with PR or stable disease proceeded to receive nivolumab in combination with ICE chemotherapy for two cycles. After six cycles of nivolumab, the ORR was 90%, and CR was 77%; if the patients who were treated with nivolumab and ICE were included, the ORR was 94%, and CR was 91%. PD-1 inhibition was well tolerated, with mainly grade 1 to 2 AEs (fatigue, rash, fever, and thrombocytopenia). The impressive response rates to PD-1 inhibition at first relapse compared with historical data with salvage chemotherapy indicate that alternative salvage strategies may be effective for chemotherapy-refractory disease. However, the durability of response after ASCT is still to be determined, with reported 1-year PFS and OS rates of 79% and 97%, respectively.

Nivolumab has also been evaluated in combination with other novel agents. In a phase I/II study, nivolumab in combination with BV was evaluated as initial salvage therapy for 62 patients with relapsed or refractory HL, resulting in an ORR of 82% with a CR rate of 61%.[128] Grade 3 or higher AEs occurred in 31% of patients with no patients discontinuing therapy because of immune-related AEs. In a separate phase II study, a risk-adapted approach was applied in patients ages 5 to 30 years with relapsed or refractory HL. Four cycles of nivolumab in combination with BV were administered, and patients achieving less than CMR after induction received additional cycles of BV plus bendamustine for intensification. Of the 44 patients who have been treated, only 11 (25%) received BV plus bendamustine intensification. The ORR, CR rate, and 1-year PFS rate were 82%, 59%, and 91%, respectively.[129] Nivolumab has also been investigated as part of a triplet combination with ipilimumab and BV in a phase I study of 64 patients with relapsed or refractory HL. Across all dose levels, the triplet combination demonstrated impressive outcomes with an ORR of 95%, CR rate of 84%, and 1-year PFS of 72%.[130] This study also compared doublet combinations of nivolumab plus BV and BV plus ipilimumab in separate arms; nivolumab-containing cohorts appeared to have superior outcomes.

Another PD-1 inhibitor, pembrolizumab, has also received FDA approval for the treatment of patients with relapsed or refractory HL based on pivotal single-agent phase II data. A total of 210 patients with relapsed or refractory HL were enrolled in three separate cohorts to receive pembrolizumab 200 mg once every 3 weeks based on prior exposure to BV or ASCT. Across all cohorts, the ORR was 72%, the CR rate was 28%, and the median duration of response 16.5 months.[131] Pembrolizumab was well tolerated with grade 3 or 4 AEs occurring in 12% of patients. Avelumab, a human IgG-1 monoclonal antibody that selectively binds to PD-L1 has been evaluated in a phase 1 study of 31 patients with relapsed or refractory HL and has promising activity with an ORR of 55% and CR rate of 6% across all dose levels.[132]

Allogeneic Stem-Cell Transplantation

The main advantage of an allo-SCT is its graft-versus-HL effect. Retrospective studies have suggested this effect because of lower relapse rates in allo-SCT patients with chronic graft-versus-host disease (GVHD) and responses after donor lymphocyte infusion.[133] Initial studies of allo-SCT in HL patients described high

rates of nonrelapse mortality (NRM), up to 61%. More recent studies evaluated therapy with reduced-intensity conditioning (RIC), treatment associated decreased treatment-related mortality (TRM); in these studies, RIC allo-SCT induced long-term remissions in about 30% of patients.[134,135]

The EBMT reviewed 168 patients who had undergone allo-SCT.[135] Seventy-nine patients received myeloablative conditioning, and 89 patients received RIC. Fifty-two percent of patients had undergone a prior ASCT, and 45% had chemotherapy-sensitive disease. The NRM was significantly lower, and OS was significantly better with RIC versus myeloablative conditioning. One-year NRM was 23%, and 5-year PFS and OS were 18% and 28%, respectively, in patients who received RIC.

At MDACC, we reviewed the outcomes of 58 patients who received RIC with fludarabine–melphalan in preparation for allo-SCT.[136] Overall, 83% of patients had undergone a prior ASCT and 52% had chemotherapy-sensitive disease at the time of allo-SCT. The TRM at 2 years was 15%, with nearly half of the TRM occurring within the first 100 days after allo-SCT. The incidence of chronic GVHD was 73%. The 2-year PFS and OS rates were 32% and 64%, respectively. There was a trend toward improvement in PFS for those with chemotherapy-sensitive disease but not for OS. Allo-SCT is still an important option for eligible patients who develop relapse after ASCT.

Chimeric Antigen Receptor T-Cell Therapy

Anti-CD30 chimeric antigen receptor (CAR) T-cell therapy attempts to overcome the limited bioavailability and short half-lives of anti-CD30 monoclonal antibodies such as BV. A phase I study evaluated an anti-CD30 CAR T product with dual CD28 and 4-1BB co-stimulatory domains in nine patients with relapsed or refractory CD30-positive lymphomas. Of the nine patients, six (67%) had HL with a CR rate of 78% and a median PFS of 13 months among all patients.[137] In a separate phase 1 study of 14 patients with relapsed or refractory HL who received an anti-CD30 CAR T product, the ORR was 67%, and the CR rate was 58% for the evaluable patients.[138] In an update, incorporating two different phase I/II studies, these latter investigators evaluated results for 41 patients with relapsed or refractory cHL who received anti-CD30 CAR-Ts.[139] The median number of prior therapies was seven (range, 2–23), and 32 of these patients received fludarabine-based T-cell depletion. Of these 31, 72% had a response, and 59% had CR. The 1-year PFS was 36%, and the OS was 94%. CAR T–related cytokine release syndrome in this study occurred in 10 patients and was grade 1; significant neurotoxicity did not occur. A longer follow-up period is required to establish whether durable remissions are observed following this promising approach.

Bispecific Antibodies and Antibody–Drug Conjugates

Bispecific antibodies are immunoglobulin molecules containing two different antigen binding sites, one directed against specific tumor antigens and the other toward native immune effector cells. A phase Ib study of a CD30 bispecific antibody targeting CD16A on natural killer cells in combination with pembrolizumab demonstrated promising clinical activity in patients with relapsed or refractory HL. Of 30 patients, the ORR and CR rates were 88% and 46%, respectively, with an estimated 6-month PFS rate of 77% at the highest dose level.[140] The treatment was well tolerated, with grade 3 or higher toxicity occurring in only 13% of patients. A separate phase 1 study investigated an anti-CD25 antibody conjugated to a pyrrolobenzodiazepine dimer toxin was investigated in a phase 1 trial in adult patients with relapsed or refractory HL. Of the 37 patients treated at the highest dose cohort, the ORR was 86% and CR rate of 43% in a heavily pretreated population without excess toxicity.[141] However, durability of responses have not been reported because of limited follow-up. Therefore, despite promising activity with bispecific antibodies and antibody–drug conjugates, longer follow-up is needed to determine durability of responses.

The MD Anderson Approach to Relapsed or Refractory Classical Hodgkin Lymphoma

Patients with relapsed or refractory HL are planned for second-line or salvage chemotherapy followed by an ASCT. We screen patients who have relapsed or refractory HL for current clinical trial options. Patients who respond to salvage chemotherapy are planned to undergo ASCT. We offer BV maintenance therapy after ASCT for patients deemed high risk based on (1) relapsed or progressive HL occurring less than 12 months from end of frontline therapy; (2) a history of refractory HL, defined as progression during or failure to achieve CR after frontline therapy; or (3) extranodal involvement at the time of pre-ASCT relapse. For patients who fail to achieve a CMR before ASCT, we use either BV in combination with salvage chemotherapy (ICE or bendamustine) or a PD-1 inhibitor (pembrolizumab or nivolumab single agent, or nivolumab in combination with BV) to deepen the response before ASCT. In patients who have refractory disease or relapse after ASCT, we consider BV (if not previously refractory to BV) as single agent or in combination with bendamustine or nivolumab. In BV-refractory patients, we consider nivolumab or pembrolizumab

as single-agent therapy. Given the benefits versus risks of allo-SCT, a subset of patients can be potentially considered for this approach, particularly otherwise healthy patients who achieve complete remission with addition therapies.

CONCLUSION

Although standard frontline chemotherapy with or without RT offers a high cure rate for patients with cHL, approximately 20% of patients develop refractory or relapsed disease. Thus, the challenge that remains is how to best develop strategies of therapy that increase the cure rates for the refractory and relapsed group of patients while decreasing both short- and long-term toxicities, including secondary malignancies, for patients who are cured of their disease with current standard approaches. Huge recent achievements have occurred on both fronts, including a decrease of both the number of cycles of chemotherapy and the doses of RT for patients with early-stage disease and introduction of BV into frontline regimens paired with chemotherapy. The advent of PD-1 inhibitors has demonstrated the ability to have significant efficacy even in patients with BV-resistant disease. Future directions are anticipated to increase the focus on evaluating the efficacy of combinations of targeted agents, with likely future trials exploring the potential activity of chemotherapy-free targeted treatment combinations in the frontline setting. Better understanding of the molecular biology of both cHL and NLPHL will also lead to more rationally designed novel agent trials and allow us to best select treatment strategies. The future of HL treatment has evolved significantly over the past decade, and these successes will only be significantly multiplied over the next decade to follow.

MD ANDERSON PRACTICE TIPS

- For favorable early-stage classical HL, omitting radiation consolidation after two cycles of ABVD based on PET negativity is associated with a risk of treatment failure based on the GHSG HD16 study.
- For unfavorable early-stage classical HL, omitting RT based on a PET-adapted strategy provides results that are noninferior to those achieved with chemotherapy plus RT based on the GHSG HD17 trial. However, therapy must be escalated BEACOPP $\times 2$, followed by ABVD $\times 2$.
- In advanced-stage classical HL, if treating with ABVD, interim PET scan should be performed after two cycles, and bleomycin may be safely omitted with a negative PET scan result based on the RATHL study.
- The A (BV)-AVD regimen is recommended for classical HL patients who are young (younger than 60 years), with stage IV disease, and with high IPS (score 4–7) because patients with these features benefited the most in the ECHELON-1 trial by the substitution of BV for bleomycin in ABVD.
- The A-AVD regimen is associated with a high risk of neutropenia, and growth factor support is required to minimize the risk of neutropenic fever.
- Before beginning salvage chemotherapy and ASCT based on PET positivity, one must confirm histopathologic relapsed or refractory classical HL.

REFERENCES

1. Swerdlow SH, Campo E, Harris NL, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. International Agency for Research on Cancer. 2017.
2. Bray F, Ferlay J, Soerjomataram I, et al. Global estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394-424.
3. Chihara D, Ito H, Matsuda T, et al. Differences in incidence and trends of haematological malignancies in Japan and the United States. *Br J Haematol*. 2014;164(4):536-545.
4. Miller K, Nogueira L, Mariotta A, et al. Cancer treatment and survivorship statistics, 2019. *CA Cancer J Clin*. 2019;69:363-385.
5. Schmitz R, Stanelle J, Hansmann ML, et al. Pathogenesis of classical and lymphocyte-predominant Hodgkin lymphoma. *Annu Rev Pathol*. 2009;4:151-174.
6. Kuppers R. Molecular biology of Hodgkin's lymphoma. *Adv Cancer Res*. 2002;84:277-312.
7. Diehl V, Sextro M, Franklin J, et al. Clinical presentation, course, and prognostic factors in lymphocyte-predominant Hodgkin's disease and lymphocyte-rich classical Hodgkin's disease: report from the European Task Force on Lymphoma Project on Lymphocyte-Predominant Hodgkin's Disease. *J Clin Oncol*. 1999;17(3):776-783.
8. Nogova L, Reineke T, Brillant C, et al. Lymphocyte-predominant and classical Hodgkin's lymphoma: a comprehensive analysis from the German Hodgkin Study Group. *J Clin Oncol*. 2008;26(3):434-439.
9. Anagnostopoulos I, Hansmann ML, Franssila K, et al. European Task Force on Lymphoma project on lymphocyte predominance Hodgkin disease: histologic and immunohistologic analysis of submitted cases reveals 2 types of Hodgkin disease with a nodular growth pattern and abundant lymphocytes. *Blood*. 2000;96(5):1889-1899.
10. Lukes RJ, Butler JJ. The pathology and nomenclature of Hodgkin's disease. *Cancer Res*. 1966;26(6):1063-1083.
11. Brune V, Tiacci E, Pfeil I, et al. Origin and pathogenesis of nodular lymphocyte-predominant Hodgkin lymphoma as revealed by global gene expression analysis. *J Exp Med*. 2008;205(10):2251-2268.
12. MacLennan KA, Bennett MH, Tu A, et al. Relationship of histopathologic features to survival and relapse in nodular sclerosing Hodgkin's disease. A study of 1659 patients. *Cancer*. 1989;64(8):1686-1693.
13. Medeiros LJ, Greiner TC. Hodgkin's disease. *Cancer*. 1995;75(1 suppl):357-369.
14. Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *J Clin Oncol*. 1989;7(11):1630-1636.
15. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32(27):3059-3068.
16. Cheson BD. Role of functional imaging in the management of lymphoma. *J Clin Oncol* 2011;29(14):1844-1854.
17. Barrington SF, Mackewn JE, Schleyer P, et al. Establishment of a UK-wide network to facilitate the acquisition of quality assured FDG-PET data for clinical trials in lymphoma. *Ann Oncol*. 2011;22(3):739-745.
18. El-Galaly TC, d'Amore F, Mylam KJ, et al. Routine bone marrow biopsy has little or no therapeutic consequence for positron emission tomography/computed tomography-staged treatment-naive patients with Hodgkin lymphoma. *J Clin Oncol* 2012;30(36):4508-4514.
19. Mauch P, Tarbell N, Weinstein H, et al. Stage IA and IIA supradiaphragmatic Hodgkin's disease: prognostic factors in surgically staged patients treated with mantle and paraaortic irradiation. *J Clin Oncol*. 1988;6(10):1576-1583.
20. Tubiana M, Henry-Amar M, van der Werf-Messing B, et al. A multivariate analysis of prognostic factors in early stage Hodgkin's disease. *Int J Radiat Oncol Biol Phys*. 1985;11(1):23-30.
21. Cosset JM, Henry-Amar M, Meerwaldt JH, et al. The EORTC trials for limited stage Hodgkin's disease. The EORTC Lymphoma Cooperative Group. *Eur J Cancer*. 1992;28A(11):1847-1850.
22. Engert A, Plutschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med*. 2010;363(7):640-652.
23. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. *N Engl J Med*. 1998;339(21):1506-15514.
24. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol*. 1999;17(4):1244.
25. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007;25(5):579-86.
26. Engert A, Haverkamp H, Kobe C, et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. *Lancet*. 2012;379(9828):1791-1799.
27. Juweid ME, Stroobants S, Hoekstra OS, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. *J Clin Oncol*. 2007;25(5):571-578.
28. Barrington SF, Phillips EH, Counsell N, et al. Positron emission tomography score has greater prognostic significance than pretreatment risk stratification in early-stage Hodgkin lymphoma in the UK RAPID Study. *J Clin Oncol*. 2019;37(20):1732-1741.
29. Kobe C, Goergen H, Baues C, et al. Outcome-based interpretation of early interim PET in advanced-stage Hodgkin lymphoma. *Blood*. 2018;132(21):2273-2279.
30. Nogova L, Reineke T, Eich HT, et al. Extended field radiotherapy, combined modality treatment or involved field radiotherapy for patients with stage IA lymphocyte-predominant Hodgkin's lymphoma: a retrospective analysis from the German Hodgkin Study Group (GHSG). *Ann Oncol*. 2005;16(10):1683-1687.
31. Schlembach PJ, Wilder RB, Jones D, et al. Radiotherapy alone for lymphocyte-predominant Hodgkin's disease. *Cancer J*. 2002;8(5):377-383.
32. Chen RC, Chin MS, Ng AK, et al. Early-stage, lymphocyte-predominant Hodgkin's lymphoma: patient outcomes from a large, single-institution series with long follow-up. *J Clin Oncol*. 2010;28(1):136-141.
33. Savage KJ, Skinnider B, Al-Mansour M, et al. Treating limited-stage nodular lymphocyte predominant Hodgkin lymphoma similarly to classical Hodgkin lymphoma with ABVD may improve outcome. *Blood*. 2011;118(17):4585-4590.
34. Advani R, Horning S, Hoppe R, et al. Mature results of a phase II study of rituximab therapy for nodular lymphocyte-predominant Hodgkin lymphoma. *J Clin Oncol*. 2014;32:912-918.
35. Eichenauer DA, Fuchs M, Pluetschow A, et al. Phase 2 study of rituximab in newly diagnosed stage IA nodular lymphocyte-predominant Hodgkin lymphoma: a report from the German Hodgkin Study Group. *Blood*. 2011;118(16):4363-5.
36. Xing KH, Connors JM, Lai A, et al. Advanced-stage nodular lymphocyte predominant Hodgkin lymphoma compared with

classical Hodgkin lymphoma: a matched pair outcome analysis. *Blood*. 2014;123(23):3567-3573.
37. Fanale MA, Cheah CY, Rich A, et al. Encouraging activity for R-CHOP in advanced stage nodular lymphocyte-predominant Hodgkin lymphoma. *Blood*. 2017;130(4):472-477.
38. Schulz H, Rehwald U, Morschhauser F, et al. Rituximab in relapsed lymphocyte-predominant Hodgkin lymphoma: long-term results of a phase 2 trial by the German Hodgkin Lymphoma Study Group (GHSG). *Blood*. 2008;111(1):109-111.
39. Al-Mansour M, Connors JM, Gascoyne RD, et al. Transformation to aggressive lymphoma in nodular lymphocyte-predominant Hodgkin's lymphoma. *J Clin Oncol*. 2010;28(5):793-799.
40. Karuturi M, Hosing C, Fanale M, et al. High-dose chemotherapy and autologous stem cell transplantation for nodular lymphocyte-predominant Hodgkin lymphoma. *Biol Blood Marrow Transplant*. 2013;19(6):991-4.
41. Rosenberg SA, Kaplan HS. The evolution and summary results of the Stanford randomized clinical trials of the management of Hodgkin's disease: 1962-1984. *Int J Radiat Oncol Biol Phys*. 1985;11(1):5-22.
42. Specht L, Gray RG, Clarke MJ, et al. Influence of more extensive radiotherapy and adjuvant chemotherapy on long-term outcome of early-stage Hodgkin's disease: a meta-analysis of 23 randomized trials involving 3,888 patients. International Hodgkin's Disease Collaborative Group. *J Clin Oncol*. 1998;16(3):830-843.
43. Dores GM, Metayer C, Curtis RE, et al. Second malignant neoplasms among long-term survivors of Hodgkin's disease: a population-based evaluation over 25 years. *J Clin Oncol*. 2002;20(16):3484-3494.
44. Engert A, Franklin J, Eich HT, et al. Two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine plus extended-field radiotherapy is superior to radiotherapy alone in early favorable Hodgkin's lymphoma: final results of the GHSG HD7 trial. *J Clin Oncol*. 2007;25(23):3495-3502.
45. Ferme C, Eghbali H, Meerwaldt JH, et al. Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. *N Engl J Med*. 2007;357(19):1916-1927.
46. Chronowski GM, Wilder RB, Tucker SL, et al. Analysis of in-field control and late toxicity for adults with early-stage Hodgkin's disease treated with chemotherapy followed by radiotherapy. *Int J Radiat Oncol Biol Phys*. 2003;55(1):36-43.
47. Raemaekers JM, Andre MP, Federico M, et al. Omitting radiotherapy in early positron emission tomography-negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse: clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial. *J Clin Oncol*. 2014;32(12):1188-1194.
48. Behringer K, Goergen H, Hitz F, et al. Omission of dacarbazine or bleomycin, or both, from the ABVD regimen in treatment of early-stage favourable Hodgkin's lymphoma (GHSG HD13): an open-label, randomised, non-inferiority trial. *Lancet*. 2015;385(9976):1418-1427.
49. Advani RH, Hoppe RT, Baer D, et al. Efficacy of abbreviated Stanford V chemotherapy and involved-field radiotherapy in early-stage Hodgkin lymphoma: mature results of the G4 trial. *Ann Oncol*. 2013;24(4):1044-1048.
50. Noordijk EM, Thomas J, Fermé C, et al. First results of the EORTC-GELA H9 randomized trials: the H9-F trial (comparing 3 radiation dose levels) and H9-U trial (comparing 3 chemotherapy schemes) in patients with favorable or unfavorable early stage Hodgkin's lymphoma (HL). *J Clin Oncol*. 2005;23(16 suppl):6505.
51. Bonadonna G, Bonfante V, Viviani S, et al. ABVD plus subtotal nodal versus involved-field radiotherapy in early-stage Hodgkin's disease: long-term results. *J Clin Oncol*. 2004;22(14):2835-2841.
52. Andre MPE, Girinsky T, Federico M, et al. Early positron emission tomography response-adapted treatment in stage I and II Hodgkin lymphoma: final results of the Randomized EORTC/LYSA/FIL H10 Trial. *J Clin Oncol*. 2017;35(16):1786-1794.
53. Radford J, Illidge T, Counsell N, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. *N Engl J Med*. 2015;372(17):1598-1607.
54. Fuchs M, Goergen H, Kobe C, et al. Positron emission tomography-guided treatment in early-stage favorable Hodgkin lymphoma: final results of the international, randomized phase III HD16 trial by the German Hodgkin Study Group. *J Clin Oncol*. 2019;37(31):2835-2845.
55. Abramson JS, Arnason JE, LaCasce AS, et al. Brentuximab vedotin, doxorubicin, vinblastine and dacarbazine for non-bulky limited stage classical Hodgkin lymphoma. *Blood*. 2019;134:606-613.
56. Bröckelmann PJ, Goergen H, Keller U, et al. Nivolumab and AVD for early-stage unfavorable Hodgkin lymphoma (NIVAHL). *Blood*. 2019;134(suppl 1):236.
57. Gordon LI, Hong F, Fisher RI, et al. Randomized phase III trial of ABVD versus Stanford V with or without radiation therapy in locally extensive and advanced-stage Hodgkin lymphoma: an intergroup study coordinated by the Eastern Cooperative Oncology Group (E2496). *J Clin Oncol*. 2013;31(6):684-691.
58. von Tresckow B, Plutschow A, Fuchs M, et al. Dose-intensification in early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD14 trial. *J Clin Oncol*. 2012;30(9):907-913.
59. Eich HT, Diehl V, Gorgen H, et al. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD11 trial. *J Clin Oncol*. 2010;28(27):4199-4206.
60. Ferme C, Thomas J, Brice P, et al. ABVD or BEACOPP baseline along with involved-field radiotherapy in early-stage Hodgkin lymphoma with risk factors: results of the European Organisation for Research and Treatment of Cancer (EORTC)-Groupe d'Etude des Lymphomes de l'Adulte (GELA) H9-U intergroup randomised trial. *Eur J Cancer*. 2017;81:45-55.
61. Meyer RM, Gospodarowicz MK, Connors JM, et al. ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. *N Engl J Med*. 2012;366(5):399-408.
62. Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. *N Engl J Med*. 1992;327(21):1478-1484.
63. Mounier N, Brice P, Bologna S, et al. ABVD (8 cycles) versus BEACOPP (4 escalated cycles >/= 4 baseline): final results in stage III-IV low-risk Hodgkin lymphoma (IPS 0-2) of the LYSA H34 randomized trial. *Ann Oncol*. 2014;25(8):1622-1628.
64. Viviani S, Zinzani PL, Rambaldi A, et al. ABVD versus BEACOPP for Hodgkin's lymphoma when high-dose salvage is planned. *N Engl J Med*. 2011;365(3):203-212.
65. Borchmann P, Haverkamp H, Diehl V, et al. Eight cycles of escalated-dose BEACOPP compared with four cycles of escalated-dose BEACOPP followed by four cycles of baseline-dose BEACOPP with or without radiotherapy in patients with advanced-stage Hodgkin's lymphoma: final analysis of the HD12 trial of the German Hodgkin Study Group. *J Clin Oncol*. 2011;29(32):4234-4242.
66. Engert A, Diehl V, Franklin J, et al. Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 years of follow-up of the GHSG HD9 study. *J Clin Oncol*. 2009;27(27):4548-4554.
67. Diehl V, Franklin J, Pfreundschuh M, et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. *N Engl J Med*. 2003;348(24):2386-2395.

68. Borchmann P, Goergen H, Kobe C, et al. PET-guided treatment in patients with advanced-stage Hodgkin's lymphoma (HD18): final results of an open-label, international, randomised phase 3 trial by the German Hodgkin Study Group. *Lancet*. 2018;390(10114):2790-2802.
69. Press OW, Li H, Schöder H, et al. US Intergroup trial of response-adapted therapy for stage III to IV Hodgkin lymphoma using early interim fluorodeoxyglucose-positron emission tomography imaging: Southwest Oncology Group S0816. *J Clin Oncol*. 2016;34(17):2020-2027.
70. Stephens DM, Li H, Schöder H, et al. Five-year follow-up of SWOG S0816: limitations and values of a PET-adapted approach for stage III/IV Hodgkin lymphoma. *Blood*. 2019;134:1238-1246.
71. Gallamini A, Rossi A, Patti C, et al. Early treatment intensification in advanced-stage high-risk Hodgkin lymphoma (HL) patients, with a positive FDG-PET scan after two ABVD courses—first interim analysis of the GITIL/FIL HD0607 clinical trial. *Blood*. 2012;120:550.
72. Gallamini A, Tarella C, Viviani S, et al. Early chemotherapy intensification with escalated BEACOPP in patients with advanced-stage Hodgkin lymphoma with a positive interim positron emission tomography/computed tomography scan after two ABVD cycles: long-term results of the GITIL/FIL HD 0607 trial. *J Clin Oncol*. 2018;36(5):454-462.
73. Johnson P, Trotman J, Federico M, et al. Interim PET-CT scan in advanced Hodgkin's lymphoma. *N Engl J Med*. 2016;375(10):999-1000.
74. Federico M, Luminari S, Iannitto E, et al. ABVD compared with BEACOPP compared with CEC for the initial treatment of patients with advanced Hodgkin's lymphoma: results from the HD2000 Gruppo Italiano per lo Studio dei Linfomi trial. *J Clin Oncol*. 2009;27(5):805-811.
75. Merli F, Luminari S, Gobbi PG, et al. Long-term results of the HD2000 trial comparing ABVD versus BEACOPP versus COPP-EBV-CAD in untreated patients with advanced Hodgkin lymphoma: a study by Fondazione Italiana Linfomi. *J Clin Oncol*. 2016;34(11):1175-1181.
76. Bellova V, Ruffer J, Haverkamp H, et al. A prospectively randomized trial carried out by the German Hodgkin Study Group (GHSG) for elderly patients with advanced Hodgkin's disease comparing BEACOPP baseline and COPP-ABVD (study HD9elderly). *Ann Oncol*. 2005;16:124-131.
77. Connors J, Jurczak W, Straus D, et al. ECHELON-1 study group. Brentuximab vedotin with chemotherapy for stage III-IV Hodgkin's lymphoma. *N Engl J Med*. 2018;378:331-344.
78. Straus D, Dlugose-Danecka M, Alekseev S, et al. Brentuximab vedotin with chemotherapy for stage III-IV classical Hodgkin lymphoma: 3-year update of the ESCHELON-1 study. *Blood*. 2020;135:735-742.
79. Ramchandren R, Advani R, Ansell S, et al. Brentuximab vedotin plus chemotherapy in North American subjects with newly diagnosed stage III or IV Hodgkin lymphoma. *Clin Cancer Res*. 2019;25:1718-1726.
80. Forrero-Torres A, Holcova B, Goldschmidt J, et al. Phase 2 study of frontline brentuximab vedotin monotherapy in Hodgkin lymphoma patients aged 60 years and older. *Blood*. 2015;126:2798-2804.
81. Yasenchak C, Bordoni R, Patel-Donnely D, et al. Frontline brentuximab vedotin as monotherapy or in combination for older Hodgkin lymphoma patients. *Am Soc Clin Oncol*. 2020;38:8032.
82. Ramchandren R, Domingo-Domenech E, Rueda A, et al. Nivolumab for newly diagnosed advanced-stage classic Hodgkin lymphoma: safety and efficacy in the phase II CheckMate 205 study. *J Clin Oncol*. 2019;37(23):1997-2007.
83. Hutchings M, Loft A, Hansen M, et al. FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. *Blood*. 2006;107(1):52-59.
84. Terasawa T, Lau J, Bardet S, et al. Fluorine-18-fluorodeoxyglucose positron emission tomography for interim response assessment of advanced-stage Hodgkin's lymphoma and diffuse large B-cell lymphoma: a systematic review. *J Clin Oncol*. 2009;27(11):1906-1914.
85. Kobe C, Dietlein M, Franklin J, et al. Positron emission tomography has a high negative predictive value for progression or early relapse for patients with residual disease after first-line chemotherapy in advanced-stage Hodgkin lymphoma. *Blood* 2008;112(10):3989-3994.
86. Gallamini A, Hutchings M, Rigacci L, et al. Early interim 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. *J Clin Oncol*. 2007;25(24):3746-3752.
87. Gallamini A, Barrington SF, Biggi A, et al. The predictive role of interim positron emission tomography for Hodgkin lymphoma treatment outcome is confirmed using the interpretation criteria of the Deauville five-point scale. *Haematologica*. 2014;99(6):1107-1113.
88. Agostinelli C, Gallamini A, Stracqualursi L, et al. The combined role of biomarkers and interim PET scan in prediction of treatment outcome in classical Hodgkin's lymphoma: a retrospective, European, multicentre cohort study. *Lancet Haematol*. 2016;3(10):e467-e479.
89. Klimm B, Goergen H, Fuchs M, et al. Impact of risk factors on outcomes in early-stage Hodgkin's lymphoma: an analysis of international staging definitions. *Ann Oncol*. 2013;24(12):3070-3076.
90. Cottereau AS, Versari A, Loft A, et al. Prognostic value of baseline metabolic tumor volume in early-stage Hodgkin lymphoma in the standard arm of the H10 trial. *Blood*. 2018;131(13):1456-1463.
91. Mettler J, Muller H, Voltin CA, et al. Metabolic tumour volume for response prediction in advanced-stage Hodgkin lymphoma. *J Nucl Med*. 2019;60:207-211.
92. Spina V, Bruscaggin A, Cuccaro A, et al. Circulating tumor DNA reveals genetics, clonal evolution, and residual disease in classical Hodgkin lymphoma. *Blood*. 2018;131(22):2413-2425.
93. Evens AM, Advani RH, Helenowski IB, et al. Multicenter phase II study of sequential brentuximab vedotin and doxorubicin, vinblastine, and dacarbazine chemotherapy for older patients with untreated classical Hodgkin lymphoma. *J Clin Oncol*. 2018;36(30):3015-3022.
94. Rubinstein PG, Moore PC, Bimali M, et al. Safety and efficacy of brentuximab vedotin in combination with AVD in stage II-IV HIV-associated classical Hodgkin lymphoma: results of the phase 2 study, AMC 085. *Blood*. 2019;134(suppl 1):130.
95. Moskowitz C, Nimer S, Zelenetz A, et al. A 2-step comprehensive high-dose second-line program for relapsed and refractory Hodgkin disease: analysis by intent to treat and development of a prognostic model. *Blood*. 2001;97:616-623.
96. Moskowitz C, Matasar M, Zelenetz A, et al. Normalization of pre-ASCT, FDG-PET imaging with second-line, non-cross-resistant, chemotherapy programs improves event-free survival in patients with Hodgkin lymphoma. *Blood*. 2012;119:1665-1670.
97. Smardova L, Engert A, Haverkamp H, et al. Successful mobilization of peripheral blood stem cells with the DHAP regimen (dexamethasone, cytarabine, cisplatinum) plus granulocyte colony-stimulating factor in relapsed Hodgkin's disease. *Leuk Lymphoma*. 2005;46:1017-1022.
98. Zinzani PL, Bendandi M, Stefoni V, et al. Value of gemcitabine treatment in heavily pretreated Hodgkin's disease patients. *Haematologica*. 2000;85(9):926-929.
99. Bartlett NL, Niedzwiecki D, Johnson JL, et al. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a

salvage regimen in relapsed Hodgkin's lymphoma: CALGB 59804. *Ann Oncol*. 2007;18(6):1071-1079.
100. Baetz T, Belch A, Couban S, et al. Gemcitabine, dexamethasone, and cisplatin is an active and non-toxic chemotherapy regimen in relapsed or refractory Hodgkin's disease: a phase II study by the National Cancer Institute of Canada Clinical Trials Group. *Ann Oncol*. 2003;14:1762-1767.
101. Santoro A, Magagnoli M, Spina M, et al. Ifosfamide, gemcitabine, and vinorelbine: a new induction regimen for refractory and relapsed Hodgkin's lymphoma. *Haematologica*. 2007;92(1):35-41.
102. Schmitz N, Pfistner B, Sextro M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. *Lancet*. 2002;359(9323):2065-2071.
103. Linch DC, Winfield D, Goldstone AH, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. *Lancet*. 1993;341(8852):1051-1054.
104. Sirohi B, Cunningham D, Powles R, et al. Long-term outcome of autologous stem-cell transplantation in relapsed or refractory Hodgkin's lymphoma. *Ann Oncol*. 2008;19(7):1312-1319.
105. Filmont JE, Gisselbrecht C, Cuenca X, et al. The impact of pre- and post-transplantation positron emission tomography using 18-fluorodeoxyglucose on poor-prognosis lymphoma patients undergoing autologous stem cell transplantation. *Cancer*. 2007;110(6):1361-1369.
106. Svoboda J, Andreadis C, Elstrom R, et al. Prognostic value of FDG-PET scan imaging in lymphoma patients undergoing autologous stem cell transplantation. *Bone Marrow Transplant*. 2006;38(3):211-216.
107. Chin C, Wirth A, Ritchie D, et al. Impact of post-transplant consolidative radiotherapy in patients with relapsed or refractory classical Hodgkin lymphoma and a PET-CT based predictive model for relapse. *Blood*. 2019;134(suppl 1):4044.
108. Josting A, Muller H, Borchmann P, et al. Dose intensity of chemotherapy in patients with relapsed Hodgkin's lymphoma. *J Clin Oncol*. 2010;28(34):5074-5080.
109. Kewalramani T, Nimer SD, Zelenetz AD, et al. Progressive disease following autologous transplantation in patients with chemosensitive relapsed or primary refractory Hodgkin's disease or aggressive non-Hodgkin's lymphoma. *Bone Marrow Transplant*. 2003;32(7):673-679.
110. Arai S, Fanale M, DeVos S, et al. Defining a Hodgkin lymphoma population for novel therapeutics after relapse from autologous hematopoietic cell transplant. *Leuk Lymphoma*. 2013;54(11):2531-2533.
111. Sutherland MS, Sanderson RJ, Gordon KA, et al. Lysosomal trafficking and cysteine protease metabolism confer target-specific cytotoxicity by peptide-linked anti-CD30-auristatin conjugates. *J Biol Chem*. 2006;281(15):10540-10547.
112. Younes A, Gopal AK, Smith SE, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol*. 2012;30(18):2183-2189.
113. Younes A, Bartlett NL, Leonard JP, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. *N Engl J Med*. 2010;363(19):1812-1821.
114. Gopal AK, Chen R, Smith SE, et al. Durable remissions in a pivotal phase 2 study of brentuximab vedotin in relapsed or refractory Hodgkin lymphoma. *Blood*. 2015;125(8):1236-1243.
115. Onishi M, Graf SA, Holmberg L, et al. Brentuximab vedotin administered to platinum-refractory, transplant-naive Hodgkin lymphoma patients can increase the proportion achieving FDG PET negative status. *Hematol Oncol*. 2015;33(4):187-191.
116. Moskowitz CH, Nadamanee A, Masszi T, et al. The AETHERA trial: results of a randomized, double-blind, placebo-controlled phase 3 study of brentuximab vedotin in the treatment of patients at risk of progression following autologous stem cell transplant for Hodgkin lymphoma. *Blood*. 2014;124:673-673.
117. Moskowitz CH, Walewski J, Nademanee A, et al. Five-year PFS from the AETHERA trial of brentuximab vedotin for Hodgkin lymphoma at high risk of progression or relapse. *Blood*. 2018;132(25):2639-2642.
118. Stamatoullas A, Ghesquieres H, Clement Filliatre L, et al. Brentuximab vedotin in first refractory/relapsed classical Hodgkin lymphoma patients treated by chemotherapy (ICE) before autologous transplantation. Final analysis of phase II study. *Blood*. 2019;134(suppl 1):132.
119. Garcia-Sanz R, Sureda A, Gonzalez AP, et al. Brentuximab vedotin plus ESHAP (BRESHAP) is a highly effective combination for inducing remission in refractory and relapsed Hodgkin lymphoma patients prior to autologous stem cell transplant: a trial of the Spanish Group of Lymphoma and Bone Marrow Transplantation (GELTAMO). *Blood*. 2016;128(22):1109.
120. Broccoli A, Argnani L, Botto B, et al. First salvage treatment with bendamustine and brentuximab vedotin in Hodgkin lymphoma: a phase 2 study of the Fondazione Italiana Linfomi. *Blood Cancer J*. 2019;9(12):100.
121. Flinn IW, van der Jagt R, Kahl BS, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. *Blood*. 2014;123(19):2944-2952.
122. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet*. 2013;381(9873):1203-1210.
123. Moskowitz AJ, Hamlin PA Jr., Perales MA, et al. Phase II study of bendamustine in relapsed and refractory Hodgkin lymphoma. *J Clin Oncol*. 2013;31(4):456-460.
124. LaCasce AS, Bociek RG, Sawas A, et al. Brentuximab vedotin plus bendamustine: a highly active first salvage regimen for relapsed or refractory Hodgkin lymphoma. *Blood*. 2018;132(1):40-48.
125. Bazarbachi A, Boumendil A, Finel H, et al. Brentuximab vedotin for recurrent Hodgkin lymphoma after allogeneic hematopoietic stem cell transplantation: a report from the EBMT Lymphoma Working Party. *Cancer*. 2019;125(1):90-98.
126. Armand P, Engert A, Younes A, et al. Nivolumab for relapsed/refractory classic Hodgkin lymphoma after failure of autologous hematopoietic cell transplantation: extended follow-up of the multicohort single-arm phase II CheckMate 205 trial. *J Clin Oncol*. 2018;36(14):1428-1439.
127. Herrera AF, Chen RW, Palmer J, et al. PET-adapted nivolumab or nivolumab plus ICE as first salvage therapy in relapsed or refractory Hodgkin lymphoma. *Blood*. 2019;134(suppl 1):239.
128. Herrera AF, Moskowitz AJ, Bartlett NL, et al. Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. *Blood*. 2018;131(11):1183-1194.
129. Cole PD, Mauz-Körholz C, Mascarin M, et al. Nivolumab and brentuximab vedotin (BV)-based, response adapted treatment in children, adolescents, and young adults (CAYA) with standard-risk relapsed/refractory classical Hodgkin lymphoma (R/R cHL): primary analysis. *J Clin Oncol*. 2020;38(15 suppl):8013.
130. Diefenbach CS, Hong F, Ambinder R, et al. Ipilimumab, nivolumab, and brentuximab vedotin combination therapy in patients with relapsed or refractory Hodgkin lymphoma: phase I results of an open-label multicentre, phase I/II trial. *Lancet Haematol*. 2020;7:e660-e670.

131. Chen R, Zinzani PL, Lee HJ, et al. Pembrolizumab in relapsed or refractory Hodgkin lymphoma: 2-year follow-up of KEYNOTE-087. *Blood*. 2019;134(14):1144-1153.
132. Chen R, Gibb AL, Collins GP, et al. Blockage of the PD-1 checkpoint with anti-PD-Li antibody avelumab is sufficient for clinical aditivity in relapsed/refractory classical Hodgkin lymphoma (CHL). Hematol Oncol. 2017;35(suppl 2):67.
133. Peggs KS, Hunter A, Chopra R, et al. Clinical evidence of a graft-versus-Hodgkin's lymphoma effect after reduced-intensity allogeneic transplantation. *Lancet*. 2005;365(9475):1934-1941.
134. Devetten MP, Hari PN, Carreras J, et al. Unrelated donor reduced-intensity allogeneic hematopoietic stem cell transplantation for relapsed and refractory Hodgkin lymphoma. *Biol Blood Marrow Transplant*. 2009;15(1):109-117.
135. Sureda A, Robinson S, Canals C, et al. Reduced-intensity conditioning compared with conventional allogeneic stem-cell transplantation in relapsed or refractory Hodgkin's lymphoma: an analysis from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. *J Clin Oncol*. 2008;26(3):455-462.
136. Anderlini P, Saliba R, Acholonu S, et al. Fludarabine-melphalan as a preparative regimen for reduced-intensity conditioning allogeneic stem cell transplantation in relapsed and refractory Hodgkin's lymphoma: the updated M.D. Anderson Cancer Center experience. *Haematologica*. 2008;93(2):257-264.
137. Wang D, Zeng C, Xu B, et al. Anti-CD30 chimeric antigen receptor T cell therapy for relapsed/refractory CD30(+) lymphoma patients. *Blood Cancer J*. 2020;10(1):8.
138. Ramos CA, Torrano V, Bilgi M, et al. CD30-chimeric antigen receptor (CAR) T cells for therapy of Hodgkin lymphoma (HL). *Hematol Oncol*. 2019;37(suppl 2):168.
139. Ramos C, Grover N, Beaver A, et al. Anti-CD30 CAR-T cell therapy in relapsed and refractory Hodgkin lymphoma. *J Clin Oncol*. 2020;38(32):3794-3804.
140. Ansell SM, Bartlett NL, Chen RW, et al. Investigating safety and preliminary efficacy of AFM13 plus pembrolizumab in patients with relapsed/refractory Hodgkin lymphoma after brentuximab vedotin failure. *Hematol Oncol*. 2019;37(suppl 2):177-178.
141. Collins G, Horwitz S, Hamadani M, et al. Analysis of clinical determinants driving safety and efficacy of camidanlumab tesirine (ADCT-301, CAMI) in relapsed/refractory (R/R classical Hodgkin lymphoma [CHL]). *Hematol Oncol*. 2019;37(suppl 2):95-97.

14

Systemic Immunoglobulin Light Chain Amyloidosis

Gregory P. Kaufman
Muzaffar H. Qazilbash
Krina Patel
Sheeba Thomas
Robert Z. Orlowski
Hans C. Lee

KEY CONCEPTS

- Systemic light chain (AL) amyloidosis is a rare protein deposition disease typically found accompanied by an indolent plasma cell dyscrasia, although it can also be found concomitantly with multiple myeloma.
- In the systemic presentation (some cases are localized), commonly affected organs may include the heart, kidneys, liver, gastrointestinal tract, and peripheral nervous system.
- Diagnosis requires histologic evidence of amyloid deposition in tissues either by aspiration of abdominal subcutaneous fat or biopsy of the organs involved, with the demonstration of clonal plasma cell disorder and abnormal free light chain in serum or urine.
- Historical cohorts of patients with severe cardiac involvement have a poor prognosis of 4 to 6 months, though recent studies show this can be greatly improved with successful treatment.
- Plasma cell–directed therapy with or without high-dose melphalan and autologous stem cell rescue is the treatment of choice for patients with confirmed systemic AL.
- Multidisciplinary care is beneficial because these patients have distinct clinical presentations, symptoms, and risks compared with patients with other plasma cell dyscrasias.

Systemic light chain (AL) amyloidosis is a rare plasma cell proliferative disorder. It results from organ deposition of amyloid fibrils that consist of the NH_2-terminal amino acid residues of the variable portion of the light chain immunoglobulin molecule. The estimated age-adjusted incidence is nine to 14 cases per million person-years, and around 4000 new cases are estimated annually in the United States. About 75% of cases are derived from lambda light chain. AL amyloidosis typically results primarily from a small plasma cell clone in the bone marrow or may rarely be associated with another B-cell malignancy. Coexisting AL amyloid deposits are identified in 10% to 15% of patients with multiple myeloma (MM).

The commonly affected organs include the heart, kidneys, liver, gastrointestinal tract, and peripheral nervous system. This leads to clinical symptomatology of nephrotic syndrome, cardiomyopathy, hepatomegaly, neuropathy, macroglossia, anemia, carpal tunnel syndrome, and periorbital purpura. Prognosis is driven primarily by the extent and severity of cardiac involvement with patients having severe cardiac involvement being at high risk for early death, although this risk is somewhat abrogated with successful plasma cell–directed treatment. However, beyond overall survival (OS), patients with AL often have chronic symptoms relating to the morbidity of amyloid organ involvement and decreased quality of life. The exact pathophysiology of organ or tissue damage in AL amyloidosis is not completely understood, but the reduction of serum free light chain concentration after chemotherapy treatment results in improved cardiac function and suggests that both circulating amyloidogenic free light chains in addition to those deposited play an important role in organ dysfunction. New therapies targeting the underlying plasma cell clone are improving hematologic response rates and potentially patient survival with the disease, and therapies that directly target the already deposited light chain amyloid continue in development at this time.

EPIDEMIOLOGY AND RISK FACTORS

Light chain amyloidosis is typically found with an underlying low-grade or indolent plasma cell population in the bone marrow, though is also found concomitantly with MM and less commonly with other hematolymphoid neoplasms. Estimates of the incidence and prevalence of AL have been drawn from population-based studies in the United States and European countries ranging from three to 14 cases per million-person years.[1–4] There are an estimated 12,000 people living in the United States with AL.

Less is known about specific risk factors for developing AL amyloidosis. Studies have identified male gender and age as risk factors, though these are also risk factors for the development of plasma cell neoplasms and monoclonal gammopathy of undetermined significance (MGUS) as well.[5,6]

PATHOPHYSIOLOGY AND GENETICS AND MOLECULAR CLASSIFICATION

The nature of the fundamental events relating to protein misfolding and amyloid fibril formation and deposition are not fully understood, though factors relating to the underlying light chain sequence and posttranslational modification, co-deposition of other proteins, and microenvironment factors in the tissue are all thought to have impact. The underlying light chain variable region gene usage (IGVL) is thought to play a role in amyloidogenesis and pattern of organ tropism. In one study of 821 AL patients, specific IGVL patterns assessed by mass spectrometry was associated with localized versus systemic AL, and specific patterns associated with organ involvement such as LV6-57 patients being more likely to have renal involvement and LV1-44 patients being more likely to have cardiac involvement.[7] Posttranslational modification including N-glycosylation has been associated with light chain amyloidosis, and its mechanism in amyloid fibrillogenesis is supported by the finding that isoelectric points of AL polypeptides spread heterogeneously and may form by electrostatic interaction of oppositely charged particles.[8] N-glycosylation of light chains in systemic AL is more prevalent compared with light chains found in non-amyloid plasma cell dyscrasias and contributes to mass or charge heterogeneity and potentially amyloidogenesis.[9,10] Co-deposition of other proteins with amyloid fibrils including serum amyloid P component and apolipoproteins is thought to play a role in fibril development and tissue deposition, though the exact mechanism is debated.[11] In addition to the deposition of amyloid fibrils, circulating amyloid light chains are thought to also play a significant role in mediating organ dysfunction, particularly cardiac dysfunction in AL. This is evidenced by studies in model organisms demonstrating worsened cardiac dysfunction after infusion of amyloid light chains, though not normal control light chains in the absence of amyloid fibril deposition, and clinical evidence showing early concordance in improvement in cardiac function with reduction of circulating involved amyloid light chains.[12–14]

In comparison with MM, plasma cells of AL amyloidosis are generally of lower clonal burden and have lower rates of proliferation.[15] The amyloid clone is often enriched for the $t^{11;14}$ structural abnormality detected by fluorescence in situ hybridization, found in up to 50% of patients with AL,[16] and genome-wide association studies show cyclin D1 playing a prominent role in AL.[17]

CLINICAL PRESENTATION AND DIAGNOSTIC WORK-UP

The clinical presentation of AL amyloidosis depends on the spectrum and severity of organ involvement. The common clinical features at diagnosis include cardiomyopathy typically presenting as heart failure with preserved ejection fraction (up to 80% of patients), nephrotic syndrome with or without renal insufficiency (up to 60% of patients), sensory axonal neuropathy, autonomic neuropathy, and hepatosplenomegaly.[18] Symptoms of systemic AL are often vague initially, and this leads frequently to delay in diagnosis of this rare condition.[19] Many patients have multisystem involvement at diagnosis (Table 14–1).

The diagnosis of AL requires histologic evidence of amyloid deposition in tissues either by aspiration of abdominal subcutaneous fat or biopsy of the organs involved, with the demonstration of clonal plasma cell disorder and abnormal free light chain in serum or urine (Table 14–2). The pathognomonic diagnostic feature of amyloid deposition is a positive tissue stain with Congo red to demonstrate apple-green birefringence under polarized light. Standard pathological tests, such as the use of antibodies for serum κ or λ light chains in immunohistochemistry, have low sensitivity for the diagnosis.[20] Mass spectrometry–based proteomic analysis of amyloid tissue should be pursued when available.[21] This helps confirm the type of amyloid protein because more than 10 forms of systemic amyloidosis are currently known, and correct typing is imperative for appropriate treatment, particularly with targeted therapies available for distinct amyloid subtypes such as transthyretin (TTR) amyloidosis.

Table 14–1 Clinical Presentations of Immunoglobulin Light Chain Amyloidosis

Organ Involvement	Clinical Presentation
Kidney	**Nephrotic syndrome Renal failure**
Heart	Abnormal electrocardiogram: low voltages in the standard leads Nondilated cardiomyopathy Arrhythmia
Peripheral and autonomic nervous system	Numbness Muscle weakness Carpal tunnel syndrome Postural hypotension Erectile dysfunction Altered bowel habit Anhidrosis
Gastrointestinal tract	Macroglossia Early satiety Diarrhea Malabsorption Gastrointestinal bleeding Hepatomegaly
Coagulation system	Periorbital purpura (raccoon eyes) Abnormal clotting tests Life-threatening bleeding

Assessment of amyloid organ involvement is performed at diagnosis with the use of serum biomarkers such as troponin-T or I, NT-proBNP (N-terminal pro b-type natriuretic peptide) levels, electrocardiography, echocardiography, cardiac magnetic resonance imaging (MRI) studies, 24-hour urine studies for albuminuria, and other studies as deemed clinically appropriate.

Table 14–2 Laboratory and Pathologic Evaluation of Immunoglobulin Light Chain Amyloidosis

Laboratory Evaluation
CBC with differential Serum creatinine Liver enzyme and bilirubin Coagulation tests: prothrombin time, partial thromboplastin time, factor X SPEP and immunofixation UPEP and immunofixation Serum free light chains 24-hour urine protein Cardiac troponin, BNP, or NT-proBNP Cardiac testing: ECG, echocardiogram, cardiac MRI, chest radiography Peripheral nervous system: EMG, nerve conduction test Pulmonary function tests
Pathologic Evaluation
Bone marrow aspiration and biopsy with immunohistochemistry staining for κ and λ light chain Abdominal fat pad aspiration or organ biopsy with Congo red staining for amyloid Mass spectrometry for amyloid protein identification

BNP, brain natriuretic peptide; ECG, electrocardiography; EMG, electromyography; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro b-type natriuretic peptide; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis.

PROGNOSIS AND STAGING

Even though patients commonly have a low burden of clonal plasma cells, long-term survival outcome is poor in those presenting with advanced cardiac involvement. However, depending on the particular pattern and severity of organ involvement, survival outcomes are very broad. We do note additionally that beyond lifespan, the patient's quality of life can be severely impacted by his or her amyloid burden even without cardiac involvement. Although patients with severe cardiac involvement at diagnosis have been reported to have a median survival period of 4 to 6 months versus 16 months in those without it, data have shown that successfully treated patients who have obtained deep hematologic responses have improved survival.[5]

Cardiac dysfunction is best assessed by the elevation of cardiac biomarkers such as brain natriuretic peptide (BNP) and NT-proBNP, as well as cardiac troponin-T (cTnT) and troponin I (cTnI). Many studies have confirmed the prognostic significance of markers of cardiac injury and dysfunction in patients with AL amyloidosis, and they been incorporated in the staging system for AL amyloidosis[22,23] (Table 14–3). The first of the two main staging systems in AL, both originating with the Mayo Clinic group, is the European modification of the Mayo 2004 staging system, which assigns points for NT-proBNP greater than 332 ng/L and cTnT greater than 0.035 ng/mL; patients with both markers elevated are then stratified by NT-proBNP levels greater than or less than 8500 ng/L to differentiate stage IIIA and IIIB. Likewise, in the Revised Prognostic Scoring System from the Mayo Clinic group, patients are assigned a score of 1 for each of the difference between involved and uninvolved light chain (FLC-diff) 18 mg/dL or greater, cTnT 0.025 ng/mL or greater, and NT-proBNP 1800 pg/mL or greater. The median OS times of patients with Mayo stage I, II, III, and IV (score 0, 1, 2, and 3, respectively) are 94, 40, 14, and 5.8 months, respectively.[24]

RESPONSE CRITERIA

The overall aims of therapy for patients with AL are to improve and stabilize organ function and improve patient quality of life and survival. Because therapy has centered on the targeting of the underlying plasma cell clone to reduce circulating light chain burden, response criteria have included both hematologic and organ-based response categories (Table 14–4). Notably, historical response criteria were validated in patients presenting with dFLC levels greater than 50 mg/L, which is denoted as measurable disease; about 90% of patients at diagnosis meet this threshold of differential free light chains (dFLC). A minority of patients present at diagnosis with low dFLC levels, and a separate hematologic response category has been validated for this population defined as achieving a dFLC below 10 mg/L.[25] More recently, analysis of achieving this less than 10 mg/L dFLC threshold has been validated in a broader cohort of patients with AL presenting with measurable disease (dFLC >50 mg/L) and termed *stringent dFLC response*, with support for superior outcomes among this population compared with historical hematologic Very Good Partial Response (VGPR) or Complete Response (CR) outcomes.[26] However, for practical purposes, a hematologic VGPR or deeper response is the goal of upfront plasma cell–directed therapy. Organ responses strongly correlate with improved patient survival and outcomes and remain a central goal of therapy. Organ response definitions are typically based on biomarker reductions and other markers of cardiac or renal function. A cardiac response requires a 30% or greater reduction in NT-proBNP levels with absolute reduction of greater than 300 ng/L, and a renal response requires a 50% reduction of at least 0.5 g/day of proteinuria on 24-hour urine collection without increase in creatinine clearance of 25% over baseline.[27] Obtaining

TABLE 14–3 Staging of Immunoglobulin Light Chain Amyloidosis

Stage	Biomarkers	Stage	Survival Period (months)
Mayo 2004 with European modification[23]	NT-proBNP >332 ng/L cTnT >0.035 ng/mL	I: 0 points II: 1 point IIIA: 2 points and NT-proBNP <8500 ng/L IIIB: 2 points and NT-proBNP >8500	86 43 17 3–5
Revised Mayo Clinic staging[24]	NT-proBNP >1800 ng/L cTnT >0.025 ng/mL dFLC >180 mg/L	I: 0 points II: 1 point III: 2 points IV: 3 points	93 62 13 6

cTnT, cardiac troponin-T; dFLC, difference between the involved and uninvolved light chains; NT-proBNP, N-terminal pro b-type natriuretic peptide.

TABLE 14–4 Immunoglobulin Light Chain Amyloidosis Response Criteria

Category	Criteria
Complete response	Normal free light chain ratio and levels; negative serum and urine immunofixation
Very good partial response	dFLC <40 mg/L
Partial response	>50% reduction in dFLC
No response	Less than partial response

dFLC, difference between the involved and uninvolved light chains.

a deep hematologic response is intrinsically linked to later obtaining an organ response and improved survival.[28] More recently, deeper biomarker-graded organ responses have been shown superior to standard definitions of binary organ response; although prognostic, the ramifications on treatment are not fully understood, and the aim of plasma cell–directed therapies continues to be deep hematologic response.[29] Still, there remains a population of need who have persistent organ morbidity because of deposited amyloid despite achieving hematologic response to upfront therapy.

TREATMENT

Treatment for patients with AL amyloidosis shares similar drug classes targeted to malignant plasma cells as that for MM, consisting mainly of various chemotherapy combinations or high-dose therapy with autologous stem cell transplantation (HDT-ASCT). The choice of treatment should be based on risk stratification. Patients with good performance status and normal cardiac markers should be considered for HDT-ASCT or induction chemotherapy followed by HDT-ASCT.

High-Dose Therapy with Autologous Stem Cell Transplantation

HDT-ASCT has been used since the early 1990s, and it is an effective treatment modality associated with hematologic and organ responses as well as long-term survival.[30,31] It is associated with high treatment-related mortality rate ranging from 13% to 43%, especially in patients with cardiac involvement. Careful patient selection based on comorbidity index and cardiac staging is the key to successful outcome of high-dose therapy in AL amyloidosis. A randomized trial comparing HDT-ASCT with standard-dose melphalan plus high-dose dexamethasone showed no differences in hematologic or organ response. Landmark analysis examining only patients surviving more than 6 months after transplant also showed no survival benefit for HDT-ASCT.[32] However, almost 25% of the patients in this study received reduced-dose melphalan conditioning, which has been associated with poor transplant outcomes. Moreover, the 24% treatment-related mortality rate in the HDT-ASCT arm was unusually high, and the lack of careful patient selection and use of tertiary transplant centers may have biased results against HDT-ASCT. A meta-analysis of 12 studies of HDT-ASCT showed no superiority of HDT-ASCT over conventional chemotherapy.[33] However, in the MD Anderson Cancer Center experience, improved 10-year survival outcomes were reported in patients undergoing HDT-ASCT compared with conventional chemotherapy.[31] At centers with extensive experience in treating patients with AL amyloidosis, HDT-ASCT provides promising outcomes with careful patient selection. Patients with organ involvement of two or fewer organs and AL amyloidosis with renal involvement show the best overall outcome with HDT-ASCT.

Induction Therapy Before High-Dose Therapy with Autologous Stem Cell Transplantation

Induction chemotherapy is frequently administered for cytoreduction before HDT-ASCT, particularly in patients with concurrent asymptomatic or symptomatic myeloma. Hematologic and organ responses with the inclusion of novel agents in induction therapy can also lead to improvement in performance status and result in transplant eligibility for newly diagnosed patients.[34] A randomized trial evaluating the role of induction therapy containing bortezomib and dexamethasone followed by HDT-ASCT versus HDT-ASCT in patients with newly diagnosed AL amyloidosis showed better responses and survival outcomes with induction therapy.[35] In our experience, incorporation of novel agent induction therapy before transplant is associated with improved survival.[36] Based on retrospective studies and clinical experience, the combination of bortezomib, cyclophosphamide, and dexamethasone (CyBorD) has evolved to become a standard-of-care chemotherapy regimen for newly diagnosed AL amyloidosis.[34,37] Whereas conventional lenalidomide-based myeloma induction regimens such as bortezomib, lenalidomide, and dexamethasone (VRD) can lead to deep hematologic

responses, lenalidomide-related toxicity even at significant dose reductions has tempered their use in AL amyloidosis patients..[38] Deep and rapid hematologic responses with the incorporation of the anti-CD38 monoclonal antibody daratumumab to CyBorD have also been reported..[39] An ongoing randomized study comparing this regimen with CyBorD alone has shown significantly improved rates of VGPR or deeper responses (79 vs 49%), leading to improved rates of cardiac organ responses at 6 months (42 vs 22%) for patients with newly diagnosed AL amyloidosis (NCT03201965).[40]

Maintenance Therapy After High-Dose Therapy with Autologous Stem-Cell Transplantation

There are minimal data to support maintenance treatment in AL amyloidosis after HDT-ASCT, and it is not routinely administered. However, decisions are individualized to a given patient and can be considered in patients with AL amyloidosis with concurrent myeloma. Moreover, consolidation or maintenance therapy (or both) can also be considered in patients achieving less than VGPR after HDT-ASCT given the prognostic significance of achieving at least a hematologic VGPR in patients with AL amyloidosis.[41]

Induction Therapy for Transplant-Ineligible Patients

The combination of melphalan and dexamethasone (MDex) has long been considered a standard of care for first-line treatment of transplant-ineligible patients and is associated with a good hematologic response (67%) and low toxicity (4%).[42] More recently, results from the EMN-03 study were reported, which evaluated the combination of MDex versus bortezomib, melphalan, and dexamethasone (BMDex) in patients not undergoing HDT-ASCT.[43] Overall response (81%) and ≥ VGPR or deeper response (64%) significantly higher with BMDex versus MDex (56% and 38%, respectively). Cardiac progression rates also favored BMDex, although at a median follow-up time of 25 months, no OS difference had yet been observed between the two regimens. CyBorD also remains an excellent option for transplant-ineligible patients with AL amyloidosis.

Relapsed or Refractory Immunoglobulin Light Chain Amyloidosis

There is no standard of care for relapsed or refractory AL amyloidosis, although a number of small studies have investigated the use of novel agents approved for the treatment of patients with MM in this setting. Lenalidomide has been evaluated in two phase 2 studies in relapsed or refractory AL amyloidosis with an overall response rate (ORR) of 67% and 39%.[44,45] However, treatment was also associated with significant toxicities such as fatigue and myelosuppression, requiring frequent lenalidomide dose reductions and treatment discontinuations. Pomalidomide has shown a similar ORR of 48% to 68%,[46–48] and its use generally favored over lenalidomide because of better tolerance in patients with AL amyloidosis. The proteasome inhibitors (PIs) carfilzomib[49] and ixazomib[50] have demonstrated ORRs of 63% and 52%, respectively, including in patients who were previously PI refractory. Given the known cardiopulmonary adverse events associated with carfilzomib, it should be used with caution in carefully selected patients and –generally avoided in patients with cardiac amyloid involvement. Finally, the safety, tolerability, and promising efficacy of daratumumab in relapsed or refractory AL amyloidosis have been reported in two recent prospective studies showing deep hematologic responses with ≥ VGPR or deeper response rates of 86% and 48%.[51,52]

CONCLUSIONS

Systemic AL remains a rare disease in which patients benefit from multidisciplinary care beyond that provided solely by the treating hematologist. Medical management of patients with cardiac amyloidosis often differs from standard heart failure treatment, and cardiologists and other specialists experienced in the management of AL such as nephrologists, hepatologists, and neurologists, often at specialized tertiary centers, do make a difference in the care of patients. With the incorporation of additional novel agents, including monoclonal antibodies, obtaining deeper hematologic responses and organ responses, patient outcomes are expected to continue to improve, though ultimately these patients require long-term follow-up with their amyloid teams because each patient's constellation of organ involvement and symptoms is unique.

MD ANDERSON PRACTICE TIPS

- Confirmation of the diagnosis with tissue mass spectrometry is beneficial when feasible.
- Be cautious of the possibility of patients presenting with concomitant MGUS and other forms of cardiac amyloidosis such as TTR (this is not as rare as one may think).
- Organ biopsies are not always required if another surrogate site can provide the diagnosis, but consider cardiac imaging ,including cardiac MRI, to carefully rule out or rule in cardiac AL involvement when in doubt.
- Quick initiation of plasma cell–directed therapy is warranted for patients with severe organ involvement; starting chemotherapy before consideration for stem cell transplantation is appropriate.
- Patients with worsening organ function because of increasing amyloid burden often require reinitiating or a change in therapy even before involved serum free light chains may formally meet criteria for hematologic relapse.
- Anti–amyloid fibril–directed antibodies continue in development and may provide a future avenue for expanding how we are able to directly treat the disease.

REFERENCES

1. Quock TP. Epidemiology of AL amyloidosis: a real-world study using US claims data. *Blood Adv*. 2018;2(10):1046-1053.
2. Kyle RA, Linos A, Beard CM, et al. Incidence and natural history of primary systemic amyloidosis in Olmsted County, Minnesota, 1950 through 1989. *Blood*. 1992;79(7):1817-1822.
3. Pinney JH, Smith CJ, Taube, et al. Systemic amyloidosis in England: an epidemiological study. *Br J Haematol*. 2013;161(4):525-532.
4. Hemminki K, Li X, Forsti A, et al. Incidence and survival in non-hereditary amyloidosis in Sweden. *BMC Public Health*. 2012;12(1):974.
5. Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. *Semin Hematol*. 1995;32(1):45-59.
6. Quarta CC, Kruger JL, Ralk RH. Cardiac amyloidosis. *Circulation*. 2012;126(12):e178-e182.
7. Kourelis TV, Dasari S, Theis JD, et al. Clarifying immunoglobulin gene usage in systemic and localized immunoglobulin light-chain amyloidosis by mass spectrometry. *Blood*. 2017;129(3):299-306.
8. Kaplan B, Livneh A, Gallo G. Charge differences between in vivo deposits in immunoglobulin light chain amyloidosis and non-amyloid light chain deposition disease. *Br J Haematol*. 2007;136(5):723.
9. Milani P, Barnidge D, Murray D, et al. Glycosylation of immunoglobulin light chains is associated with amyloidosis. *Clin Lymphoma Myeloma Leuk*. 2017;17(1 suppl):E104.
10. Kumar S, Dispenzieri A, Dasari S, et al. Mass spectrometric approach to identify N-glycosylation of light chain in patients with immunoglobulin light chain amyloidosis (AL). *Cancer Res*. 2018;33:254–257.
11. Gallo G, Wisniewski T, Choi-Miura NH, et al. Potential role of apolipoprotein-E in fibrillogenesis. *Am J Pathol*. 1994;145(3):526.
12. Palladini G, Lavatelli F, Russo P, et al. Circulating amyloidogenic free light chains and serum N-terminal natriuretic peptide type B decrease simultaneously in association with improvement of survival in AL. *Blood*. 2006;107(10):3854-3858.
13. Liao R, Jain M, Teller P, et al. Infusion of light chains from patients with cardiac amyloidosis causes diastolic dysfunction in isolated mouse hearts. *Circulation*. 2001;104(14):1594-1597.
14. Oberti L, Rognoni P, Barbiroli A, et al. Concurrent structural and biophysical traits link with immunoglobulin light chain amyloid propensity. *Sci Rep*. 2017;7(1):16809.
15. Gertz MA, Kyle RA, Greipp PR. The plasma cell labeling index: a valuable tool in primary systemic amyloidosis. *Blood*. 1989;74(3):1108-1111.
16. Paiva B, Martinez-Lopez J, Corchete LA, et al. Phenotypic, transcriptomic , and genomic features of clonal plasma cells in light-chain amyloidosis *Blood*. 2016;127(24):3035-3039.
17. Da Silva Filho MI, Forsti A, Weinhold N, et al. Genome-wide association study of immunoglobulin light chain amyloidosis in three patient cohorts: comparison with myeloma. *Leukemia*. 2017;31(8):1735-1742.
18. Milani P, Merlini G, Palladini G. Light chain amyloidosis. *Mediterr J Hematol Infect Dis*. 2018. 10(1):e2018022.
19. Lousada I, Comenzo RL, Landau H, et al. Light chain amyloidosis: patient experience esurvey from the Amyloidosis Research Consortium. *Adv Ther*. 2015;32(10):920-928.
20. Satoskar A, Burdge K, Cowden D, et al. Typing of amyloidosis in renal biopsies: diagnostic pitfalls. *Arch Pathol Lab Med*. 2007;131(6):917-922.
21. Vrana J, Gamez J, Madden B, et al. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens. *Blood*. 2009;114(24):4957-4959.
22. Dispenzieri A, Gertz M, Kyle R, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. *J Clin Oncol*. 2004;22(18):3751-3757.
23. Wechalekar AD, Shonland SO, Kastritis E, et al. A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis. *Blood*. 2013;121(17):3420-3427.
24. Kumar S, Dispenzieri A, Lacy MQ, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. *J Clin Oncol*. 2012;30(9):989-995.
25. Milani P, Basset M, Russo F, et al. Patients with light-chain amyloidosis and low free light-chain burden have distinct clinical features and outcome. *Blood*. 2017;130(5):625-631.
26. Manwani R, Cohen O, Sharpley F, et al. A prospective observational study of 915 patients with systemic AL amyloidosis treated with upfront bortezomib. *Blood*. 2019;134(25):2271-2280.
27. Comenzo RL, Reece D, Palladini G, et al. Consensus guidelines of the conduct and reporting of clinical trials in systemic light-chain amyloidosis. *Leukemia* 2012; 26:2317.
28. Kaufman GP, Dispenzieri A, Gertz MA, et al. Kinetics of organ response and survival following normalization of the serum free light chain ratio in AL amyloidosis. *Am J Hematol*. 2015;90(3):181-186.
29. Eckhert E, Witteles R, Kaufman G, et al. Grading cardiac response in AL amyloidosis: implications for relapse and survival. *Br J Haematol*. 2019. 186(1):144-146.
30. Jaccard A, Moreau P, Leblond V, et al. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. *N Engl J Med*. 2007;357(11):1083-1093.
31. Parmar S, Kongtim P, Champlin R, et al. Auto-SCT improves survival in systemic light chain amyloidosis: a retrospective analysis with 14-year follow-up. *Bone Marrow Transplant*. 2014;49(8):1036-1041.
32. Madan S, Kumar SK, Dispenzieri A, et al. High-dose melphalan and peripheral blood stem cell transplantation for light-chain amyloidosis with cardiac involvement. *Blood*. 2012;119(5):1117-1122.
33. Mhaskar R, Kumar A, Behera M, et al. Role of high-dose chemotherapy and autologous hematopoietic cell transplantation in primary systemic amyloidosis: a systematic review. *Bio Blood Marrow Transplant*. 2009;15(8):893-902.
34. Mikhael JR, Schuster SR, Jimenez-Zepeda VH, et al. Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis. *Blood*. 2012;119(19):4391-4394.
35. Huang X, Wang Q, Chen W, et al. Induction therapy with bortezomib and dexamethasone followed by autologous stem cell transplantation versus autologous stem cell transplantation alone in the treatment of renal AL amyloidosis: a randomized controlled trial. *BMC Med*. 2014;12:2..
36. Afrough A, Saliba RM, Hamdi A, et al. Impact of induction therapy on the outcome of immunoglobulin light chain amyloidosis after autologous hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2018;24(11):2197-2203.
37. Palladini G, Sachchithanantham S, Milani P, et al. A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis. *Blood*. 2015;126(5):612-615.
38. Kastritis E, Dialoupi I, Gavriatopoulou M, et al. Primary treatment of light-chain amyloidosis with bortezomib, lenalidomide, and dexamethasone. *Blood Adv*. 2019;3(20):3002-3009.
39. Palladini G, Kastritis E, Maurer MS, et al. Daratumumab plus CyBorD for patients with newly diagnosed AL amyloidosis: safety run-in results of ANDROMEDA. *Blood*. 2020;136(1):71-80.

40. Kastritis E, Palladini G, Minnema MC, et al. Subcutaneous daratumumab + cyclophosphamide, bortezomib, and dexamethasone (CyBorD) in patients with newly diagnosed light chain (AL) amyloidosis: primary results from the phase 3 Andromeda study. Abstract Book: 25th Congress of the European Hematology Association Virtual Edition. HemaSphere 2020;4:1-1168.
41. Landau H, Hassoun H, Rosenzweig MA, et al. Bortezomib and dexamethasone consolidation following risk-adapted melphalan and stem cell transplantation for patients with newly diagnosed light-chain amyloidosis. *Leukemia*. 2013;27(4):823-828.
42. Palladini G, Russo P, Nuvolone M, et al. Treatment with oral melphalan plus dexamethasone produces long-term remissions in AL amyloidosis. *Blood*. 2007;110(2):787-788.
43. Kastritis E, Leleu X, Arnulf B, et al. A randomized phase iii trial of melphalan and dexamethasone (MDex) Versus bortezomib, melphalan and dexamethasone (BMDex) for untreated patients with AL amyloidosis. *Blood*. 2016;128(22).
44. Sanchorawala V, Wright DG, Rosenzweig M, et al. Lenalidomide and dexamethasone in the treatment of AL amyloidosis: results of a phase 2 trial. *Blood*. 2007;109(2):492-496.
45. Dispenzieri A, Klein CJ, Mauermann ML. Lenalidomide therapy in a patient with POEMS syndrome. *Blood*. 2007;110(3):1075-1076.
46. Sanchorawala V, Shelton AC, Lo S, et al. Pomalidomide and dexamethasone in the treatment of AL amyloidosis: results of a phase 1 and 2 trial. *Blood*. 2016;128(8):1059-1062.
47. Dispenzieri A, Buadi F, Laumann K, et al. Activity of pomalidomide in patients with immunoglobulin light-chain amyloidosis. *Blood*. 2012;119(23):5397-5404.
48. Palladini G, Milani P, Foli A, et al. A phase 2 trial of pomalidomide and dexamethasone rescue treatment in patients with AL amyloidosis. *Blood*. 2017;129(15):2120-2123.
49. Cohen AD, Landau H, Scott EC, et al. Safety and efficacy of carfilzomib (CFZ) in previously-treated systemic light-chain (AL) amyloidosis. *Blood*. 2016;128(22):645.
50. Sanchorawala V, Palladini G, Kukreti V, et al. A phase 1/2 study of the oral proteasome inhibitor ixazomib in relapsed or refractory AL amyloidosis. *Blood*. 2017;130(5):597-605.
51. Sanchorawala V, Sarosiek S, Schulman A, et al. Safety, tolerability, and response rates of daratumumab in relapsed al amyloidosis: results of a phase II study. *Blood*. 2020135(18):1541-1547.
52. Roussel M, Merlini G, Chevret S, et al. A prospective phase 2 trial of daratumumab in previously treated systemic light-chain amyloidosis. *Blood*. 2020;135(18):1531-1540.

This page intentionally left blank

15 Waldenström Macroglobulinemia

Melody Becnel
Gregory P. Kaufman
Elisabet E. Manasanch
Krina Patel
Hans C. Lee
Robert Z. Orlowski
Sheeba Thomas

KEY CONCEPTS

- Waldenström macroglobulinemia (WM) is synonymous with lymphoplasmacytic lymphoma as well as the presence of a monoclonal immunoglobulin (Ig) M gammopathy.
- Most cases are associated with a mutation in MYD88, which offers a better prognosis than MYD88 wild-type cases.
- CXCR4 mutations are associated with increased IgM levels and a higher risk of hyperviscosity.
- Patients with WM are at risk for symptomatic hyperviscosity syndrome, which may present with visual disturbances, dizziness, cardiopulmonary symptoms, decreased consciousness, and a bleeding diathesis. Therapy for hyperviscosity consists of prompt initiation of plasma exchange followed by systemic therapy.
- As with other low-grade lymphoid malignancies, asymptomatic patients and those without significant cytopenias or other end-organ manifestations can be observed with close follow-up.
- Therapy should be initiated for symptomatic hyperviscosity, hemoglobin less than 10 g/dL, platelet count 100,000 K/uL or less, bulky adenopathy, symptomatic organomegaly, symptomatic cryoglobulinemia, or significant peripheral neuropathy

BACKGROUND

Waldenström macroglobulinemia (WM) is an uncommon, low-grade malignancy characterized by the presence of lymphoplasmacytic cells together with the presence of a monoclonal immunoglobulin (Ig) M paraproteinemia.[1] The median age at diagnosis is between 63 and 68 years of age, men are more commonly affected than women, and the disease is more common among whites than those of other populations.[2] Approximately, 90% of WM cases are associated with a mutation of the myeloid differentiation primary response 88 (*MYD88*) gene located on chromosome 3p22. WM cases having wild-type *MYD88* are associated with worse outcomes and a higher propensity to transform into an aggressive lymphoma compared with cases having the *MYD88* mutation.[3–11] Of WM cases having the *MYD88* mutation, approximately one third also have a mutation of chemokine receptor 4 (CXCR4); CXCR4 mutations are often associated with higher IgM levels and therefore increased risk of hyperviscosity.[11,12]

CLINICAL PRESENTATION AND DIAGNOSTIC WORK-UP

Many patients with WM are asymptomatic at the time of diagnosis. When symptoms develop, they are caused by tumor infiltration (cytopenias, hepatomegaly, splenomegaly), circulating IgM (hyperviscosity, cryoglobulinemia, cold agglutinin anemia), or tissue deposition of IgM (neuropathy, glomerular disease, amyloidosis). Patients with symptomatic hyperviscosity syndrome may present with visual disturbances, dizziness, cardiopulmonary symptoms, decreased consciousness, and a bleeding diathesis. Polyneuropathies are common. Some are associated with antigenic targets of the monoclonal serum IgM, including myelin-associated glycoprotein (MAG) and sulfatide. Others are caused

by direct tumor infiltration, tissue deposition of IgM, the amount and properties of the circulating monoclonal IgM, binding of unidentified antigens, or associated amyloidosis.[2] Patients may also present with cold or warm autoimmune hemolytic anemia, iron-deficiency anemia, or dilutional anemia.[2]

Initial evaluation (Table 15–1) of patients with suspected WM should include a complete blood count with differential, serum chemistries, liver function tests, viral hepatitis serologies, serum protein electrophoresis (SPEP) and immunofixation, quantitative immunoglobulin levels, and a β_2-microglobulin. In patients suspected of having cryoglobulinemia, a cryocrit should be drawn and together with SPEP and quantitative immunoglobulin specimens should immediately be placed in a 37°C water bath to facilitate accurate assessment.[13] A serum viscosity level and a cold agglutinin titer or Coombs test should be drawn if hyperviscosity or hemolytic anemia is suspected. Iron-deficiency studies should be considered for patients with a microcytic anemia.[13] Bone marrow biopsy should be performed to demonstrate infiltration by lymphoplasmacytic cells; determine the cause of anemia; and when indicated, evaluate for systemic light chain (AL) amyloidosis. Flow cytometry typically demonstrates a pattern of sIgM$^+$, CD19$^+$, CD20$^+$, CD22$^+$, CD79$^+$.[14] Testing for the MYD88 L265P gene mutation in the marrow or peripheral blood can help distinguish WM from marginal zone lymphoma and multiple myeloma, in which the incidence of this mutation is low.[3–10] Patients should have baseline computed tomography (CT) scans (neck, chest, abdomen, and pelvis) or positron emission tomography (PET)–CT scans to evaluate for extramedullary disease. An ophthalmologic examination should be performed to look for retinal changes (hemorrhages or "sausage vessels") in patients with suspected hyperviscosity syndrome.[15,16] In patients with neuropathy, standard evaluation for endocrinopathies and vitamin deficiencies should be accompanied by evaluation with nerve conduction studies, electromyography, and serum studies for antimyelin associated glycoprotein (MAG) and antiganglioside 1 (GM1) antibodies.[11,16] Abdominal fat pad biopsy with Congo red staining should also be performed to evaluate for associated amyloidosis.

PROGNOSTIC STRATIFICATION

Patients with symptomatic WM may be risk stratified according to the International Prognostic Scoring System for WM (ISSWM). This system considers five covariates, namely, advanced age (older than 65 years), hemoglobin 11.5 g/dL or less, platelet count 100 × 10^9/L or less, β_2-microglobulingreater than 3 mg/L, and serum monoclonal protein concentration greater than 7.0 g/dL. Low risk is defined as having one or no adverse characteristics except for advanced age, intermediate-risk as two adverse characteristics or only advanced age, and high risk as more than two adverse characteristics. In a series, of 587 patients, 5-year survival rates were 87%, 68%, and 36%, for these respective subgroups (P <.001).[17] Among those

Table 15–1 Initial Work-up for Waldenström Macroglobulinemia

Essential Testing	Useful Under Certain Circumstances
History and physical examination	Fundoscopic examination[c]
CBC with differential, BUN, creatinine, electrolytes, liver function tests, uric acid, LDH, β_2-microglobulin	Coombs test
Peripheral blood smear	Anti-MAG) antibody and anti-GM1 antibody
Quantitative immunoglobulins (IgG, IgM, IgA)	EMG and NCS
Serum light chain assay (kappa and lambda)	Congo red staining of abdominal fat pad biopsy and/or bone marrow biopsy
SPEP and immunofixation	Coagulation testing and vWD testing if there is bleeding or bruising
24-hour UPEP and immunofixation	
Serum viscosity[a]	
Hepatitis B and C serology	
Cryocrit[b]	
Cold agglutinin titer	
Unilateral bone marrow aspirate and biopsy with immunohistochemistry and/or flow cytometry and CXCR4 and MYD88 L265P AS-PCR testing	
PET-CT or CT of the neck, chest, abdomen, and pelvis	

[a]Most patients with serum viscosity of <4 cP will not have symptoms of hyperviscosity.
[b]If cryocrit result is positive, then initial and follow-up cryocrit and serum protein electrophoresis (SPEP) samples should be measured under warm conditions.
[c]When hyperviscosity is suspected or immunoglobulin (Ig)M >/-3g/dL.
AS-PCR, Allele-specific polymerase chain reaction; BUN, blood urea nitrogen; CBC, complete blood count; CT, computed tomography; EMG, electromyography; LDH, lactate dehydrogenase; NCS, nerve conduction study; PET, positron emission tomography; UPEP, urine protein electrophoresis; vWD, von Willebrand disease.

deemed to be high risk, elevated lactate dehydrogenase increases the likelihood of death from WM (90% vs 60%).[18]

MANAGEMENT

Asymptomatic patients and those without significant cytopenias or other end-organ manifestations can be followed every 3 months during the first year (with longer follow-up intervals thereafter in the setting of disease stability).[19] In such patients, lifelong follow-up is necessary because the risk of developing symptomatic disease is approximately 6% in the first year, 39% at 3 years, and 55% at 5 years.[19] Higher M protein and marrow infiltration have been associated with increased risk of progression to symptomatic disease.[19]

Therapy should be initiated for symptomatic hyperviscosity, hemoglobin less than 10 g/dL, platelet count 100,000 K/uL or less, bulky adenopathy, symptomatic organomegaly, symptomatic cryoglobulinemia, or significant peripheral neuropathy (Table 15–2).[20] Therapy for hyperviscosity consists of prompt initiation of plasma exchange followed by systemic therapy.[21] Given the risk of precipitating symptomatic hyperviscosity in patients with high levels of circulating IgM, packed red cell transfusions should be used conservatively and preferably administered after plasma exchange in high-risk patients.

Frontline Therapy

When autologous stem cell transplant (ASCT) may be considered at relapse, nucleoside analogs should be avoided before stem cell harvest, and primary therapy with a proteasome inhibitor or alkylator, together with rituximab with or without dexamethasone should be considered.[21–26] Combinations of bortezomib-rituximab with or without dexamethasone result in an overall response rate (ORR) of 57% to 83%. Carfilzomib–rituximab–dexamethasone showed an ORR of 68%.[25,26] Comparable ORRs (77%–96%) have been seen with alkylating agent-based regimens (R-CHOP [rituximab, cyclophosphamide, doxorubicin hydrochloride, = Oncovin, and prednisone], Rituximab, cyclophosphamide, vincristine, prednisone, R-cyclophosphamide–dexamethasone, and rituximab-bendamustine); however, of these, R-bendamustine is the preferred regimen given improved progression-free survival (PFS) and fewer adverse effects.[11,27–30] The use of single-agent rituximab should be reserved for patients unable to tolerate combination chemotherapy because ORRs and PFS are low (20%–50% and 12–24 months, respectively).[11,31,32] Rituximab must be used with caution in patients with highly elevated IgM levels because of the potential for an associated IgM flare. In these cases, it is prudent to delay administration of rituximab until after the patient has received cytoreductive therapy.[33] In 2015, the Bruton tyrosine kinase (BTK) inhibitor ibrutinib was approved by the Food and Drug Administration for patients with symptomatic WM. In a phase II trial of 63 patients, ibrutinib was associated with a single-agent partial response rate of 57% and an ORR of 90% in previously treated patients.[11,34] In subset analysis, patients with MYD88 L265P mutations responded better (major response rate, 80%) to ibrutinib than did those without the mutation. However, patients with CXCR4 mutations in addition to MYD88 mutations had a less favorable response (major response rate, 60%).[11] Of note, ibrutinib is not cytotoxic and therefore must be continued until evidence of progression or unacceptable toxicity. A phase 3 trial comparing ibrutinib–rituximab versus rituximab in both newly diagnosed and relapsed or refractory patients with WM noted an ORR of 95% in the combination group compared with 48% in the rituximab arm.[35,36]

When future ASCT is not a consideration, nucleoside analog–based combinations with either fludarabine or cladribine could be considered as alternatives to previously detailed regimens.[37–40] In a trial by the Waldenström's Macroglobulinemia Clinical Trials Group, fludarabine–rituximab demonstrated an ORR of 96% and median PFS of 51.2 months.[40] Cladribine has also been studied alone and in combination with cyclophosphamide and/or rituximab. In 18 previously untreated patients with WM who received two cycles of cladribine, cyclophosphamide, and rituximab, the ORR was 94%, and the median time to response was 2.4 months; at 5 years, 83% of patients remained alive.[39] However, the use of nucleoside analogs must be weighed against the risk (~6%–12%) of second malignancies and transformation to large-cell lymphoma.[41]

Table 15–2 Treatment Indications for Waldenström Macroglobulinemia

- Symptomatic hyperviscosity (eye grounds, neurologic changes)
- Hemoglobin <10 g/dL (caused by marrow involvement, hypersplenism, or cold agglutinin hemolytic anemia)
- Platelet count ≤100,000/μL
- Bulky adenopathy
- Symptomatic organomegaly
- Symptomatic cryoglobulinemia
- Amyloidosis
- Neuropathy
- Cryoglobulinemia
- Pseudo von Willebrand disease

Regimen Selection

Choice of therapy should take into consideration both disease- and patient-related factors, including genomic information, comorbidities, and presenting signs and symptoms. In patients with both MYD88 and CXCR4 mutations who need rapid therapeutic benefit, the preferred regimen is rituximab with either and bendamustine or bortezomib and dexamethasone. However, if a rapid response is not needed, treatment with ibrutinib with or without rituximab could also be considered. In patients with MYD88 mutations but wild-type CXCR4, all of these regimens are likely to be effective, so the choice of regimen is primarily based on the side effect profile. In patients with neither mutation, a chemotherapy-based regimen as described earlier is the preferred first-line agent.[12]

With respect to patient-related factors, providers should consider the patient's age, functional status, and comorbidities when selecting a regimen. Bortezomib can be associated with a significant risk of neuropathy; therefore, in patients with baseline neuropathy, this agent ideally should be avoided as frontline therapy. Carfilzomib can be used in lieu of bortezomib in patients with neuropathy, but caution should be used in older adult patients and in those with cardiopulmonary disease, given the risk for toxicity. In patients with cardiac disease, ibrutinib should also be used cautiously, given the risk of atrial fibrillation. For patients with a history of atrial fibrillation or who develop treatment-emergent atrial fibrillation, careful co-management with a cardiologist is essential. Additionally, because antithrombotic therapy with aspirin or anticoagulation is needed in most patients with atrial fibrillation, further caution is needed with the use of ibrutinib given the increased risk for bleeding with this agent. Newer BTK inhibitors with less off-target effects of bleeding and arrhythmias are being evaluated as single agents and in combination therapy in various ongoing trials.

Maintenance

Although retrospective studies have shown improved PFS and overall survival (OS) in patients who received maintenance rituximab (the recommendation is for eight infusions over 2 years),[42] the prospective, randomized, multicenter MAINTAIN trial did not note any improvement in PFS or OS for the group that received 2 years of maintenance rituximab.[12,43] In light of this, the use of maintenance rituximab remains controversial and cannot be routinely recommended at this time.

TREATMENT AT DISEASE RELAPSE

At relapse, patients may be retreated with a previously successful regimen if their initial remission lasted at least 1 year. When the initial disease-free-interval is shorter, use of one of the other regimens (detailed earlier) should be considered.

For patients intolerant to rituximab, the fully human monoclonal anti-CD20 antibody ofatumumab may be useful. In patients who have previously received rituximab, two cycles of ofatumumab were associated with an ORR of 52%.[44]

The role of stem cell transplantation in patients with WM is still being defined. In a retrospective review of 158 patients (32% had at least three prior lines of therapy) the 5-year PFS and OS with ASCT were 39.7% and 68.5%, respectively.[45] Several groups have also studied allogeneic stem cell transplantation in patients with WM. The 5-year PFS was between 49% and 56% but with notable treatment-related mortality.[46]

FUTURE DIRECTIONS

Many new therapies are under study for patients with WM. These include next-generation proteasome inhibitors (eg, ixazomib), phosphoinositide 3-kinaseinhibitors, the histone deacetylase inhibitor panobinostat, immune checkpoint inhibitors, monoclonal antibodies such as the anti-CD38 antibody daratumumab, and chimeric antigen receptor T-cell therapies. Some of the most promising agents are the BCL2 inhibitor venetoclax and the CXCR4 inhibitor ulocuplumab.[47] In addition, second-generation Bruton tyrosine kinase inhibitors, such as zanubrutinib, and ERK pathway inhibitors are also being evaluated. The development of these and other agents together with emerging knowledge about the molecular drivers of this disease continues to propel the field forward and allow for more rational targeted therapies.[11,12,47]

MD ANDERSON PRACTICE TIPS

- Many patients present asymptomatically. The work-up should include laboratory studies (refer to the text for specifics), staging CT or PET-CT scans, bone marrow biopsy, and CXCR4 testing of the marrow or blood. Ophthalmology evaluation should be performed. Other testing should be guided by the patient's symptoms.
- In patients with WM and neuropathy, nerve conduction studies, electromyography, and serum studies for anti-MAG and anti-GM1 antibodies should be evaluated.
- Higher M protein and marrow infiltration have been associated with increased risk of progression to symptomatic disease. However, M protein levels alone should not be used to determine the timing of treatment.
- In patients with both MYD88 and CXCR4 mutations who need rapid therapeutic benefit, the preferred regimen is rituximab with either and bendamustine or bortezomib and dexamethasone. If a rapid response is not needed, ibrutinib with or without rituximab could also be considered. In patients with neither mutation, a chemotherapy-based regimen such as rituximab–bendamustine is the preferred frontline regimen given improved PFS and fewer adverse effects.
- Rituximab should be used with caution in patients with significantly high IgM levels because IgM flare can occur.
- At relapse, patients may be retreated with a previously successful regimen if their initial remission lasted at least 1 year.

REFERENCES

1. Owen RG, Treon SP, Al-Katib A, et al. Clinicopathological definition of Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. *Semin Oncol*. 2003;30:110-115.
2. Dimopoulos MA, Panayiotidis P, Moulopoulos LA, et al. Waldenström's macroglobulinemia: clinical features, complications, and management. *J Clin Oncol*. 2000;18:214.
3. Treon SP, Xu L, Yang G, et al. MYD88 L265P somatic mutation in Waldenstrom's macroglobulinemia. *N Engl J Med*. 2012;367:826-833.
4. Gachard N, Parrens M, Soubeyran I, et al. IGHV gene features and MYD88 L265P mutation separate the three marginal zone lymphoma entities and Waldenstrom macroglobulinemia/lymphoplasmacytic lymphomas. *Leukemia*. 2013;27:183-189.
5. Jimenez C, Sebastian E, Chillon MC, et al. MYD88 L265P is a marker highly characteristic of, but not restricted to, Waldenstrom's macroglobulinemia. *Leukemia*. 2013;27:1722-1728.
6. Landgren O, Tageja N. MYD88 and beyond: novel opportunities for diagnosis, prognosis and treatment in Waldenstrom's macroglobulinemia. *Leukemia*. 2014;28:1799-1803.
7. Mori N, Ohwashi M, Yoshinaga K, et al. L265P mutation of the MYD88 gene is frequent in Waldenstrom's macroglobulinemia and its absence in myeloma. *PloS One*. 2013;8:e80088.
8. Poulain S, Roumier C, Decambron A, et al. MYD88 L265P mutation in Waldenstrom macroglobulinemia. *Blood*. 2013;121:4504-4511.
9. Varettoni M, Arcaini L, Zibellini S, et al. Prevalence and clinical significance of the MYD88 (L265P) somatic mutation in Waldenstrom's macroglobulinemia and related lymphoid neoplasms. *Blood*. 2013;121:2522-2528.
10. Xu L, Hunter ZR, Yang G, et al. MYD88 L265P in Waldenstrom macroglobulinemia, immunoglobulin M monoclonal gammopathy, and other B-cell lymphoproliferative disorders using conventional and quantitative allele-specific polymerase chain reaction. *Blood*. 2013;121:2051-2058.
11. Castillo JJ, Treon SP. What is new in the treatment of Waldenstrom macroglobulinemia? *Leukemia*. 2019;33:2555-2562.
12. Vaxman I, Gertz M. Waldenstrom's macroglobulinemia in the era of immunotherapy. *Leuk Lymphoma*. 2020:1-13.
13. Treon SP. How I treat Waldenstrom macroglobulinemia. *Blood*. 2009;114:2375-2385.
14. Konoplev S, Medeiros LJ, Bueso-Ramos CE, et al. Immunophenotypic profile of lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia. *Am J Pathol*. 2005;124:414-420.
15. Menke MN, Feke GT, McMeel JW, Treon SP. Ophthalmologic techniques to assess the severity of hyperviscosity syndrome and the effect of plasmapheresis in patients with Waldenstrom's macroglobulinemia. *Clin Lymphoma Myeloma*. 2009;9:100-103.
16. Dimopoulos MA, Kastritis E. How I treat Waldenstrom macroglobulinemia. *Blood*. 2019;134:2022-2035.
17. Morel P, Duhamel A, Gobbi P, et al. International prognostic scoring system for Waldenstrom macroglobulinemia. *Blood*. 2009;113:4163-4170.
18. Kastritis E, Kyrtsonis MC, Hadjiharissi E, et al. Validation of the International Prognostic Scoring System (IPSS) for Waldenstrom's macroglobulinemia (WM) and the importance of serum lactate dehydrogenase (LDH). *Leuk Res*. 2010;34:1340-1343.
19. Kyle RA, Therneau TM, Dispenzieri A, et al. Immunoglobulin m monoclonal gammopathy of undetermined significance and smoldering Waldenstrom macroglobulinemia. *Clin Lymphoma Myeloma Leuk*. 2013;13:184-186.
20. Kyle RA, Treon SP, Alexanian R, et al. Prognostic markers and criteria to initiate therapy in Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. *Semin* Oncol. 2003;30:116-120.
21. Dimopoulos MA, Kastritis E, Owen RG, et al. Treatment recommendations for patients with Waldenstrom macroglobulinemia (WM) and related disorders: IWWM-7 consensus. *Blood*. 2014;124:1404-1411.
22. Dimopoulos MA, Garcia-Sanz R, Gavriatopoulou M, et al. Primary therapy of Waldenstrom macroglobulinemia (WM) with weekly bortezomib, low-dose dexamethasone, and rituximab (BDR): long-term results of a phase 2 study of the European Myeloma Network (EMN). *Blood*. 2013;122:3276-3282.
23. Ghobrial IM, Xie W, Padmanabhan S, et al. Phase II trial of weekly bortezomib in combination with rituximab in untreated patients with Waldenstrom macroglobulinemia. *Am J Hematol*. 2010;85:670-674.
24. Thomas SK, Haygood TM, Qazilbash MH, et al. et al. A phase II trial of bortezomib-rituximab followed by autologous stem cell harvest (SCH) and cladribine-cyclophosphamide-rituximab (2CdA-Cy-Rit) consolidation as primary therapy of Waldenström's macroglobulinemia (WM). *Blood*, 122(21):4396.
25. Treon SP, Ioakimidis L, Soumerai JD, et al. Primary therapy of Waldenstrom macroglobulinemia with bortezomib, dexamethasone, and rituximab: WMCTG clinical trial 05-180. *J Clin Oncol*. 2009;27:3830-3835.
26. Treon SP, Tripsas CK, Meid K, et al. Carfilzomib, rituximab, and dexamethasone (CaRD) treatment offers a neuropathy-sparing approach for treating Waldenstrom's macroglobulinemia. *Blood*. 2014;124:503-510.
27. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet*. 2013;381:1203-1210.
28. Rummel M, Lerchenmüller C, Greil R. Bendamustine-rituximab induction followed by observation or rituximab maintenance for newly diagnosed patients with Waldenstrom's macroglobulinemia: results from a prospective randomized, multicenter study (StiL NHL 7-2008 -MAINTAIN-; ClinicalTrials.gov Identifier: NCT00877214). *Blood*. 2012;120(21):2739.
29. Dimopoulos MA, Anagnostopoulos A, Kyrtsonis MC, et al. Primary treatment of Waldenstrom macroglobulinemia with dexamethasone, rituximab, and cyclophosphamide. *J Clin Oncol*. 2007;25:3344-3349.
30. Ioakimidis L, Patterson CJ, Hunter ZR, et al. Comparative outcomes following CP-R, CVP-R, and CHOP-R in Waldenstrom's macroglobulinemia. *Clin Lymphoma Myeloma*. 2009;9:62-66.
31. Gertz MA, Rue M, Blood E, et al. Multicenter phase 2 trial of rituximab for Waldenstrom macroglobulinemia (WM): an Eastern Cooperative Oncology Group Study (E3A98). *Leuk Lymphoma*. 2004;45:2047-2055.
32. Dimopoulos MA, Zervas C, Zomas A, et al. Treatment of Waldenstrom's macroglobulinemia with rituximab. *J Clin Oncol*. 2002;20:2327-2333.
33. Ghobrial IM, Fonseca R, Greipp PR, et al. Initial immunoglobulin M "flare" after rituximab therapy in patients diagnosed with Waldenstrom macroglobulinemia: an Eastern Cooperative Oncology Group Study. *Cancer*. 2004;101:2593-2598.
34. Treon SP, Tripsas CK, Yang G, et al. A prospective multicenter study of the Bruton's tyrosine kinase inhibitor ibrutinib in patients with relapsed or refractory Waldenstrom's macroglobulinemia *Blood*. 2013;122:251.
35. Dimopoulos MA, Tedeschi A, Trotman J, et al. Phase 3 trial of ibrutinib plus rituximab in Waldenström's macroglobulinemia. *N Engl Med*. 2018;378:2399-2410.

36. Buske C, Tedeschi A, Trotman J, et al. Ibrutinib treatment in Waldenström's macroglobulinemia: follow-up efficacy and safety from the iNNOVATETM study. *Blood*. 2018;132:149.
37. Laszlo D, Andreola G, Rigacci L, et al. Rituximab and subcutaneous 2-chloro-2'-deoxyadenosine combination treatment for patients with Waldenstrom macroglobulinemia: clinical and biologic results of a phase II multicenter study. *J Clin Oncol*. 2010;28:2233-2238.
38. Leblond V, Johnson S, Chevret S, et al. Results of a randomized trial of chlorambucil versus fludarabine for patients with untreated Waldenstrom macroglobulinemia, marginal zone lymphoma, or lymphoplasmacytic lymphoma. *J Clin Oncol*. 2013;31:301-307.
39. Weber DM, Dimopoulos MA, Delasalle K, et al. 2-Chlorodeoxyadenosine alone and in combination for previously untreated Waldenstrom's macroglobulinemia. *Semin Oncol*. 2003;30:243-247.
40. Treon SP, Branagan AR, Ioakimidis L, et al. Long term outcomes to fludarabine and rituximab in Waldenstrom's macroglobulinemia. *Blood*. 2009;113:3673-3678.
41. Leleu X, Tamburini J, Roccaro A, et al. Balancing risk versus benefit in the treatment of Waldenström's Macroglobulinemia patients with nucleoside analogue-based therapy. *Clin Lymphoma Myeloma*. 2009;9:71-73.
42. Treon SP, Hanzis C, Manning RJ, et al. Maintenance rituximab is associated with improved clinical outcome in rituximab naive patients with Waldenstrom macroglobulinaemia who respond to a rituximab-containing regimen. *Br J Haematol*. 2011;154:357-362.
43. Rummel MJ, Lerchenmüller C, Hensel M, et al. Two years rituximab maintenance vs. observation after first line treatment with bendamustine plus rituximab (B-R) in patients with Waldenström's macroglobulinemia (MW): results of a prospective, randomized, multicenter phase 3 study (the StiL NHL7-2008 MAINTAIN trial). *Blood*. 2019;134 (suppl 1):343.
44. Furman RR EH, DiRienzo CG, Hayman SR, et al. A phase II trial of ofatumumab in subjects with Waldenstrom's macroglobulinemia. *Blood*. 2011;118:3701.
45. Kyriakou C, Canals C, Sibon D, et al. High-dose therapy and autologous stem-cell transplantation in Waldenstrom macroglobulinemia: the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. *J Clin Oncol*. 2010;28:2227-2232.
46. Kyriakou C, Canals C, Cornelissen JJ, et al. Allogeneic stem-cell transplantation in patients with Waldenström macroglobulinemia: report from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. *J Clin Oncol*. 2010;28:4926-4934.
47. Zanwar S, Abeykoon JP, Kapoor P. Novel treatment strategies in the management of Waldenstrom macroglobulinemia. *Curr Hematol Malig Rep*. 2020;15:31-43.

This page intentionally left blank

16 Multiple Myeloma

Paul Lin
Gregory P. Kaufman
Hans C. Lee
Elisabet E. Manasanch
Melody Becnel
Sheeba Thomas
Donna Weber
Robert Z. Orlowski
Krina Patel

KEY CONCEPTS

- The updated International Myeloma Working Group (IMWG) criteria for multiple myeloma includes patients with bone marrow plasmacytosis of at least 60%, an involved-to-uninvolved serum-free light-chain ratio of at least 100, or more than one focal lesion on magnetic resonance imaging (MRI) studies of at least 5 mm in size in addition to the criteria of hypercalcemia, renal disease, anemia, and bone disease (CRAB).
- The IMWG now recommends advanced imaging, such as whole-body low-dose computed tomography (CT), positron emission tomography–computed tomography (PET-CT), or MRI to evaluate for bone disease because it can detect up to 80% more lesions compared with plain film radiographs.
- Triplet therapies, such as with a proteasome inhibitor, immunomodulatory drugs, and steroids have shown significant improvement over doublet therapy. Ongoing trials are investigating quadruplet therapy, with promising initial results, and they could become standard of care in the future.
- As of 2020, autologous transplant after induction chemotherapy remains the standard of care and has shown significant improvement in progression-free survival. This might change in the future depending on disease risk status, and minimal residual disease testing.
- Maintenance therapy after autologous transplant is recommended because it has been shown to significantly improve progression-free survival.
- As of 2020, there is no indication to treat patients with smoldering myeloma. However, this could change in the future, because recent trials have shown that treatment of high-risk smoldering myeloma can potentially delay its progression to myeloma.

Plasma cell dyscrasias are heterogeneous disorders arising from the proliferation of a monoclonal population of plasma cells. Some of these disorders can present serendipitously as benign processes that can be observed; others are highly aggressive and require immediate intervention. The most common plasma cell dyscrasia is monoclonal gammopathy of undetermined significance (MGUS), a benign condition that can be observed. Related disorders include smoldering multiple myeloma (SMM), multiple myeloma (MM), solitary plasmacytoma of the bone, extramedullary plasmacytoma, Waldenström macroglobulinemia, primary amyloid light-chain amyloidosis, heavy-chain disease, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, and TEMPI (telangiectasias, elevated erythropoietin and erythrocytosis, monoclonal gammopathy, perinephric fluid collection, and intrapulmonary shunting) syndrome. The spectrum of MGUS, SMM, and MM represents a natural progression of the same disease. This chapter focuses on the etiology, genetics, biology, diagnosis, clinical features, and current therapy of MM.

Major recent discoveries have changed the way we understand, diagnose, and treat plasma cell dyscrasias. The initial sequencing of the myeloma genome and single-cell genetic analysis paved the way for the concept of intraclonal heterogeneity and Darwinian selection of clones. Increasingly sensitive diagnostic and monitoring techniques allow for more accurate diagnosis, minimal residual disease (MRD) monitoring, and detection of early relapse. New diagnostic criteria for MM have been implemented, and the introduction of novel classes of agents such as immunomodulatory

drugs and proteasome inhibitors has led to improved overall survival. In addition, immunotherapy using monoclonal antibodies against different myeloma targets including CD38 and SLAMF7 (CS1) has significantly improved outcomes for patients with relapsed and/or refractory disease.

MULTIPLE MYELOMA

MM is a malignant proliferation of plasma cells. In virtually all cases, myeloma cells (as well as their precursors MGUS and SMM) secrete immunoglobulins (Igs). Usually, myeloma cells secrete IgG (60%); other types are less common (IgA 20%, IgD 2%, IgE <0.1%, biclonal <1%). Light-chain-only secretion is noted in 18%; less than 5% of patients do not secrete a heavy- or light-chain immunoglobulin (nonsecretory MM).

Epidemiology and Risk Factors

In 2019, approximately 32,000 people were diagnosed with MM in the United States with, 12,960 deaths from the disease. The median age at diagnosis is 69 years. The incidence is highest in the age range of 65 to 74 years (27.7%), followed by the 75- to 84-year-old range (24.7%). The annual age-adjusted incidence of the disease per 100,000 population is 7.2 among white men and 4.3 among white women. Among Blacks, the frequency doubles to 14.8 in men and 10.5 in women. There is also a difference in mortality by racial group. The annual age-adjusted mortality rate per 100,000 is 4.0 and 2.5 in White men and women, respectively, and 7.7 and 5.3 in Black men and women, respectively. The incidence and mortality rates are lowest among Asians and Pacific Islanders.

Risk factors that predispose to MGUS and MM point toward common shared etiologic environmental and genetic factors. Age is a risk factor for MGUS, because its prevalence is four times higher among individuals at least 80 years old than among those 50 to 59 years old. Increased risk of MGUS has also been reported in first-degree family members of patients with MGUS and MM (risk ratio between 2 and 3). In a study of Black and White women of similar socioeconomic status, obesity, black race, and increasing age conferred an increased risk of MGUS. Personal and family history of autoimmune or inflammatory disorders as well as infections have been linked to an increased risk of MGUS and MM. Exposure to infections has been hypothesized to be involved in the malignant transformation of MM, or it could represent impaired immunity associated with MGUS and SMM, which often precedes a diagnosis of MM. Radiation exposure, pesticides, and cleaners are also associated with an increased risk of MGUS and MM.

Although MM is not an inherited disease, more than 100 familial cases have been reported in the literature. The largest series described 39 unique families with 79 cases of MM. Both dominant and recessive inherited traits may play a role in familial MM. Large genomic studies have identified low penetrant genetic variants that confer a modest increase in the risk of developing MM.[1,2] Based on epidemiologic and familial aggregation studies, most of the inherited risk of developing MM may result from different genetic polymorphisms, each of which has only a small effect on the predisposition to develop disease.[3]

Pathophysiology and Genetics/Molecular Classification

MM arises from terminally differentiated B cells or even early committed B cells (germinal-center B cells) that manifest clinically as more differentiated plasma cells. The major role of normal differentiated plasma cells is to produce Igs (antibodies) to fight infections. To become an effective part of the adaptive immune system, B cells must undergo Ig gene rearrangement and affinity maturation in response to antigens presented by antigen-presenting cells within the lymph node germinal center. For this to occur, hypervariable regions in the Ig heavy-chain locus (IGH in chromosome 14q32) undergo programmed mutations (somatic hypermutation) through which, among others, double DNA strand breaks and chromosomal translocations are generated. The primary etiology of MM has been linked to *IGH* translocations and increased copies of odd-numbered chromosomes (hyperdiploidy), which result in cyclin D dysregulation. These events can be observed early in the course of monoclonal gammopathies (such as in MGUS or SMM) as well as in MM, suggesting that they are primary genetic events. Initial whole-genome and exome sequencing in 38 patients with MM confirmed the complexity of genetic alterations seen in MM and uncovered secondary mechanisms of transformation to MM.[4] Secondary events included mutations in the oncogene *MYC* (most commonly observed in plasma cell leukemia or aggressive forms of MM), mutations in the nuclear factor-κβ (NF-κβ) pathway, including *BRAF* and *RAS*, and chromosome copy number abnormalities such as deletions, amplifications, or additions. Changes in DNA methylation patterns are also important secondary events leading to increased tumor diversity and more aggressive forms of plasma cell dyscrasias.

Different tests for gene expression profiling (GEP) are available for molecular classification of MM. As of this writing, molecular profiling of MM is mostly used for research purposes (eg, identification of high-risk MM for inclusion in clinical trials). These tests may

become increasingly important as we develop more personalized treatment for MM.

Serial genomic analysis during the disease course of patients with myeloma has identified different MM subclones within the same tumor. This has been termed *intraclonal heterogeneity*. In this model, different myeloma subclones compete for selection as they are exposed to the microenvironment and therapeutic pressures.[5] Single-cell genetic analysis at diagnosis confirmed that MM is highly heterogeneous and characterized by the accumulation of a diverse range of mutations at the subclonal level.[6] In this scenario, the acquisition of new mutations leads to new subclones with different clinical phenotypes and sensitivities to therapy. Intraclonal heterogeneity in myeloma has many potential implications for therapy, suggesting that subclonal targeting in combination therapies may be needed to eradicate the multiple subclones. Increasing genetic complexity is seen with progression from MGUS to MM and plasma cell leukemia, which may suggest that earlier treatment may result in improved clinical outcomes.

The bone marrow microenvironment also plays a role in the etiology of MM and its related disorders. Upregulation of cytokines that increase vascular permeability, proliferation, or cell homing (interleukin [IL]-6, vascular endothelial growth factor, and insulin-like growth factor) have been involved in the progression to MM. Gene expression profiling has revealed that modulation of certain genes can lead to a permissive microenvironment that promotes growth of myeloma subclones, leading to active disease.[7] Thus, targeting the microenvironment is an area of extensive research that, combined with therapeutic targeting of myeloma subclones, may lead to improved outcomes. New and effective antimyeloma combination therapies and well-designed clinical trials are needed to test these hypotheses.

Clinical Presentation

The clinical presentation of MM and its precursors is variable. Patients with MGUS or SMM are often incidentally diagnosed based on workup for a low albumin-to-globulin ratio, high serum protein, or other conditions such as autoimmune diseases, peripheral neuropathy, skin rashes, or hemolytic anemias.

In contrast, patients initially presenting with MM usually have at least one of the CRAB criteria (hyperCalcemia, Renal disease, Anemia, and Bone disease), classically used to define symptomatic MM. Anemia is the most common finding, occurring in 73% of patients, and is typically a normocytic, normochromic anemia. Anemia can be caused by a variety of factors, including marrow replacement or cytokine production by plasma cells, which lead to decreased erythropoiesis, or decreased erythropoietin levels as a result of renal disease.[8]

Bone pain is common, occurring in 60% of patients, and related to increased resorption of bone, leading to lytic bone lesions. Painful vertebral compression fractures can occur and may represent a medical emergency when associated with symptoms of cord compression. Increased bone resorption has been attributed to factors such as RANK ligand (RANKL), osteoprotegerin (OPG), macrophage inflammatory protein (MIP)-1α, IL-6, and IL-3, which stimulate osteoclast activity in areas infiltrated by plasma cells as a result of interactions between plasma cells and the microenvironment (Fig. 16–1).

An elevated creatinine is a presenting sign in 50% of patients. Renal disease is often attributed to light-chain cast nephropathy resulting from precipitation of light chains that bind to Tamm-Horsfall mucoproteins secreted by cells in the ascending loop of Henle. These precipitated complexes obstruct the distal convoluted tubules and collecting ducts, leading to tubular atrophy and interstitial fibrosis. Other causes of renal failure include hypercalcemia, leading to nephrocalcinosis, as well as amyloidosis, heavy-chain disease, and light-chain disease.

Hypercalcemia of higher than 11 mg/dL is present in 10% of patients and represents a medical emergency requiring hydration with isotonic saline and bisphosphonate therapy with zoledronic acid or pamidronate in moderate or severe cases. Calcitonin can also be used to rapidly reduce serum calcium levels.

Other common presenting symptoms include fatigue (32%) and weight loss (20%). As a result of immune dysfunction, patients are at risk for infections. About 7% to 18% of patients may present with extramedullary plasmacytomas. Less common symptoms include fever, splenomegaly, hepatomegaly, and lymphadenopathy.



FIGURE 16–1 Radiographic image of the skull showing "punched out" osteolytic lesions characteristic of multiple myeloma.

Diagnostic Workup

Once a plasma cell dyscrasia is suspected, a comprehensive diagnostic workup should be initiated to demonstrate the presence or absence of a clonal plasma cell disorder, to determine whether end-organ damage is present, and to evaluate laboratory markers related to prognosis. These should include the following components.

Laboratory Studies

- Complete blood count
- Serum chemistries including creatinine, calcium, albumin, lactate dehydrogenase (LDH), β_2-microglobulin, and immunoglobulin levels (IgG, IgA, IgM)
- Serum protein electrophoresis with immunofixation to quantify monoclonal protein (M-protein) and determine immunoglobulin isotype
- Serum-free light-chain assay to evaluate the ratio of serum κ to λ light chains
- Urinalysis with 24-hour urine collection with protein electrophoresis and immunofixation (Fig. 16–2)

Imaging Studies

- The International Myeloma Working Group (IMWG) now recommends that advanced imaging with either whole-body low-dose computed tomography (CT), positron emission tomography–computed tomography (PET-CT), or magnetic resonance imaging (MRI) be used because they can detect up to 80% more lesions compared with plain film radiographs.[9]
  - An advanced imaging modality is particularly recommended in the diagnosis of SMM to detect subtle bone lesions that would warrant the initiation of treatment. It is also helpful in assessing baseline disease burden as an adjunct to serum and urine markers before initiation of treatment in MM.
  - A CT scan can be helpful in the characterization of soft tissue masses in the case of extramedullary plasmacytomas and can direct to an area to be biopsied.
  - An MRI scan is useful for evaluating the axial skeleton in the presence of symptoms and assessing for spinal cord compression. It can also identify abnormal marrow uptake because T1-weighted images will show a diffuse decrease in marrow signal intensity but will enhance with the administration of contrast.
  - PET-CT can be prone to false-positive findings but has more specificity because of its increased metabolic uptake at the site of lytic lesions, and is the preferred initial baseline advanced imaging modality at the MDACC, in combination with skeletal surveys.
  - There is no role for nuclear bone imaging because bone scan isotopes are not taken up by lytic lesions.

Bone Marrow Aspiration and Biopsy

- Morphologic review and immunohistochemistry (Fig. 11–3)
- Flow cytometry for immunophenotyping of plasma cells:
  - Plasma cells are positive for CD38 and CD138.
  - Normal plasma cells have higher expression of CD19 and CD45; malignant plasma cells typically lack these surface antigens.
  - Malignant plasma cells have increased expression of CD56 and CD117; normal plasma cells have weak expression of these markers.
- Conventional cytogenetic karyotyping.

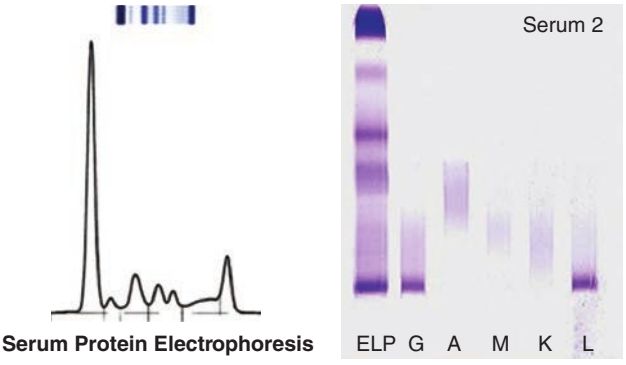


FIGURE 16–2 Serum protein electrophoresis demonstrates an M-protein peak *(left)*. Immunofixation confirms it to be monoclonal IgG lambda type.

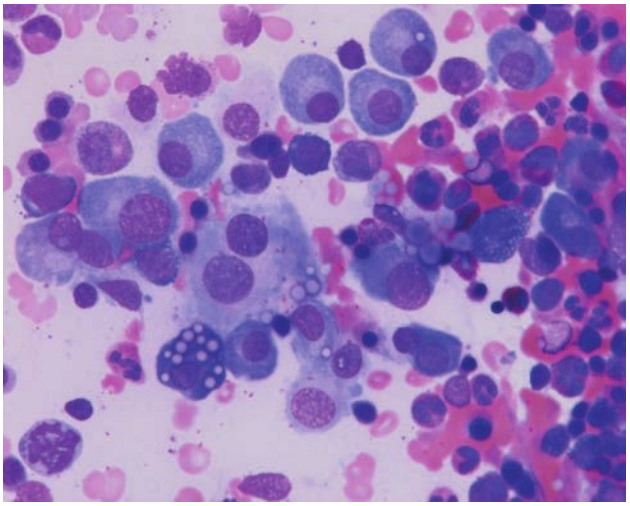


FIGURE 16–3 Multiple myeloma bone marrow aspirate. Some plasma cells have cytoplasmic immunoglobulin inclusions (Wright-Giemsa, 500×).

- Fluorescent in situ hybridization (FISH) for recurrent chromosomal deletions, amplifications, and translocations that have prognostic significance. These include:
  - Deletion 13q14, deletion 17p13 (*TP53*), and deletion of 1p32.
  - Amplification of 1q21.
  - Translocations involving the immunoglobulin heavy-chain locus on chromosome 14q32 and its common partners, including 11q13 (*CCND1*), 4p16 (*FGFR3* and *MMSET*), 16q23 (*c-MAF*), 6p21 (*CCND3*), and 20q12 (*MAFB*).
- GEP of the CD138+ bone marrow aspirate plasma cells to identify high-risk MM and to facilitate inclusion in clinical trials.

Other Tests

- Abdominal wall fat pad biopsy (warranted if there are signs and symptoms suggestive of amyloidosis; see separate chapter), which should be stained with Congo red. Amyloid fibrils show green birefringence under polarized light.
- Serum viscosity (if there are concerns for hyperviscosity usually caused by elevated IgM levels in Waldenström macroglobulinemia; see separate chapter). Hyperviscosity should be a clinical diagnosis, and therapeutic plasma exchange should not be delayed while waiting for the results of serum viscosity level.

Myeloma Diagnostic Criteria

Based on the above workup, a diagnosis of a plasma cell dyscrasia may be made, as summarized in Table 16–1.[10] Historically, SMM and MM have been distinguished by the presence of end-organ damage as defined by CRAB criteria. The 2014 updated IMWG criteria were revised to reclassify some SMM patients as having MM (even in the absence of symptoms) if the patient has clonal bone marrow plasmacytosis of at least 60%, an involved-to-uninvolved serum-free light-chain ratio of at least 100, or more than one focal lesion on MRI studies of at least 5 mm in size. Patients with SMM and at least one of these biomarkers have a 70% to 80% chance of progression to MM at 2 years compared with 20% (10% per year) in the absence of these high-risk features.

Staging and Risk Stratification

The course of MM is heterogeneous. Risk stratification using staging and prognostic tools can help stratify patients in clinical trials and may help guide therapy.

Table 16–1 Definitions of MGUS, SMM, and MM by 2014 IMWG Criteria

		Definition	Progression Rate
Premalignant	Monoclonal gammopathy of undetermined significance (MGUS)	• Monoclonal protein <3 g/dL • Clonal bone marrow plasma cells <10% • Absence of CRAB[a] criteria related to plasma cell clonal disorder • In light-chain MGUS[b], urinary monoclonal protein must be <500 mg/24 h	• 1% per year for MGUS • 0.3% per year for light-chain MGUS
	Smoldering multiple myeloma (SMM)	• Serum monoclonal protein ≥3 g/dL or urinary monoclonal protein ≥500 mg/24 h and/or bone marrow plasmacytosis 10%–60% • Absence of CRAB criteria[a] or amyloidosis	10% per year (see Table 16-4 for risk stratification in SMM)
	Multiple myeloma (MM)	• Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma AND • Evidence of end-organ damage attributed to a plasma cell disorder as defined by CRAB[a] criteria OR ≥1 biomarker of malignancy, which includes bone marrow clonal plasmacytosis ≥60%, involved-to-uninvolved serum-free light chains ≥100, or >1 focal lesion on MRI studies that is at least 5 mm in size	Not applicable

[a]CRAB criteria:
1. HyperCalcemia: Serum calcium >1 mg/dL above the upper limit of normal or >11 mg/dL.
2. Renal insufficiency: creatinine clearance <40 mL/min or serum creatinine >2 mg/dL.
3. Anemia: hemoglobin <2 g/dL below the lower limit of normal or <10 g/dL.
4. Bone lesions: one or more osteolytic lesions on skeletal survey, CT scan, or PET-CT.

[b]Defined as abnormal free light-chain ratio (<0.26 or >1.65) in the absence of immunoglobulin heavy-chain expression on immunofixation.

Adapted with permission from Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma, *Lancet Oncol* 2014 Nov;15(12):e538-e548.

Table 16–2 Risk Stratification of Newly Diagnosed Multiple Myeloma

Revised International Staging System	
Stage I	**Parameters:** Albumin ≥3.5 g/dL, β_2-microglobulin <3.5 mg/L, normal LDH, no high-risk chromosomal abnormalities **Median Overall Survival:** Not reached
Stage II	**Parameters:** Neither stage I nor stage III **Median Overall Survival:** 83 months
Stage III	**Parameters:** β_2-microglobulin ≥5.5 mg/L and either high LDH or high-risk chromosomal abnormalities **Median Overall Survival:** 43 months High-risk chromosomal abnormalities as determined by interphase FISH: del(17p), t(4;14), t(14;16)
Risk Stratification	
Standard risk	t(11;14) t(6;14) Hyperdiploid karyotype
Intermediate risk	t(4;14) Del 13q Hypodiploid karyotype
High risk	Del 17p13 Amplification of 1q21 t(14;20) t(14;16) Lactate dehydrogenase ≥2× institutional upper limit of normal Plasma cell leukemia High-risk gene expression profiling signature

International Staging System

The International Staging System (ISS) was established in 2005 by the IMWG after a retrospective analysis of the outcomes of more than 10,000 patients across 17 different centers. In this study, β_2-microglobulin and albumin were powerful correlates of median survival, and patients could be categorized into three stages based on serum levels at diagnosis. The staging system was subsequently revised to include LDH and high-risk chromosomal abnormalities (Table 16–2). Because β_2-microglobulin is excreted renally, high levels may be found in the presence of renal failure, which makes the interpretation of the ISS in this setting challenging. The ISS is the preferred staging method and has supplanted the previously used Durie-Salmon staging system, which was confounded by observer-dependent variables. It is important to note that the ISS has only been validated at the time of diagnosis in patients with MM and should not be extrapolated to patients with MGUS or SMM.

Risk Stratification

In addition to the ISS, patients can be stratified into standard-, intermediate-, and high-risk categories based on cytogenetic findings by both conventional karyotyping and FISH. The presence of del(17p), t(4;14), t(14;16), t(14;20) gain 1q, or p53 mutation is considered high-risk MM. Recently, high-risk myeloma was further defined as double-hit myeloma when two high-risk factors are present, and triple-hit myeloma when three or more high-risk factors are present. More risk factors portend worse outcomes. Risk stratification based on these criteria is summarized in Table 16–2.

Response Criteria

International Myeloma Working Group Uniform Response Criteria

The IMWG proposed new guidelines in 2006 to standardize response criteria in MM and to define disease progression to facilitate comparisons of outcomes between treatment centers and for reporting results in clinical trials. These International Uniform Response Criteria guidelines are summarized in Table 16–3. Assessment of response with M-protein measurements using serum protein electrophoresis, urine protein electrophoresis, and serum-free light-chain assay is recommended prior to each cycle of therapy. Bone marrow biopsy is necessary to monitor disease in the absence of a measurable M-protein in the serum or urine or to document a complete or stringent complete

Table 16–3 IMWG International Uniform Response Criteria

Response Category	Criteria
sCR	Meets criteria for CR PLUS Normal free light chain ratio AND No clonal cells in bone marrow by immunohistochemistry or immunofluorescence
CR	Negative serum and urine immunofixation AND Disappearance of any soft tissue plasmacytomas AND ≤5% plasma cells in bone marrow
VGPR	Serum and urine M-protein detectable by immunofixation but negative M-protein OR ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
PR	≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h If unmeasurable serum and urine M-protein, ≥50% decrease in the difference between involved and uninvolved FLC levels If unmeasurable serum and urine M-protein serum FLC assay, ≥50% reduction in plasma cells is required in place of M-protein, as long as baseline bone marrow plasma cell percentage was ≥30% In addition to above criteria, a ≥50% reduction in the size of any baseline soft tissue plasmacytoma is required
SD	Not meeting criteria for CR, VGPR, PR, or progressive disease
PD	Increase of ≥25% from baseline in at least one of the following: • Serum M-component (the absolute increase must be ≥0.5 g/dL) • Urine M-component (the absolute increase must be ≥200 mg/24 h • Difference between involved and uninvolved FLC levels if serum and urine M-protein are unmeasurable (the absolute increase must be >10 mg/dL) • Bone marrow plasma cell percentage (the absolute % must be ≥10%) Development of new bone lesions or soft tissue plasmacytomas or definite increase in size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia >11.5 mg/dL related to plasma cell dyscrasia

CR, complete response; FLC, free light chain; IMWG, International Myeloma Working Group; M-protein, monoclonal protein; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.
Adapted with permission from Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma, *Leukemia* 2006 Sep;20(9):1467-1473.

response. Serial imaging assessments may be required if soft tissue plasmacytomas are present at baseline.

Minimal Residual Disease

In recent years, the fraction of patients achieving deep responses, including complete remission, after initial MM therapy has increased significantly. This correlates with improved progression-free survival (PFS) and overall survival (OS) in several studies[11] With a deepened level of remission, more sensitive methods to assess and monitor MRD have been investigated. These include flow cytometry, allele-specific polymerase chain reaction, and next-generation sequencing–based assays.[12] MRD may soon be used as a valid surrogate end point to compare treatment strategies and advise on consolidation and maintenance therapies. As of this writing, MRD assessment by multiparameter flow cytometry is the most reproducible method in MM. It has a sensitivity of 10^{-5} if at least 2×10^6 cells from bone marrow aspirates are analyzed. An international effort to adopt standardized or harmonized MRD detection assay and analysis by multiparameter flow cytometry in clinical practice and in clinical trials is ongoing.

Treatment of Newly Diagnosed Multiple Myeloma

After the diagnostic workup and risk stratification are complete, patients who meet the criteria for MM as defined by IMWG criteria should initiate therapy. The most important initial assessment is whether a patient is a candidate for high-dose chemotherapy and autologous stem cell transplantation (SCT), largely based on existing comorbidities and age. In the transplant-eligible population, current MM standard of care involves frontline chemotherapy, followed by consolidative high-dose melphalan and autologous SCT, followed by maintenance therapy. Some chemotherapy agents (eg, melphalan) may adversely affect stem cell collection and should be avoided in the initial therapy of transplant-eligible patients. Melphalan may be included in the frontline therapy of transplant-ineligible patients.

Frontline Therapy for Transplant-Eligible Patients

A number of different regimens can be used in the frontline setting for transplant-eligible patients. These usually consist of two- or three-drug combinations, and the choice of therapy is individualized based on factors such as patient comorbidities (neuropathy, diabetes), preferred route of administration (oral, intravenous, or subcutaneous), and underlying disease biology (eg, bortezomib in t(4;14) and del 13q). Patients are usually given two to four cycles of therapy before stem cell collection to reduce disease burden before proceeding to high-dose chemotherapy and autologous stem cell rescue. Given the evidence that the depth and duration of response may translate into improved long-term outcomes, we generally prefer the three-drug regimens over the two-drug regimens as initial therapy in newly diagnosed patients.

Lenalidomide and Dexamethasone

The efficacy of the second-generation immunomodulatory drug (IMiD) lenalidomide was shown in a randomized phase 3 study comparing lenalidomide plus high-dose dexamethasone (Len/Dex) versus placebo plus high-dose dexamethasone.[13] Overall response rates (ORR), defined as a partial response or greater, and very good partial response (VGPR) rates were significantly higher in the Len/Dex arm (78% and 63%, respectively) versus the placebo/Dex arm (48% and 16%, respectively). The one-year PFS rate was also higher in the Len/Dex arm (78% vs 52%), although there was no significant difference in OS between the two groups (94% vs 88%). Grade 3 or 4 neutropenia was higher with Len/Dex (21% vs 5%), as was the rate of venous thromboembolism (23.5% vs 5%) despite aspirin prophylaxis.

To possibly decrease the dexamethasone dose, a randomized study was conducted with lenalidomide in combination with high-dose dexamethasone (40 mg on days 1–4,8–11, and 17–20 every 4 weeks) versus low-dose dexamethasone (40 mg on days 1,8, 15, and 22 every 4 weeks).[14] Patients receiving high-dose dexamethasone achieved a higher ORR (79% vs 68%) after four cycles of therapy. However, a second interim analysis at one year demonstrated a statistically significant superior OS in the low-dose dexamethasone arm compared with the high-dose arm (96% vs 87%). This was attributed to increased toxicities of high-dose dexamethasone therapy including venous thromboembolism and infections. Based on this study, lenalidomide is recommended to be given in combination with low-dose dexamethasone.

Bortezomib and Dexamethasone

The proteasome inhibitor bortezomib in combination with dexamethasone was studied as frontline therapy in a large phase 3 trial comparing bortezomib and dexamethasone versus vincristine, doxorubicin, and dexamethasone (VAD) therapy before autologous SCT.[15] Postinduction ORR (78.5% vs 62.8%), higher VGPR rates (37.7% vs 15.1%), and complete response (CR) or near complete response rates (14.8% vs 6.4%) all favored the bortezomib and dexamethasone arm over the VAD arm. There was also a trend toward improved median PFS in the bortezomib and dexamethasone arm (36.0 vs 29.7 months) but no difference in OS. In a separate analysis, initial treatment with bortezomib and dexamethasone before autologous SCT was shown to overcome the adverse prognostic features of t(4;14) in relation to event-free survival (EFS) and OS compared with VAD, although del 17p remained a poor prognostic factor regardless of the treatment regimen. Herpes simplex prophylaxis with acyclovir or valacyclovir should be given with bortezomib-containing regimens. Subcutaneous administration of bortezomib is preferred because it has similar efficacy as the intravenous route with decreased peripheral neuropathy.[16]

Cyclophosphamide, Bortezomib, and Dexamethasone

The addition of oral cyclophosphamide to bortezomib and dexamethasone (CyBorD) was studied in phase 2 trials. In the EVOLUTION phase 2 trial, patients were randomly assigned to receive bortezomib, lenalidomide, and dexamethasone (VRD); bortezomib, lenalidomide, cyclophosphamide, and dexamethasone); or CyBorD, all followed by maintenance bortezomib for four 6-week cycles.[17] The study was later amended to add an additional day 15 dose of cyclophosphamide, in addition to days 1 and 8, in patients receiving CyBorD. Patients receiving the modified CyBorD regimen achieved an ORR of 82%, with a VGPR or better rate of 53% and a CR rate of 47%. The one-year PFS rate was 100%.

In another phase 2 study, standard twice-weekly (days 1,4, 8, and 11) bortezomib was compared with weekly bortezomib (days 1,8, 15, and 22) in combination with weekly cyclophosphamide and dexamethasone.[18] ORR (88% vs 93%) and VGPR rates (60% vs 61%) were similar in both the twice-weekly and weekly bortezomib groups. In addition to demonstrating the efficacy of the three-drug combination of CyBorD, this study also suggested that weekly (instead of twice-weekly) bortezomib could be used to reduce treatment-related toxicity because it resulted in fewer grade 3 and 4 adverse events compared with the twice-weekly schedule (37% and 3% vs 48% and 12%, respectively).

Bortezomib, Lenalidomide, and Dexamethasone

The efficacy of VRD has also been demonstrated in several phase 2 and 3 trials. As mentioned, VRD was

also included as one of the arms in the phase II EVOLUTION trial, which resulted in an 85% ORR, with a VGPR or better rate of 51% and a CR rate of 24%.[17] The phase 3 Southwest Oncology Group (SWOG) S0777 trial showed a median progression free survival (mPFS) of 41 months for VRd vs 29 months for Rd and a medium OS (mOS) for VRd that was not reached vs 69 months.[19] In addition, the role and timing of autologous SCT are being reexamined in the era of novel agents in a large international phase 3 trial of frontline VRD followed by lenalidomide maintenance therapy (with the option of SCT at the time of relapse) versus VRD followed by autologous SCT per the current standard of care (NCT01208662). The phase 3 ENDURANCE trial evaluating the second-generation proteasome inhibitor carfilzomib in combination with lenalidomide and dexamethasone (KRd) in the frontline setting showed similar results to RVD.[20] These studies will clarify the role of triplet combinations in the frontline setting and provide insight as to whether deeper responses, including molecular responses, with the multiple novel agents in combination, ultimately translate into improved long-term outcomes.

Monoclonal antibodies have been gaining interest in the frontline setting as quadruplet therapies, such as in the GRIFFIN trial with daratumumab (CD38 antibody) combined with bortezomib, lenalidomide, dexamethasone, which have shown promising results with superior stringent CR rates.[21] However, not all quadruplet therapies are beneficial, because the addition of elotuzumab (SLAMF7 antibody) to bortezomib, lenalidomide, dexamethasone did not improve PFS in the phase 2 SWOG-1211 trial.[22]

Frontline Therapy for Transplant-Ineligible Patients

Initial treatment regimens for transplant-eligible patients can also be used in transplant-ineligible patients. Without the need to collect autologous stem cells, the alkylating agent melphalan can be incorporated into frontline therapy in nontransplant candidates. For 40 years, melphalan and prednisone (MP) represented the standard of care for transplant-ineligible patients. Trials adding other novel therapies to the MP backbone such as thalidomide,[23] lenalidomide,[24,25] and bortezomib[26] demonstrated improved ORR and PFS. More recently the phase 3 ALCYCONE trial showed that the addition of daratumumab to bortezomib plus MP (VMP) resulted in a 36-month rate of OS of 78% in the D-VMP group compared with 67.9% in the VMP group after a median follow-up of 40.1 months.[27] However, in the US, non–melphalan-containing combinations now form the new standard of preferred regimens.

Lenalidomide and low-dose dexamethasone (Rd) in 4-week cycles until disease progression versus the same regimen for a fixed duration of 72 weeks versus melphalan, prednisone, and thalidomide (MPT) in 6-week cycles for 72 weeks were compared in a randomized phase 3 study in more than 1500 transplant-ineligible patients.[28] Although the ORRs were similar between the three arms, median PFS favored continuous Rd (25.5 months) versus 18 cycles of Rd (20.7 months) and MPT (21.2 months). There was a trend toward improved 3-year OS with continuous Rd (59%) versus fixed-duration Rd (56%) and MPT (51%). There was also a trend toward fewer grade 3 and 4 adverse events in the continuous Rd arm (70%) compared with the MPT arm (78%), in particular grade 3 and 4 neutropenia and neuropathy. However, there was a higher incidence of grade 3 and 4 infections with continuous Rd (29%), likely related to the longer duration of glucocorticoid use.

A community-based phase 3B trial compared bortezomib and dexamethasone (BD) versus bortezomib, thalidomide, and dexamethasone (BTD) versus melphalan, prednisone, and bortezomib (MPB) followed by maintenance bortezomib.[29] The ORR, PFS, and OS were similar across all three arms. Discontinuation because of adverse events was highest in the BTD arm (35%) compared with BD (24%) and MPB (30%). This demonstrates the safety and efficacy of the use of BD in the elderly population. RVD can also be used because patients in the SWOG S0777 trial mentioned above were not required to receive transplant. Furthermore, a regimen with decreased dose of lenalidomide (15 mg instead of the usual 25 mg) and dexamethasone (20 mg vs 40 mg) termed "RVD lite" can also be considered in more frail patients because it was shown to have an ORR of 86% with a mPFS of 35.1 months.[30] In general, the incorporation of novel agents to combination therapy has improved ORR and long-term outcomes in older adult, transplant-ineligible patients. However, treatment must be individualized based on comorbidities and disease characteristics as well as the patient's own goals of care.

Stem Cell Transplantation

Autologous Stem Cell Transplantation

High-dose melphalan without autologous SCT was first reported in 1983 by McElwain and colleagues from the Royal Marsden Hospital. Compared with chemotherapy alone, intensified chemotherapy followed by autologous SCT appears to prolong OS in previously untreated patients with MM. One comparative study and two randomized trials showed that autologous SCT provided survival benefits of approximately 12 months.

In the French IFM 90 trial, high-dose chemotherapy supported by autologous SCT was compared with conventional chemotherapy in 200 previously untreated patients younger than 65 years old with MM.[31] The results showed a higher CR rate (22% vs

5%) and higher rates of 5-year EFS (28% vs 10%) and OS (52% vs 12%) in the autologous SCT group. The median OS in patients assigned to the SCT arm was 13 months longer (57 vs 44 months).

The Medical Research Council Myeloma VII trial compared conventional-dose chemotherapy with high-dose therapy and autologous SCT in 401 previously untreated patients younger than 65 years old with MM.[32] The rates of CR were significantly higher in the autologous SCT group (44% vs 8%). Intent-to-treat analysis showed a significantly higher rate of OS and PFS with SCT. Compared with standard therapy, autologous SCT increased median OS by almost 12 months (54.1 vs 42.3 months). There was a trend toward a greater survival benefit in patients with poor prognosis (defined by β_2-microglobulin level >8 mg/L).

In three other randomized studies, however, there has been no survival benefit with autologous SCT.[33–35] Comparison among these trials is difficult because of the variability in patient eligibility, including age, induction chemotherapy, conditioning regimen for SCT, and definitions of response. The timing of transplantation given the existence of the new triplet regimens was evaluated in the large 700-patient French IFM 2009 trial.[36] Patients received either VRD for eight cycles or VRD for three cycles followed by autologous SCT and two additional cycles of VRD, with both arms receiving lenalidomide maintenance for one year. The transplant group had a significantly longer mPFS of 50 months vs 36 months with a higher CR of 59% versus 48% and MRD negativity of 79% versus 65%. The nontransplant group underwent transplantation after salvage therapy for relapsed disease. Overall survival at four years was not significantly different (82% vs 81%). Thus, autologous SCT has become the standard of care for eligible patients based on performance status and organ function.

Many different preparative regimens have been assessed over the last 20 years, but few have compared the different regimens. One prospective randomized trial by the IFM directly compared two different preparative regimens[37] in 282 newly diagnosed patients younger than 65 years old and found that high-dose melphalan at 200 mg/m^2 to be superior to a combination of melphalan 140 mg/m^2 plus 8 Gy of total-body irradiation, mainly because of reduced toxicity including mucositis and transplant-related mortality. A recent phase 3 randomized clinical trial from MDACC compared busulfan and melphalan with melphalan alone and found that the combination resulted in a median PFS of 64.7 months vs 43.5 months, but at a cost of increased grade 2–3 mucositis (74% vs 14%).[38] Melphalan remains the standard of care, but the addition of novel agents to conditioning is being investigated, especially in high-risk patients.

Transplantation can be performed either early after induction therapy or later at disease progression. Fermand et al compared early and late autologous SCT and reported a similar OS.[35] However, the average time without symptoms, treatment, and treatment toxicity were significantly better with early autologous SCT. A retrospective study of 167 patients who received induction therapy containing at least one of three novel agents (lenalidomide, thalidomide, or bortezomib) followed by autologous SCT, either within 12 months of diagnosis or later, found a higher CR rate in the early autologous SCT arm but no difference in PFS or OS. The potential benefit of early versus late autologous SCT was assessed in a trial that randomly assigned patients between 55 and 65 years of age to either conventional chemotherapy alone or chemotherapy followed by autologous SCT. With a median follow-up of 120 months, a trend toward better event free survival (EFS), but no OS benefit, was observed in patients undergoing early transplantation.[35] Finally, the US Intergroup Trial S9321 found no PFS or OS benefit with early SCT.[33] A recent cost analysis study by Pandya et al suggests that early autologous SCT is cost effective compared with delayed autologous SCT.[39]

At MDACC, we offer autologous SCT to all eligible patients after induction therapy regardless of age. We use a preparative regimen of melphalan 200 mg/m^2 or busulfan and melphalan (unless the patient is treated in a clinical trial with a novel preparative regimen). In selected patients (>70 years old or dialysis dependent), we lower the melphalan dose to 140 mg/m.[2] We offer tandem autologous SCT only in the setting of a clinical trial or if there is significant residual disease after first autologous SCT. A second salvage transplant is an option for patients with relapsed disease; we offer this mainly to patients whose benefit from transplant was more than 18 months and whose disease burden can be significantly reduced by salvage chemotherapy. We offer maintenance therapy after transplantation (discussed later).

At MDACC, we only perform reduced-intensity allogeneic SCT. We use the tandem autologous plus allogeneic SCT approach only in the setting of a clinical trial. Allogeneic SCTs are offered to patients with relapsed, chemotherapy-sensitive disease who are less than 70 years old, have an HLA-identical sibling or unrelated donor, and are in good general physical condition because toxicity is significant. Our preparative regimen is a combination of fludarabine and melphalan (100 or 140 mg/m^2), with antithymocyte globulin added for unrelated donor SCT.

To improve outcomes of autologous transplantation by adding a graft-versus-myeloma component, current laboratory research and clinical trials at MDACC are focused on eradicating MRD after autologous SCT using cellular therapy and vaccines.

Maintenance Therapy

To delay the time to disease recurrence, maintenance therapy after autologous SCT has been explored to limit growth of residual malignant plasma cells. Initial maintenance strategies included interferon-α, although treatment-related toxicities made it challenging to administer. The approval of thalidomide in the late 1990s renewed interest in maintenance therapy. Multiple trials showed improvements in PFS and sometimes OS with thalidomide maintenance after autologous SCT. Toxicities related to long-term therapy, notably peripheral neuropathy, made it difficult to tolerate.

Given its more favorable side effect profile, lenalidomide maintenance therapy after autologous SCT was next explored. The Cancer and Leukemia Group B (CALGB) study randomized patients to lenalidomide or placebo maintenance starting 100 days after autologous SCT.[40,41] With a median follow-up of 91 months, mPFS was significantly greater in the lenalidomide arm (57.3 vs 28.9 months) as was the mOS (113.8 months vs 84.1 months). The IFM reported a similar trial in which patients received two 4-week cycles of consolidation with lenalidomide 25 mg after autologous SCT before being randomly assigned to lenalidomide maintenance versus placebo.[42] PFS also favored lenalidomide maintenance (median PFS, 41 vs 23 months), but there was no difference in OS at four years. Finally, in the Myeloma XI trial, from the UK, PFS was also improved (39 vs 20 months), though with no difference in OS after a median follow-up of 31 months. However, prespecified subset analysis showed that the 3-year OS in transplantation-eligible patients was 87.5% versus 80.2% in the control group. The transplant-ineligible group showed no significant OS benefit. The longer lenalidomide maintenance appears to increase the time of response. In one study, they found that lenalidomide continued for more than 24 months led to an improved mPFS after transplant of 77 months compared with patients who had 12 to 24, and less than 12 months of maintenance, with a mPFS of 6.5 and 26 months, respectively.[43]

Studies have reported an increase in second primary malignancies with lenalidomide maintenance (8% in the CALGB and IFM studies) versus placebo (3% in CALGB and 4% in IFM). However, when all competing factors for death are considered (including death from relapsed MM), patients have a much higher risk of mortality from other causes rather than secondary malignancies.[44,45] Potential risks and benefits of lenalidomide maintenance should be discussed with patients to make informed decisions. Lenalidomide maintenance can also be considered in nontransplant patients after initial therapy based on the phase 3 MPL-L versus MPL versus MP study.[24]

Alternative maintenance strategies have been investigated. Bortezomib maintenance was investigated in the phase 3 Hemato-Oncologie voor Volwassenen Nederland (HOVON)-65/German Multicenter Myeloma Group (GMMG)-HD4 trial, where patients were randomly assigned to receive either vincristine, doxorubicin, dexamethasone (VAD), or bortezomib, doxorubicin, and dexamethasone (PAD) induction, followed by high-dose melphalan and autologous SCT.[46] Patients were then randomized again to receive either thalidomide or bortezomib maintenance therapy for two years. The CR, PFS, and OS rates all favored bortezomib-containing induction and maintenance regimens, and benefit was also noted in high-risk patients with del 17p. The phase 3 TOURMALINE-MM3 study investigated the oral proteasome inhibitor, ixazomib, as maintenance after transplantation and found an increase in mPFS to 26.5 months compared with 21.3 months with placebo.[47] There is an ongoing noninferiority trial comparing ixazomib with lenalidomide maintenance (NCT02253316). In addition, other doublet combination maintenance trials are ongoing; the phase 3 AURIGA (MMY3021) trial is currently evaluating the rate of conversion to MRD negativity after one year of treatment (NCT03901963).

In general, at MDACC we offer patients lenalidomide maintenance therapy after autologous SCT. In the setting of high-risk cytogenetic features, a combination proteasome inhibitor with IMiD maintenance should be considered based on available data for bortezomib and carfilzomib.[48,49]

Treatment of Relapsed/Refractory Multiple Myeloma

We recommend enrollment in clinical trials when possible for all patients with relapsed/refractory MM. Alternatively, there are a number of therapeutic options that have gained regulatory approval that may be considered in this setting. Treatment usually involves combinations of triplets.

Immunomodulatory Drugs

Many patients may already be on maintenance lenalidomide at the time of disease recurrence.

Pomalidomide is a third-generation IMiD with greater in vivo potency than thalidomide and lenalidomide. In a phase 3 study in relapsed/refractory MM, patients were randomly assigned to receive either pomalidomide plus low-dose dexamethasone (Pd) versus only high-dose dexamethasone.[50] Around 75% patients were double refractory to both lenalidomide and bortezomib. The ORR was 35% with Pd versus 10% with high-dose dexamethasone. The median PFS was 4.0 months with Pd versus 1.9 months with

high-dose dexamethasone. Based on these results, pomalidomide gained FDA approval for refractory MM with prior bortezomib and lenalidomide exposure.

Proteasome Inhibitors

Bortezomib has shown efficacy in relapsed MM in two large randomized phase 3 trials. The APEX phase 3 trial compared intravenous bortezomib to high-dose dexamethasone; ORR, PFS, and OS were all superior in the bortezomib arm. As mentioned, subcutaneous bortezomib is favored over the intravenous route because of similar efficacy and less peripheral neuropathy.[16]

Bortezomib has also been studied in combination with other agents. The addition of pegylated liposomal doxorubicin in combination with bortezomib gained regulatory approval after demonstrating superior PFS compared with bortezomib monotherapy in relapsed/refractory bortezomib-naïve patients with MM, although the ORRs were not statistically different between the two groups.[51] Phase 2 data of VRD in relapsed/refractory MM resulted in an ORR of 64%. Median PFS was 8.5 months, and median OS was 30 months.[52] The CyBorD regimen may also be considered in relapsed MM based on phase 2 data.

The second-generation proteasome inhibitor carfilzomib has gained regulatory approval for patients exposed to bortezomib and an IMiD and whose disease was refractory to the last therapy. Like bortezomib, carfilzomib inhibits the chymotrypsin-like activity of the 20S proteasome, but its unique structural properties allow for greater specificity and irreversible binding to its target. The efficacy of carfilzomib in relapsed/refractory MM was established in a single-arm phase 2 trial of 266 patients, with an ORR of 24%, all of whom received prior IMiD therapy, and all but one patient received prior bortezomib.[53] Only 12% of patients reported any grade of treatment-emergent peripheral neuropathy. In the phase 3 ENDEAVOR study, carfilzomib was compared with bortezomib,[54] with approximately 50% of the patients receiving prior bortezomib, and approximately 70% receiving a prior immunomodulatory agent. The mPFS was 18.7 versus 9.4 months, which led to an increase in the mOS to 47.6 compared with 40 months.

The role of carfilzomib in relapsed and/or refractory MM continues to evolve while it is being tested in combination with other novel agents. Results of the phase 3 ASPIRE study comparing KRd with lenalidomide and dexamethasone (Rd) have been reported.[55] In this study, 66% of patients received prior bortezomib and 20% received prior lenalidomide. The mPFS was significantly longer with KRd compared with Rd (26.1 vs 16.6 months), and the mOS was 48.3 vs 40.4 months. The combination of carfilzomib, pomalidomide, and dexamethasone has also shown promising results,[56] with one study showing an ORR of 87% with 31% CR when given at first relapse.[57] OS results are still immature. Although earlier studies established the maximum tolerated dose of carfilzomib at 20 mg/m^2 for cycle 1 and 27 mg/m^2 twice weekly for subsequent cycles, phase 1 and 2 data have emerged demonstrating the safety and efficacy of higher doses of carfilzomib up to 56 mg/m^2 administered over 30 minutes compared with a 2- to 10-minute intravenous bolus given in earlier studies.[58] However, the SWOG randomized phase 2 study comparing high-dose versus low-dose carfilzomib (with dexamethasone in both arms) demonstrated no difference in response rate, PFS, or OS, but with higher rates of fatigue, thrombocytopenia, and peripheral neuropathy with the higher dose.[59] Finally, based on the ENDEAVOR, A.R.R.O.W., and CHAMPION-1 trials, weekly dosing of carfilzomib at 70 mg/m^2 has an efficacy profile comparable with carfilzomib at twice-weekly dosing of 56 mg/m^2 and offers a convenient and well-tolerated option. Regression analyses of all patients in the trials who received carfilzomib 70 mg/m^2 weekly versus 56 mg/m^2 twice weekly, estimated a PFS hazard ratio of 0.91 and an ORR odds ratio of 1.12.[60]

Monoclonal Antibodies

The FDA has approved the anti-CD38 antibodies, daratumumab and isatuximab, and the anti-SLAMF7 antibody, elotuzumab. Antibody therapy has modest to no efficacy as monotherapy and is thus used in combination with other drugs.

A number of different proteasomes, IMiD combinations with daratumumab, have been tested. For example, the phase 3 POLLUX trial comparing lenalidomide, dexamethasone with or without daratumumab in patients with one or more prior treatments, found that after a follow-up of more than 3.5 years, the ORR was 92.9% with daratumumab versus 76.4% without, leading to a mPFS of 44.5 months versus 17.5 months.[61] Patients who only had one prior therapy had a mPFS that was not reached compared with 19.6 months with lenalidomide, dexamethasone alone. In patients with two prior lines of therapy, daratumumab has been combined with pomalidomide and dexamethasone, which led to an ORR of 60%, with a mPFS of 8.8 months, and mOS of 17.5 months.[62] Daratumumab and PI combinations have also shown improved outcomes for relapsed or refractory myeloma. Per the CASTOR trial, daratumumab with bortezomib and dexamethasone demonstrated a 1-year PFS rate of 60.7% versus 26.9% in the control group of bortezomib and dexamethasone.[63] More recently, the CANDOR trial showed a significant improvement in PFS for the triplet combination of daratumumab, carfilzomib, and dexamethasone versus carfilzomib and dexamethasone

(median PFS not reached vs 15.8 months, respectively, with a median follow-up of 17 months).[64]

Intravenous daratumumab has been associated with a high rate of infusion reactions, and thus requires prolonged infusion times. To overcome this, subcutaneous daratumumab was developed and was recently approved by the FDA based on the PAVO trial, which showed similar responses to IV daratumumab.[65]

Isatuximab has also been FDA approved based on the phase 3 ICARIA-MM trial. In patients who progressed on two prior treatments including lenalidomide and a proteasome inhibitor, patients who received isatuximab with pomalidomide and dexamethasone had a mPFS of 11.5 months compared with 6.47 months with pomalidomide, dexamethasone alone.[66]

Elotuzumab has not been effective as a single agent.[67] However, in the phase 3 ELOQUENT-2 trial of patients who have received one to three prior lines of therapy, elotuzumab in combination with lenalidomide and dexamethasone had a mPFS of 19.4 months compared with 14.9 months with lenalidomide and dexamethasone alone,[68] which led to a mOS of 48.3 months versus 39.6 months after patients had been followed for at least 5.9 years.[69] Later in the randomized phase 2 ELOQUENT-3 trial, elotuzumab in combination with pomalidomide and dexamethasone demonstrated a mPFS of 10.3 months versus 4.7 months for pomalidomide and dexamethasone.[70]

Nuclear Export Inhibitor

It has been found that myeloma cells overexpress the nuclear exporter protein, exportin 1 (XPO1).[71] XPO1 is involved in the movement of many proteins across the nucleus, including important tumor suppressor proteins such as p53, retinoblastoma, and proteins that regulate the cell cycle, immune response, and more. Recently, an XPO1 inhibitor, selinexor, was tested in triple-refractory patients who had progressed on a proteasome inhibitor, IMiD, and daratumumab.[72] There was an ORR of 26% with a mPFS of 3.7 months and a mOS of 8.6 months. Thrombocytopenia and anemia were major adverse events, with 58% and 44%, respectively, having grade 3 or 4 toxicity. Fatigue, nausea, decreased appetite, and weight loss were also significant adverse events with 73%, 72%, 56%, and 50%, respectively, having any grade toxicity. Based on these results, the FDA has approved the medication for patients who have received at least four prior therapies and have progressed on at least two proteasome inhibitors, two IMiDs, and an anti-CD38 antibody. The ongoing phase 3 BOSTON trial will introduce selinexor in combination with bortezomib and dexamethasone to patients after one to three prior treatments (NCT03110562).

Antibody Drug Conjugate

An antibody drug conjugate couples an antibody with a chemotherapeutic agent to deliver a higher dose of the chemotherapy to a cancer cell than is normally possible because of toxicity. The phase 2 DREAMM-2 study tested belantamab mafodotin, an anti–B-cell maturation antigen (BCMA) antibody coupled to a microtubule-disrupting agent, mono-methyl auristatin F (MMAF), as single-agent treatment in triple-refractory patients who have progressed on at least three prior lines of treatment including a proteasome inhibitor, IMiD, and anti-CD38 antibody.[73] The study compared two doses and achieved a response rate of 31% to 34%. The mPFS ranged from 2.9 to 4.9 months. The most serious adverse event was keratopathy, which affected 70% to 74% of patients and was the most common reason treatment was discontinued. Recently, the FDA approved single-agent use in relapsed refractory patients with a rigorous REMS program. The ongoing DREAMM-6 trial combines belantamab with bortezomib and dexamethasone in patients with one or more prior lines of therapy (NCT03544281).

Histone Deacetylase Inhibitor

Although histone deacetylase (HDAC) inhibitors only have modest activity as single agents, the potential of HDAC inhibitors has been most pronounced in combination with other anti-MM drugs, namely bortezomib. Disruption of aggresome formation by HDAC inhibition may provide potent synergy with proteasome inhibition by interfering with protein turnover and inducing the unfolded protein response. Based on this rationale, the pan-deacetylase inhibitor panobinostat was studied in combination with bortezomib and dexamethasone and compared with placebo, bortezomib, and dexamethasone in a large phase 3 trial.[74] Patients receiving panobinostat with bortezomib and dexamethasone had a significantly longer mPFS of 12 versus 8.1 months, although OS was not significantly different between the groups. Concerns have been raised about drug efficacy (measured only by PFS) in the setting of significant toxicities, particularly grade 3 and 4 thrombocytopenia, diarrhea, and fatigue.

Unfortunately, other HDAC inhibitor trials have shown mixed benefits. For example, the phase 3 VANTAGE 088 trial comparing bortezomib in combination with or without vorinostat showed only a modest improvement in mPFS of 7.6 months versus 6.8 with placebo, and the trial with belinostat was stopped due to instances of toxicity.[75]

In the future, more selective HDAC inhibitors with fewer off-target effects may need to be developed and tested for the full potential of this therapeutic approach to be realized.

Investigational Agents

Although IMiDs and proteasome inhibitors now form the backbone of most MM regimens, both in the upfront and relapsed settings, several promising new classes of investigational agents have shown both safety and promising efficacy in phase 1 and 2 clinical trials.

Chimeric Antigen Receptor T Cells

Cellular therapy with chimeric antigen receptor (CAR) T cells are T cells modified with an activating receptor that binds to specific antigens present on the myeloma cell surface. The most popular target is the BCMA, which is an ideal target because it is primarily found only on mature B cells. CAR T cells against BCMA alone is being investigated in more than 60 trials around the world. The largest and most mature trial to date is the phase 2 KarMMA trial, which tested the BCMA CAR T cell, idecabtagene vicleucel, at three different doses in patients with three or more prior treatments.[76] They found an ORR of 73% in the 128 patients treated in all doses combined with a mPFS of 8.6 months or 11.3 months at the highest dose. Like other CAR therapies, cytokine release syndrome was common, affecting 84% of patients, though most were grade 1 or 2. Neurotoxicity was also present in 18% of patients across all doses. Other BCMA CAR T cell trials include the EVOLVE trial, which tests different ratios of CD4 to CD8 T cells and modified antigen–binding domain,[77] or the CARTITUDE-1 trial, which tests two BCMA-binding domains in a single CAR.[78] Early results also showed high response rates of 91% to 100%, though with smaller numbers and shorter follow-up compared with the KarMMA trial.

A number of other targets on the myeloma cell surface are also being investigated, such as CD38, CS1, and others.[79] CAR T cells have also been combined with other medications such as with a gamma-secretase inhibitor that prevents the cleavage of BCMA from the myeloma cell surface, which leads to increased BCMA surface expression and decreased circulating BCMA that could act to neutralize BCMA therapy.[80] To overcome the possibility of complete antigen loss, CAR T cells that target multiple antigens simultaneously are also being investigated.[81]

Bispecific T-Cell Engager

A bispecific T-cell engager (BITE) is an antibody that couples a tumor-binding domain with an anti-CD3 domain, thus bringing the tumor cells in close proximity to T cells. In a dose-finding study, a BITE coupling anti-BCMA to CD3, AMG 420, has been tested in patients who progressed after two or more lines of treatment, and was found to have an overall response rate of 31% with a response rate of 70% at the maximum tolerated dose.[82] Unfortunately, the antibody requires four weeks of continuous infusion. The longer-acting and thus shorter-infusion version, AMG 701, is also being investigated in a phase 1/2 trial (NCT03287908).

CELMoDs

Unique from immunomodulatory drugs such as lenalidomide and pomalidomide, CELMoDs are larger molecules that are potent modulators of the Cereblon E3 ligase complex and work by quickly degrading the proteins Ikaros and Aiolos. Data from the phase 1 trial for Iberdomide (CC-220) revealed that the dose ranged from 0.3 to 1.2 mg; however, the maximum tolerated dose (MTD) was not reached. Grade 3–4 adverse events were reported in 72% patients and included neutropenia, thrombocytopenia, neuropathy, and fatigue (in 26%, 11%, 2%, and 0% patients, respectively). This study is ongoing, including combinations with daratumumab and bortezomib.[83] Recently, the phase 1 data from a trial evaluating CC-92480 confirmed the maximum tolerated dose of 1 mg for 21 or 28 days, and a 55% ORR in a group of patients where 90% were refractory to lenalidomide and pomalidomide and had a median of six lines of therapy. Grade 3–4 adverse events were reported in 88% of patients and included neutropenia (53%), infections (30%), anemia (29%), and thrombocytopenia (17%), with 9% having grade 3 fatigue.[84]

BCL-2 Inhibitor

The BCL-2 inhibitor, venetoclax, has also been investigated in MM. The phase 3 BELLINI trial investigated venetoclax in combination with bortezomib and dexamethasone in patients who had received one to three prior lines of therapy.[85] The addition of venetoclax showed a significantly longer mPFS of 23.2 months compared with 11.4 months with placebo. However, this resulted in a decrease in OS, with the venetoclax arm having a mOS of 33.5 versus not reached with the placebo. Subset analysis found that most of the response came from the t(11:14) patients, and those patients had improved OS compared with the non-t(11:14) patients treated with venetoclax. There is now an ongoing phase 3 trial looking at just the t(11:14) subset of patients comparing venetoclax with pomalidomide in combination with dexamethasone (NCT03539744).

Melflufen

Melflufen is a peptide drug conjugate between an alkylating agent and a lipophilic peptide. When the drug enters myeloma cells, the peptide is cleaved, which traps the hydrophilic alkylating agent within the cell.[86]

The HORIZON study looked at patients who were refractory to pomalidomide or anti-CD38 and had received two or more lines of therapy and found that patients who received melflufen and dexamethasone had an ORR of 29%, with a mPFS of 4.2 months and mOS of 11.6 months.[87] The phase 3 OCEAN trial is ongoing (NCT03151811).

Kinesin-Spindle Protein

Kinesin-spindle protein (KSP) is a protein involved in the separation of the centrosome during cell division. A KSP inhibitor, filanesib is being evaluated as a single agent or in combination with other medications such as bortezomib. In a phase 1 trial investigating filanesib, carfilzomib, and dexamethasone in patients with a median of five prior lines of therapy, the ORR was 37%.[88]

Monoclonal Gammopathy of Undetermined Significance

The 2014 IMWG guidelines define MGUS as a serum M-protein less than 3 g/dL, less than 10% clonal marrow plasma cells, and absence of end-organ damage (CRAB criteria and myeloma-defining events; see Table 16–1) attributed to an underlying plasma cell proliferative disorder. The 2014 standard of care for MGUS is surveillance every 6 to 12 months with a physical examination and typical MM serum and urine studies. Patients with MGUS can also be risk stratified for progression to MM according to established models, with some arguing for only history and physical examination in low-risk MGUS (IgG subtype, M-protein <1.5g/dL, normal serum-free light-chain ratio) because risk of progression at 20 years is only 5% in this group (Table 16–4).[89]

Table 16–4 Risk Stratification Models for MGUS and SMM

MGUS			
Mayo Clinic[100]	**No. of Risk Factors**	**No. of Patients**	**20-Year Progression (%)**
Risk factors: 1) M-protein >1.5 g/dL 2) Non-IgG MGUS 3) FLC ratio <0.26 or >1.65	0 1 2 3 **Total**	449 420 226 53 **1148**	5% 21% 37% 58% **20%**
PETHEMA[101]			**5-year progression (%)**
Risk factors 1. ≥95% abnormal PCs by bone marrow flow cytometry 2. DNA aneuploidy	0 1 2 **Total**	127 133 16 **276**	2% 10% 46% **8.5%**
SMM			
Mayo Clinic[102]	**No. of Risk Factors**	**No. of Patients**	**5-Year Progression (%)**
Risk factors: 1. Bone marrow plasma cells ≥10% 2. M-protein ≥3g/dL 3. FLC ratio <0.125 or >8	1 2 3 **Total**	76 115 82 **273**	25% 51% 76% **51%**
PETHEMA[101]			
Risk factors: 1. ≥95% abnormal PC 2. Immunoparesis	0 1 2 **Total**	28 22 39 **89**	4% 46% 72% **46%**
SWOG[103]			**2-Year Progression (%)**
Risk factors: 1. GEP70 score >–0.26[104] 2. M-protein >3 g/dL 3. Involved serum FLC >25 mg/dL	0 1 ≥2 **Total**	33 29 17 **79**	3% 29.1% 70.6% **34.2%**

FLC, free light chain; GEP70, gene expression profiling 70; IgG, immunoglobulin G; immunoparesis, decreased in uninvolved immunoglobulins below the lower limit of normal; MGUS, monoclonal gammopathy of undetermined significance; PC, plasma cells; PETHEMA, Program para el Tratamiento de Hemopatias Malignas; SMM, smoldering multiple myeloma; SWOG, Southwest Oncology Group.

Smoldering Multiple Myeloma

Smoldering MM is defined as having a serum M-protein of at least 3.0 g/dL and/or at least 10% more marrow plasma cells without evidence of end-organ damage as defined by CRAB criteria and MM-defining events (see Table 16–1). Compared with MGUS, this premalignant clonal plasma cell proliferation carries a higher risk of progression to overt MM. In a large retrospective study of 276 patients with SMM followed over 26 years, the risk of progression to MM was 10% per year for the first 5 years, 3% per year for the next 5 years, and 1% per year for the last 10 years.

There is great heterogeneity in the SMM disease course. Some patients may remain asymptomatic for the rest of their lives, whereas others may rapidly develop disease that meets MM criteria. Efforts have been made to risk stratify SMM to help predict the clinical course, guide surveillance strategies, and design trials for early intervention. The Mayo 2008 risk stratification model found that patients with both clonal bone marrow plasmacytosis of at least 10% and serum M-protein at least 3 g/dL had an 87% chance of MM progression at 15 years compared with 70% with only 10% or more marrow plasma cells (but monoclonal protein of <3 g/dL) and 39% with only monoclonal protein of at least 3 g/dL (but <10% bone marrow plasma cells).[90] The model was later revised in the Mayo 2018 risk stratification, where they found that bone marrow plasma cells higher than 20%, M-protein more than 2 g/dL, and free light-chain ratio more than 20 where independent predictors of progression.[91] Patients with no risk factor had a time to progression of 110 months compared with 68 months if patients had one risk factor, and 29 months with two or more risk factors. A number of other factors have been shown to increase the risk of progression such as high-risk cytogenetics (del 17p, t(4;14), amplification of 1q21), ≥95% aberrant marrow plasma cells by flow cytometry, IgA M-protein, immunoparesis of uninvolved immunoglobulins, circulating plasma cells by slide-based immunofluorescence, and proteinuria.[92]

The benefits of preemptive treatment of high-risk SMM are still unclear. Until this is further clarified, treatment of high-risk SMM should be undertaken preferentially through clinical trials. A phase 3 trial from the Spanish myeloma group comparing lenalidomide and dexamethasone versus observation in high-risk patients found an improvement in median PFS in the treatment arm (median PFS, not reached vs 26 months) and a significant 3-year OS benefit (94% vs 80%, $P = .03$).[93] However, the excessive mortality rate in the observation arm for patients with SMM has raised concerns that some of these patients should have been classified as having symptomatic myeloma given that advanced imaging was not used to detect bone metastasis. A recent phase 3 trial addressed this issue by using modern imaging techniques and found that the 3-year PFS was 91% for the lenalidomide group compared with 66% in the observation group.[94] The benefit was found in all risk groups, though it was more pronounced in the Mayo 2018 high-risk group with a HR of 0.09. No OS benefit has been shown yet and 51% of the patients on the lenalidomide arm came off trial with a median of 11 cycles of treatment; 15.6% of these patients came off as a result of disease progression.

At MDACC, we recommend that patients with high-risk SMM be enrolled in a clinical trial. In the absence of clear data, we would otherwise recommend observation and close surveillance in these patients, although this practice may change soon as we gather data from relevant trials focused on high-risk SMM.

Solitary Plasmacytoma of Bone

A solitary plasmacytoma of bone is defined by the presence of a plasmacytoma without bone marrow evidence of monoclonal plasma cells, lytic bony lesions, or other clinically significant sequelae of MM. About 24% to 72% of patients with a solitary plasmacytoma have a monoclonal protein in the serum or urine. Initial workup should include all of the aforementioned serum and urine laboratory studies used in evaluation of MM, as well as advanced imaging with PET-CT or MRI to rule out multifocal disease that would upstage the disease to MM. Biopsy of the solitary plasmacytoma to demonstrate clonal plasma cells and a unilateral bone marrow biopsy to rule out systemic disease are necessary. Treatment should include radiation therapy of at least 40 Gy, although one may consider a dose of up to 50 Gy for lesions greater than 5 cm. After radiation therapy, surveillance should be performed with serial measurements of serum and urine M-protein levels and imaging studies, initially done every three months and then less frequently. Patients who progress to overt MM during surveillance should follow the treatment guidelines for MM.

Patients with solitary plasmacytoma of bone often progress to MM within 2 to 4 years, with a median OS of 7.5 to 12 years. In one study, persistence of a serum M-protein one year after radiation therapy was an adverse prognostic factor predicting a 10-year myeloma-free survival of 29% compared with 91% with undetectable M-protein. Another study found that an abnormal free light-chain ratio and a serum M-protein greater than 0.5 g/dL were significant adverse factors for disease progression at 5 years.

POEMS Syndrome

POEMS syndrome, also known as osteosclerotic myeloma, is a paraneoplastic syndrome related to an underlying clonal plasma cell disorder. The major

diagnostic criteria are polyneuropathy, monoclonal gammopathy, sclerotic bone lesions, elevated vascular endothelial growth factor (VEGF), and Castleman disease. Minor features include organomegaly, endocrinopathy, characteristic skin changes, papilledema, extravascular volume overload, and thrombocytosis. The diagnosis of POEMS syndrome is made with three of the major criteria, two of which must include polyneuropathy and a clonal plasma cell neoplasm, and at least one of the minor criteria (Table 16–5).[95] Patients may have delays in diagnosis because it is rare and resembles other neurologic diseases, most commonly chronic inflammatory demyelinating polyradiculoneuropathy. The natural history of POEMS syndrome is defined by progressive polyneuropathy and sclerotic bone disease, which leads to significant morbidity, along with mortality if respiratory compromise occurs. POEMS syndrome should be distinguished from the Castleman disease variant of POEMS syndrome, which has no clonal plasma cell association and usually no peripheral neuropathy.

The pathogenesis of this syndrome is not known. Risk stratification is based solely on the clinical phenotype. The extent of plasma cell clonal disease correlates with prognosis in POEMS, but the number of clinical criteria does not. Treatment is aimed at eradicating the underlying plasma cell clone and control of symptoms. With one to three sclerotic plasmacytomas (usually <1 cm in diameter each) without marrow infiltration, localized radiation therapy may suffice. For patients with a dominant sclerotic bone lesion, frontline radiation therapy may be appropriate. Patients with diffuse sclerotic lesions, disseminated marrow involvement, or relapsed disease within 6 months of completing radiation therapy should receive systemic therapy adapted largely from therapy for MM. Alkylators such as melphalan are the mainstay of treatment; lenalidomide has shown promise with manageable toxicity.[96,97] Therapies based on CHOP also show responses. Thalidomide and bortezomib have activity but could exacerbate disease-related peripheral neuropathy. Benefit from anti-VEGF antibodies is unproven.[96]

High-dose melphalan and autologous SCT can lead to prolonged remission and significant improvement in clinical symptoms. Sixteen patients with POEMS syndrome underwent autologous SCT at MDACC[99,100]; all had significant or complete resolution of clinical symptoms, and 4-year PFS and OS rates for the entire cohort were 80.2% and 100%, respectively. Ten-year PFS and OS rates were 59.4% and 80%, respectively. Prompt recognition and institution of supportive care measures and therapy directed against the plasma cell clone result in the best outcomes.

Table 16–5 Diagnostic Criteria for POEMS Syndrome

Major criteria	**Polyneuropathy** **Monoclonal plasma cell disorder** Sclerotic bone lesion Castleman disease VEGF elevation
Minor criteria	Organomegaly Extravascular volume overload Endocrinopathy Skin changes Papilledema Thrombocytosis/polycythemia
Other	Pulmonary hypertension Clubbing Weight loss Hyperhidrosis Thrombosis Low vitamin B_{12} level

Diagnosis of POEMS syndrome is made with three of the major criteria, two of which must include polyneuropathy and a clonal plasma cell neoplasm, and at least one of the minor criteria.
VEGF, vascular endothelial growth factor.

FUTURE DIRECTIONS

The last decade has seen unprecedented advances in the treatment of plasma cell dyscrasias. The advent of novel agents, notably proteasome inhibitors, IMiDs, and monoclonal antibodies have resulted in a doubling of the life expectancy in patients with MM. Many challenges remain. For example, MM is still considered mostly an incurable disease, and a subgroup of patients with high-risk MM have not benefited as substantially from recent therapeutic advances. Promising investigational agents including immunotherapeutic approaches and rational combinations to overcome resistance are being tested.

Future work involves identifying predictive biomarkers to help individualize therapy in MM and related plasma cell dyscrasias to help maximize efficacy while balancing treatment toxicity. In high-risk SMM, the role of early preemptive therapy needs to be clarified. Improving our understanding of the molecular pathogenesis of MM and its genetic drivers through molecular profiling and refining current risk stratification models remain our key priorities. Another important question is the role and timing of autologous SCT in the era of novel agents. Finally, as new drug combinations induce deeper responses in the frontline setting, significance of achieving molecular remissions is an area of intense research focus. Bridging these knowledge gaps will improve on the advances achieved over the last decade and offer greater individualized treatment approaches, leading to possible cure of MM and its related disorders.

MD ANDERSON PRACTICE TIPS

- Patients suspected to have MM, and all smoldering myeloma patients should receive advanced imaging, such as whole-body low-dose CT, PET-CT, or MRI to evaluate for asymptomatic bone disease.
- Transplant-eligible patients should receive a three-drug combination up front, comprised of a proteasome inhibitor, immunomodulatory drug, and steroids.
- Patients should receive autologous SCT after induction chemotherapy. The treatment regimen is melphalan, but high-risk patients receive busulfan/melphalan.
- Patients should be placed on maintenance after autologous SCT with either single-agent lenalidomide or bortezomib. High-risk patients should be placed on doublet maintenance.
- Proteasome inhibitors, immunomodulatory drugs, and CD38 monoclonal antibodies represent drugs used in up-front and early relapse therapies.
- Supportive therapies such as shingles prophylaxis (monoclonal antibodies and PIs), appropriate anticoagulation for DVT prevention (IMiDs and steroids), bisphosphonate therapy for bone strengthening, and bacterial prophylaxis for frail patients are imperative.

REFERENCES

1. Broderick P, Chubb D, Johnson DC, et al. Common variation at 3p22.1 and 7p15.3 influences multiple myeloma risk. *Nat Genet.* 2011;44(1):58-61.
2. Chubb D, Weinhold N, Broderick P, et al. Common variation at 3q26.2, 6p21.33, 17p11.2 and 22q13.1 influences multiple myeloma risk. *Nat Genet.* 2013;45(10):1221-1225.
3. Morgan GJ, Johnson DC, Weinhold N, et al. Inherited genetic susceptibility to multiple myeloma. *Leukemia.* 2014;28(3):518-524.
4. Chapman MA, Lawrence MS, Keats JJ, et al. Initial genome sequencing and analysis of multiple myeloma. *Nature.* 2011;471(7339):467-472.
5. Keats JJ, Chesi M, Egan JB, et al. Clonal competition with alternating dominance in multiple myeloma. *Blood.* 2012;120(5):1067-1076.
6. Melchor L, Brioli A, Wardell CP, et al. Single-cell genetic analysis reveals the composition of initiating clones and phylogenetic patterns of branching and parallel evolution in myeloma. *Leukemia.* 2014;28(8):1705-1715.
7. Kaiser MF, Johnson DC, Wu P, et al. Global methylation analysis identifies prognostically important epigenetically inactivated tumor suppressor genes in multiple myeloma. *Blood.* 2013;122(2):219-226.
8. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027;78(1):21-33.
9. Hillengass J, Usmani S, Rajkumar SV, et al. International myeloma working group consensus recommendations on imaging in monoclonal plasma cell disorders. *Lancet Oncol.* 2019;20(6):e302-e312.
10. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol.* 2014;15(12):e538-e548.
11. Paiva B, Gutiérrez NC, Rosinol L, et al. High-risk cytogenetics and persistent minimal residual disease by multiparameter flow cytometry predict unsustained complete response after autologous stem cell transplantation in multiple myeloma. *Blood.* 2012;119(3):687-691.
12. Martínez-López J, Lahuerta JJ, Pepin F, et al. Prognostic value of deep sequencing method for minimal residual disease detection in multiple myeloma. *Blood.* 2014;123(20):3073-3079.
13. Zonder JA, Crowley J, Hussein MA, et al. Lenalidomide and high-dose dexamethasone compared with dexamethasone as initial therapy for multiple myeloma: a randomized Southwest Oncology Group trial (S0232;116(26):5838-5841.
14. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. *Lancet Oncol.* 2010;11(1):29-37.
15. Harousseau J-L, Attal M, Avet-Loiseau H, et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. *J Clin Oncol.* 2010;28(30):4621-4629.
16. Moreau P, Pylypenko H, Grosicki S, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. *Lancet Oncol.* 2011;12(5):431-440.
17. Kumar S, Flinn I, Richardson PG, et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. *Blood.* 2012;119(19):4375-4382.
18. Reeder CB, Reece DE, Kukreti V, et al. Once- versus twice-weekly bortezomib induction therapy with CyBorD in newly diagnosed multiple myeloma. *Blood.* 2010;115(16):3416-3417.
19. Durie BGM, Hoering A, Sexton R, et al. Longer term follow-up of the randomized phase III trial SWOG S0777: bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT). *Blood Cancer J.* 2020;10(5):53-11.
20. Kumar S, Jacobus SJ, Cohen AD, et al. Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomised, controlled trial. *Lancet Oncol.* 2020;21(10):1317-1330.
21. Voorhees PM, Kaufman JL, Laubach J, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. *Blood* 2020;136(8):936–945.
22. Usmani SZ, Ailawadhi S, Sexton R, et al. Bortezomib, lenalidomide, and dexamethasone with or without elotuzumab in patients with untreated, high-risk multiple myeloma (SWOG-1211): primary analysis of a randomised, phase 2 trial. *Lancet Haematol.* 2021;8(1):e45-e54.
23. Palumbo A, Bringhen S, Caravita T, et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. *Lancet.* 2006;367(9513):825-831.
24. Palumbo A, Hajek R, Delforge M, et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. *N Engl J Med.* 2012;366(19):1759-1769.
25. Hulin C, Facon T, Rodon P, et al. Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. *J Clin Oncol.* 2009;27(22):3664-3670.
26. San-Miguel JF, Schlag R, Khuageva NK, et al. Persistent overall survival benefit and no increased risk of second malignancies with bortezomib-melphalan-prednisone versus melphalan-prednisone in patients with previously untreated multiple myeloma. *J Clin Oncol.* 2013;31(4):448-455.
27. Mateos M-V, Cavo M, Bladé J, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. *Lancet.* 2020;395(10218):132-141.
28. Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. *N Engl J Med.* 2014;371(10):906-917.
29. Niesvizky R, Flinn IW, Rifkin R, et al. Efficacy and safety of three bortezomib-based combinations in elderly, newly diagnosed multiple myeloma patients: results from all randomized patients in the community-based, phase 3b UPFRONT study. *Blood.* 2011;118(21):478-478.
30. O'Donnell EK, Laubach JP, Yee AJ, et al. A phase 2 study of modified lenalidomide, bortezomib and dexamethasone in transplant-ineligible multiple myeloma. *Br J Haematol.* 2018;182(2):222-230.
31. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Français du Myélome. *N Engl J Med.* 1996;335(2):91-97.
32. Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med.* 2003;348(19):1875-1883.
33. Barlogie B, Kyle RA, Anderson KC, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple

myeloma: final results of phase III US Intergroup Trial S9321. *J Clin Oncol.* 2006;24(6):929-936.
34. Bladé J, Rosinol L, Sureda A, et al. High-dose therapy intensification compared with continued standard chemotherapy in multiple myeloma patients responding to the initial chemotherapy: long-term results from a prospective randomized trial from the Spanish cooperative group PETHEMA. *Blood.* 2005;106(12):3755-3759.
35. Fermand J-P, Katsahian S, Divine M, et al. High-dose therapy and autologous blood stem-cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: long-term results of a randomized control trial from the Group Myelome-Autogreffe. *J Clin Oncol.* 2005;23(36):9227-9233.
36. Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. *N Engl J Med.* 2017;376(14):1311-1320.
37. Moreau P, Facon T, Attal M, et al. Comparison of 200 mg/m(2) melphalan and 8 Gy total body irradiation plus 140 mg/m(2) melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myélome 9502 randomized trial. *Blood.* 2002;99(3):731-735.
38. Bashir Q, Thall PF, Milton DR, et al. Conditioning with busulfan plus melphalan versus melphalan alone before autologous haemopoietic cell transplantation for multiple myeloma: an open-label, randomised, phase 3 trial. *Lancet Haematol.* 2019;6(5):e266-e275.
39. Pandya C, Hashmi S, Khera N, et al. Cost-effectiveness analysis of early vs. late autologous stem cell transplantation in multiple myeloma. *Clin Transplant.* 2014;28(10):1084-1091.
40. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med.* 2012;366(19):1770-1781.
41. Holstein SA, Jung S-H, Richardson PG, et al. Updated analysis of CALGB (Alliance) 100104 assessing lenalidomide versus placebo maintenance after single autologous stem-cell transplantation for multiple myeloma: a randomised, double-blind, phase 3 trial. *Lancet Haematol.* 2017;4(9):e431-e442.
42. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med.* 2012;366(19):1782-1791.
43. Amsler IG, Jeker B, Mansouri Taleghani B, et al. Prolonged survival with increasing duration of lenalidomide maintenance after autologous transplant for multiple myeloma. *Leuk Lymphoma.* 2019;60(2):511-514.
44. Thomas A, Mailankody S, Korde N, et al. Second malignancies after multiple myeloma: from 1960s to 2010s. *Blood.* 2012;119(12):2731-2737.
45. Palumbo A, Bringhen S, Kumar SK, et al. Second primary malignancies with lenalidomide therapy for newly diagnosed myeloma: a meta-analysis of individual patient data. *Lancet Oncol.* 2014;15(3):333-342.
46. Sonneveld P, Schmidt-Wolf IGH, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. *J Clin Oncol.* 2012;30(24):2946-2955.
47. Dimopoulos MA, Gay F, Schjesvold F, et al. Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial. *Lancet.* 2019;393(10168):253-264.
48. Joseph NS, Kaufman JL, Dhodapkar MV, et al. Long-term follow-up results of lenalidomide, bortezomib, and dexamethasone induction therapy and risk-adapted maintenance approach in newly diagnosed multiple myeloma. *J Clin Oncol.* 2020;38(17):1928-1937.
49. Zimmerman TM, Griffith KA, Jasielec J, et al. Phase II MMRC trial of extended treatment with carfilzomib (CFZ), lenalidomide (LEN), and dexamethasone (DEX) plus autologous stem cell transplantation (ASCT) in newly diagnosed multiple myeloma (NDMM). *J Clin Oncol.* 2015;33(suppl 15):8510-8510.
50. Miguel JS, Weisel K, Moreau P, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2013;14(11):1055-1066.
51. Orlowski RZ, Nagler A, Sonneveld P, et al. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. *J Clin Oncol.* 2007;25(25):3892-3901.
52. Richardson PG, Xie W, Jagannath S, et al. A phase 2 trial of lenalidomide, bortezomib, and dexamethasone in patients with relapsed and relapsed/refractory myeloma. *Blood.* 2014;123(10):1461-1469.
53. Siegel DS, Martin T, Wang M, et al. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. *Blood.* 2012;120(14):2817-2825.
54. Dimopoulos MA, Goldschmidt H, Niesvizky R, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. *Lancet Oncol.* 2017;18(10):1327-1337.
55. Siegel DS, Dimopoulos MA, Ludwig H, et al. Improvement in overall survival with carfilzomib, lenalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma. *J Clin Oncol.* 2018;36(8):728-734.
56. Shah JJ, Stadtmauer EA, Abonour R, et al. A multi-center phase I/II trial of carfilzomib and pomalidomide with dexamethasone (Car-Pom-d) in patients with relapsed/refractory multiple myeloma. *Blood.* 2012;120(21):74-74.
57. Sonneveld P, Zweegman S, Cavo M, et al. Carfilzomib, pomalidomide and dexamethasone (KPd) in patients with multiple myeloma refractory to bortezomib and lenalidomide. The EMN011 Trial. *Blood.* 2018;132(suppl 1):801.
58. Lendvai N, Hilden P, Devlin S, et al. A phase 2 single-center study of carfilzomib 56 mg/m2 with or without low-dose dexamethasone in relapsed multiple myeloma. *Blood.* 2014;124(6):899-906.
59. Ailawadhi S, Sexton R, Lentzsch S, et al. Low-dose versus high-dose carfilzomib with dexamethasone (S1304) in patients with relapsed-refractory multiple myeloma. *Clin Cancer Res.* 2020;26(15):3969-3978.
60. Moreau P, Stewart KA, Dimopoulos M, et al. Once-weekly (70 mg/m2) vs twice-weekly (56 mg/m2) dosing of carfilzomib in patients with relapsed or refractory multiple myeloma: A post hoc analysis of the ENDEAVOR, A.R.R.O.W., and CHAMPION-1 trials. *Cancer Med.* 2020;9(9):2989-2996.
61. Bahlis NJ, Dimopoulos MA, White DJ, et al. Daratumumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: extended follow-up of POLLUX, a randomized, open-label, phase 3 study. *Leukemia.* 2020;28(suppl_4):iv52–10.
62. Chari A, Suvannasankha A, Fay JW, et al. Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. *Blood.* 2017;130(8):974-981.
63. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N Engl J Med.* 2016;375(8):754-766.
64. Dimopoulos M, Quach H, Mateos M-V, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple

myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study. *Lancet.* 2020;396(10245):186-197.
65. Usmani SZ, Nahi H, Mateos M-V, et al. Subcutaneous delivery of daratumumab in relapsed or refractory multiple myeloma. *Blood.* 2019;134(8):668-677.
66. Attal M, Richardson PG, Rajkumar SV, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. *Lancet.* 2019;394(10214):2096-2107.
67. Zonder JA, Mohrbacher AF, Singhal S, et al. A phase 1, multicenter, open-label, dose escalation study of elotuzumab in patients with advanced multiple myeloma. *Blood.* 2012;120(3):552-559.
68. Dimopoulos MA, Lonial S, Betts KA, et al. Elotuzumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: extended 4-year follow-up and analysis of relative progression-free survival from the randomized ELOQUENT-2 trial. *Cancer.* 2018;124(20):4032-4043.
69. Dimopoulos MA, Weisel K, Lonial S, et al. Elotuzumab plus lenalidomide/dexamethasone for relapsed/refractory multiple myeloma: final overall survival results from the phase 3 ELOQUENT-2 trial. *Clin Lymphoma Myeloma Leuk.* 2019;19(10):e15-e16.
70. Dimopoulos MA, Dytfeld D, Grosicki S, et al. Elotuzumab plus pomalidomide and dexamethasone for multiple myeloma. *N Engl J Med.* 2018;379(19):1811-1822.
71. Gandhi UH, Senapedis W, Baloglu E, et al. Clinical implications of targeting XPO1-mediated nuclear export in multiple myeloma. *Clin Lymphoma Myeloma Leuk.* 2018;18(5):335-345.
72. Chari A, Vogl DT, Gavriatopoulou M, et al. Oral selinexor-dexamethasone for triple-class refractory multiple myeloma. *N Engl J Med.* 2019;381(8):727-738.
73. Lonial S, Lee HC, Badros A, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. *Lancet Oncol.* 2020;21(2):207-221.
74. San-Miguel JF, Yoon S-S, Beksac M, et al. Overall survival of patients with relapsed multiple myeloma treated with panobinostat or placebo plus bortezomib and dexamethasone (the PANORAMA 1 trial): a randomised, placebo-controlled, phase 3 trial. *Lancet Haematol.* 2016;3(11):e506-e515.
75. Dimopoulos M, Siegel DS, Lonial S, et al. Vorinostat or placebo in combination with bortezomib in patients with multiple myeloma (VANTAGE 088): a multicentre, randomised, double-blind study. *Lancet Oncol.* 2013;14(11):1129-1140.
76. Munshi NC, Anderson LD Jr, Shah N, et al. Idecabtagene vicleucel (ide-cel; bb2121), a BCMA-targeted CAR T-cell therapy, in patients with relapsed and refractory multiple myeloma (RRMM): initial KarMMa results. *J Clin Oncol.* 2020;38(suppl 15):8503-8503.
77. Mailankody S, Jakubowiak AJ, Htut M, et al. Orvacabtagene autoleucel (orva-cel), a B-cell maturation antigen (BCMA)-directed CAR T cell therapy for patients (pts) with relapsed/refractory multiple myeloma (RRMM): update of the phase 1/2 EVOLVE study (NCT03430011). *J Clin Oncol.* 2020;38(suppl 15):8504-8504.
78. Berdeja JG, Madduri D, Usmani SZ, et al. Update of CARTITUDE-1: A phase Ib/II study of JNJ-4528, a B-cell maturation antigen (BCMA)-directed CAR-T-cell therapy, in relapsed/refractory multiple myeloma. *J Clin Oncol.* 2020;38(suppl 15):8505-8505.
79. Martínez-Cingolani C, Bories JC. Development of chimeric antigen receptors for multiple myeloma. *Biochem Soc Trans.* 2016;44(2):397-405.
80. Pont MJ, Hill T, Cole GO, et al. γ-Secretase inhibition increases efficacy of BCMA-specific chimeric antigen receptor T cells in multiple myeloma. *Blood.* 2019;134(19):1585-1597.
81. Fernández de Larrea C, Staehr M, Lopez AV, et al. Defining an optimal dual-targeted CAR T-cell therapy approach simultaneously targeting BCMA and GPRC5D to prevent BCMA escape–driven relapse in multiple myeloma. *Blood Cancer Discov.* 2020;1(2):146-154.
82. Topp MS, Duell J, Zugmaier G, et al. Anti–B-cell maturation antigen BiTE molecule AMG 420 induces responses in multiple myeloma. *J Clin Oncol.* 2020;38(8):775-783.
83. Lonial S, van de Donk NWCJ, Popat R, et al. First clinical (phase 1b/2a) study of iberdomide (CC-220; IBER), a CELMoD, in combination with dexamethasone (DEX) in patients (pts) with relapsed/refractory multiple myeloma (RRMM). *J Clin Oncol.* 2019;37(suppl 15):8006.
84. Richardson PG, Vangsted AJ, Ramasamy K, et al. First-in-human phase I study of the novel CELMoD agent CC-92480 combined with dexamethasone (DEX) in patients (pts) with relapsed/refractory multiple myeloma (RRMM). *J Clin Oncol.* 2020;38(suppl 15):8500.
85. Kumar S, Harrison SJ, Cavo M, et al. Updated results from BELLINI, a phase III study of venetoclax or placebo in combination with bortezomib and dexamethasone in relapsed/refractory multiple myeloma. *J Clin Oncol.* 2020;38(suppl 15):8509.
86. Wickström M, Nygren P, Larsson R, et al. Melflufen - a peptidase-potentiated alkylating agent in clinical trials. *Oncotarget.* 2017;8(39):66641-66655.
87. Mateos M-V, Oriol A, Larocca A, et al. Clinical activity of melflufen in patients with triple-class refractory multiple myeloma and poor-risk features in an updated analysis of HORIZON (OP-106), a phase 2 study in patients with relapsed/refractory multiple myeloma refractory to pomalidomide and/or daratumumab. *Blood.* 2019;134(suppl 1):1883.
88. Lee HC, Shah JJ, Feng L, et al. A phase 1 study of filanesib, carfilzomib, and dexamethasone in patients with relapsed and/or refractory multiple myeloma. *Blood Cancer J.* 2019;9(10):1-5.
89. Go RS, Rajkumar SV. How I manage monoclonal gammopathy of undetermined significance. *Blood.* 2018;131(2):163-173.
90. Kyle RA, Remstein ED, Therneau TM, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. *N Engl J Med.* 2007;356(25):2582-2590.
91. Lakshman A, Rajkumar SV, Buadi FK, et al. Risk stratification of smoldering multiple myeloma incorporating revised IMWG diagnostic criteria. *Blood Cancer J.* 2018;8(6):59-10.
92. Dispenzieri A, Stewart AK, Chanan-Khan A, et al. Smoldering multiple myeloma requiring treatment: time for a new definition? *Blood.* 2013;122(26):4172-4181.
93. Mateos M-V, Hernández MT, Giraldo P, et al. Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. *N Engl J Med.* 2013;369(5):438-447.
94. Lonial S, Jacobus S, Fonseca R, et al. Randomized trial of lenalidomide versus observation in smoldering multiple myeloma. *J Clin Oncol.* 2020;38(11):1126-1137.
95. Dispenzieri A. POEMS syndrome: 2017 Update on diagnosis, risk stratification, and management. *Am J Hematol.* 2017;92(8):814-829.
96. Dispenzieri A, Klein CJ, Mauermann ML. Lenalidomide therapy in a patient with POEMS syndrome. *Blood.* 2007;110(3):1075-1076.
97. Jaccard A, Abraham J, Recher C, et al. Lenalidomide therapy in nine patients with POEMS syndrome. *Blood.* 2009;114(22):3872-3872.
98. Sekiguchi Y, Misawa S, Shibuya K, et al. Ambiguous effects of anti-VEGF monoclonal antibody (bevacizumab) for POEMS syndrome. *J Neurol Neurosurg Psychiatry.* 2013;84(12):1346-1348.

99. Patel K, Nusrat M, Shah N, et al. Durable responses with autologous hematopoietic SCT in patients with POEMS syndrome. *Bone Marrow Transplant.* 2014;49(3):465-466.
100. Saini NY, Patel RD, Varma A, et al. Long-term durable efficacy of autologous stem cell transplantation in POEMS syndrome. *Am J Hematol*. 2019;94(3):E72-E74.
101. Rajkumar SV, Kyle RA, Therneau TM, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. *Blood*. 2005;106(3):812-817.
102. Perez-Persona E, Vidriales MB, Mateo G, et al. New criteria to identify risk of progression in monoclonal gammopathy of uncertain significance and smoldering multiple myeloma based on multiparameter flow cytometry analysis of bone marrow plasma cells. *Blood*. 2007;110(7):2586-2592.
103. Dispenzieri A, Kyle RA, Katzmann JA, et al. Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. *Blood*. 2008;111(2):785-789.
104. Dhodapkar MV, Sexton R, Waheed S, et al. Clinical, genomic, and imaging predictors of myeloma progression from asymptomatic monoclonal gammopathies (SWOG S0120). *Blood*. 2014;123(1):78-85.
105. Zhan F, Huang Y, Colla S, et al. The molecular classification of multiple myeloma. *Blood*. 2006;108(6):2020-2028.

17 Cellular Therapy for Lymphoma

Sairah Ahmed
Simrit Parmar
Sattva Neelapu

KEY CONCEPTS

- Adoptive cellular immunotherapy with chimeric antigen receptor (CAR) T-cell therapy has changed the treatment landscape of B-cell non-Hodgkin lymphoma (NHL), especially for aggressive B-cell lymphomas.
- CAR T-cell therapy is FDA approved for poor-risk diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL) when no other effective treatment options are available, and it has shown long-term remissions in up to 40% of patients without other treatment options.
- CAR T-cell–related toxicities remain important potential complications of this therapy, which includes acute toxicity with cytokine-release syndrome and neurotoxicity, as well as long-term complications such as infection and cytopenias.
- Relapse after CAR T-cell therapy remains a significant challenge and, although the exact mechanisms causing tumor escape remain unknown, relapse after CAR T-cell therapy that targets the CD19 antigen can be categorized broadly as (1) antigen loss, (2) lack of CAR T-cell persistence, or (3) host-specific factors.
- Real-world analyses highlight that patient response rates and toxicity profiles were similar to the pivotal trials, while being inclusive of patients who would not fit within the highly restrictive parameters of clinical trials.
- Trials are ongoing in multiple lymphoma histologies including T-cell lymphoma and Hodgkin lymphoma, in addition to novel autologous CAR constructs and allogeneic CAR T and natural killer (NK) cells.

For decades, the standard treatment for hematologic malignancies has been systemic chemotherapy, radiation, and stem cell transplantation (SCT). Exploiting the immune system to attack cancer cells is not a novel concept. In fact, the development of allogeneic stem cell transplantation (allo-HCT) first highlighted the potential of T-cells to eliminate cancer cells. As of this writing, immune effector cells, including T-cells and natural killer (NK) cells, which have been genetically engineered to express a chimeric antigen receptor (CAR), constitute a powerful new class of therapeutic agents to treat patients with hematologic malignancies, and have resulted in a paradigm shift in the treatment of relapsed lymphoma in particular. However, this emerging therapy also brings with it a different toxicity profile compared with chemotherapy and challenges in management related to cytokine-release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (Fig. 17–1). Adoptive cell therapy is FDA approved for the treatment of certain non-Hodgkin lymphoma (NHL) types, as well as B-cell acute lymphoblastic leukemia (ALL) and is currently being evaluated in clinical trials for follicular lymphoma (FL), marginal zone lymphoma (MZL), T-cell lymphoma (TCL), and Hodgkin lymphoma (HL). There are more than 750 cellular therapies in development, and approximately half of these are in clinical trials.[1] This chapter will review current paradigms in cellular therapy for lymphoma.

CAR T-CELL DESIGN

The concept of using CAR T-cells to target tumor surface antigens was described in the late 1980s, but first-generation CARs, which included only the receptor component CD3ζ as an intracellular domain, showed limited efficacy.[2] These first-generation designs did

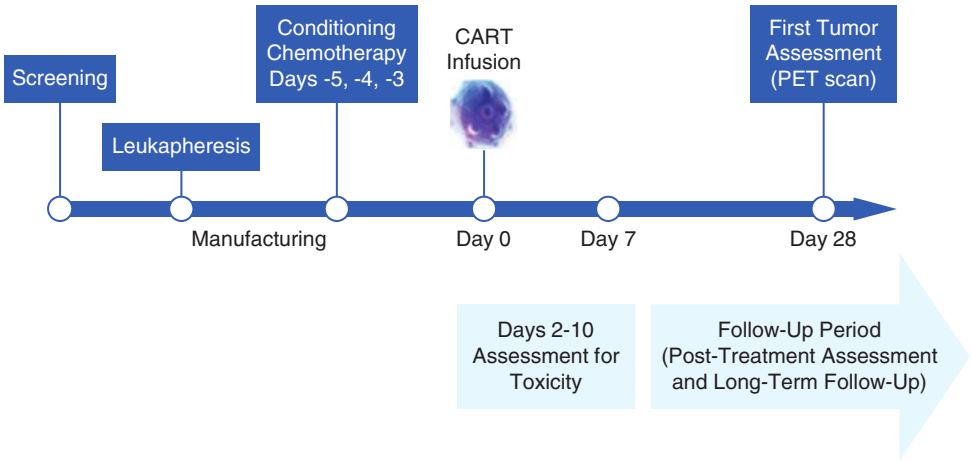


FIGURE 17–1 Graphic representation of CAR T-cell therapy from screening to post-treatment assessment.

not include costimulatory domains and, as such, did not provide a second signal for full T-cell activation; were more prone to apoptosis; and had limited in vivo expansion potential, resulting in poor cytotoxicity.[3]

Significant responses were observed only after researchers went back to the gene construct and added a single costimulatory domain derived from either CD28 or 4-1BB—the so-called "second-generation" CAR T-cells.[4] The addition of costimulatory signaling domains and intracellular signal transduction molecule (CD3ζ, derived from the T-cell receptor) in second-generation CARs led to improvement in T-cell activation, enhanced survival capabilities, and a more selective expansion of modified T-cells in vivo. A viral vector is usually used to deliver the genetic material, which includes the targeting antibody-based single-chain fragment variable region, a hinge and transmembrane domain, a costimulatory domain, and the CD3ζ signaling domain, into the patient's T-cells. These second-generation receptors form the basis of the currently approved CAR T-cell therapies. It is now becoming increasingly clear that each type of costimulatory domain has specific roles in CAR T-cell signaling; for example, CD28-based CAR T-cells exhibit more potent effector cell functions but limited persistence, whereas 4-1BB tends to drive the CAR T-cells toward a central memory phenotype, resulting in improved persistence.[5,6] Third-generation CAR T-cells combine the signaling potential of two costimulatory domains (eg, both CD28 and 4-1BB), with the aim to further improve proliferation, cytokine secretion, and in vivo persistence; and in comparison with the outcomes of second-generation CAR T-cells, they have shown improved effector functions and in vivo persistence in preclinical studies.[7]

The CAR molecule is composed of three key domains: an ectodomain, a transmembrane domain, and an endodomain. The extracellular part redirects the specificity of the receptor to recognize antigens on the cell surface independently of major histocompatibility complex molecules. CD19 has frequently been the target antigen in B-cell lymphoid malignancy because of its frequent and high-level expression in these malignancies, the fact that it has higher expression relative to other potential targets like CD20 or CD22, and its inherent restriction to B-cell lineages in healthy tissue. The transmembrane domain of the CAR construct primarily plays a role in stabilizing the CAR, whereas the intracellular endodomain provides the necessary signals to activate the T-cells after antigen recognition. The intracellular part is based on the structure of the T-cell receptor (TCR) coupled with one or more costimulatory domains, allowing to transduce the antigen recognition into T-cell activation.[8]

The antitumor activity of fourth-generation CAR T-cells are even further enhanced by additional genetic modifications—for example, by the addition of transgenes for cytokine secretion (eg, interleukin [IL]-12).[9–11]

CAR T-CELL MANUFACTURING AND ADMINISTRATION

Most CARs are manufactured from autologous T-cells, collected from the patients via leukapheresis. The process typically involves washing of the apheresis product, T-cell selection, T-cell activation, gene transfer, T-cell expansion, formulation, and cryopreservation. The T-cells are stimulated ex vivo, a viral vector or alternative transfer technology (ie, electroporation) is used to transmit genes containing the CAR to the T-cell, the CAR T-cells are expanded, and a pharmaceutical intravenous cell infusion product is usually administered as a single infusion. The median time from leukapheresis to CAR T-cell administration differs depending on the product and manufacturing process but usually

requires two to five weeks, and the entire process from referral to infusion can take up to two months.[12] Many of the initial clinical trials did not allow bridging therapy; however, in practice many patients require therapy for disease control before infusion of CAR T-cells. The optimal therapeutic regimen for bridging depends on the patient's treatment history and prior toxicities; however, it is important that enough time be allowed between bridging and CAR T-cell infusion—a washout period—to allow recovery from any adverse events. In general, recommended washout times are at least two weeks for systemic chemotherapy, four weeks for pegylated l-asparaginase, and 72 hours for steroids.[13] Bridging therapy can include steroids for symptom control, radiation, chemotherapy, or a combination.

Lymphodepleting (LD) chemotherapy is administered before the infusion of CAR T-cells and most commonly consists of fludarabine and cyclophosphamide. The choice of drug used for LD chemotherapy may impact adoptively transferred T-cell expansion and persistence because LD decreases the number of T-cells in vivo, including regulatory T-cells, and consequently upregulates cytokines such as IL-7 and IL-15, which promote T-cell expansion and enhance the anti-lymphoma activity of the CAR T-cells.[14,15] Patients with B-ALL and B-cell lymphoma who received cyclophosphamide and fludarabine lymphodepletion before CAR T-cell infusion had better in vivo CAR T-cell expansion and persistence, compared with those who received cyclophosphamide alone who had shorter in vivo persistence of CAR T-cells.[16–18] Patients generally receive LD chemotherapy for three days (days –5 to –3), followed two days later by a single infusion of cells on day 0; this can take place outpatient or inpatient based on institutional preference.

CAR T-CELL THERAPY IN AGGRESSIVE B-CELL LYMPHOMA

As of this writing, two CAR T-cell products, tisagenlecleucel (tisa-cel) and axicabtagene ciloleucel (axi-cel), have approval by the FDA for the treatment of certain B-cell NHL types in adults; and a third, lisocabtagene maraleucel (liso-cel), is also submitted to the FDA for approval. Both tisa-cel and axi-cel are commercially available for relapsed or refractory (rel/ref) large B-cell lymphoma in patients who have received at least two prior regimens.

Axi-cel is an anti-CD19 CAR T-cell product generated using a retroviral vector and uses a CD28 costimulatory domain. The pivotal phase 1/2 registration trial, ZUMA-1, enrolled 111 patients with the diagnoses of DLBCL (n = 77), transformed follicular lymphoma (n = 16), and primary mediastinal B-cell lymphoma (n = 8).[19] All patients had chemotherapy-refractory disease, defined as refractory to second-line or subsequent therapy, or relapsed disease within one year after autologous SCT (auto-SCT). Median age was 58 years and the oldest patient treated was 76 years. Eligibility criteria included Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, an absolute lymphocyte count greater than 100 cells/μL, and adequate bone marrow and organ function. Patients with primary or secondary central nervous system (CNS) lymphoma were not eligible, and patients could not have received prior allogeneic SCT. The patient population was heavily pretreated with a median of three prior therapies.[19]

Of 111 patients enrolled, axi-cel was successfully manufactured for 110, and 101 were treated. Median time from leukapheresis to the delivery of the T-cell product to the treating center was 17 days. Per protocol, bridging chemotherapy after apheresis was not allowed. LD chemotherapy consisted of 500 mg/m^2 per day of cyclophosphamide and 30 mg/m^2 per day of fludarabine on days –5 to –3, and the axi-cel dose was 2 × 10^6 CAR T-cells per kilogram of body weight. The best overall response rate (ORR) as determined was 83%, including 58% of patients who achieved complete response (CR). At two years of follow-up, 39% of patients were in ongoing remission. Median progression-free survival (PFS) for the entire population was 5.9 months, median duration of response was 11.1 months, and the two-year rate of overall survival (OS) for the entire population was 50.5%.

The incidence of any grade CRS was 93% occurring at a median of 2 days from CAR T-cell infusion, though only 13% of patients had severe CRS (grade 3–5). Sixty-four percent of patients experienced neurotoxicity with a median time to onset of 5 days, whereas 28% experienced severe neurotoxicity (grade ≥3). This study used the grading criteria by Lee and colleagues for CRS and Common Terminology Criteria for Adverse Events criteria for neurologic toxicity.[19,20] Among all patients, 43% and 27% received tocilizumab and corticosteroids, respectively. Additional toxicities included cytopenias and hypogammaglobulinemia. Four adverse event–related deaths occurred on study, two of which were attributed to axi-cel.

Tisa-cel targets the same CD19 antigen as axi-cel but uses a lentiviral vector and a 4-1BB costimulatory domain.[21] Eligibility for this trial included patients having received at least two prior lines of therapy for DLBCL, transformed follicular lymphoma, or high-grade B-cell lymphoma with rearrangements of MYC and BCL2 or BCL6 (double-/triple-hit lymphoma). As with axi-cel, adequate organ and bone marrow function were required, and patients could not have received prior allo-SCT or have history of CNS disease. LD chemotherapy preceding tisa-cel infusion was most commonly cyclophosphamide (250 mg/

m^2/day) and fludarabine (25 mg/m^2/day) for 3 days, although bendamustine (90 mg/m^2/day) for 2 days was permissible. The dose of tisa-cel was 0.6–6.0 × 10^8 CAR T-cells. One hundred sixty-five patients were enrolled, of whom 111 received tisa-cel infusion. Patients had a median age of 56 years, and the oldest patient was 76 years. Of 70 patients assessed for gene arrangement, 27% had double-/triple-hit lymphoma, and the median number of prior treatments for all patients was three. Approximately one-half of patient had experienced relapse after an auto-SCT. In contrast to ZUMA-1, the majority (92%) of patients received bridging therapy after apheresis, while median time from enrollment to infusion was 54 days. The best ORR was 52%, with 40% of patients achieving CR and at 1 year, approximately one-third of all treated patients were in an ongoing remission including 65% of those who responded to treatment, and 1-year overall survival was 49%.

In contrast to axi-cel, CRS was graded using the University of Pennsylvania scale and observed in 58% of patients, occurring at a median of 3 days after treatment. Twenty-three percent of patients had severe CRS and 21% had neurologic toxicity, of which 12% was categorized as severe. Tocilizumab was administered to 14% of patients, with 10% of patients receiving corticosteroids. No deaths were attributable to CAR T-cell therapy with tisa-cel. As with other anti-CD19 CAR T-cell products, cytopenias were common and could be prolonged. On-target B-cell depletion and hypogammaglobulinemia were observed, with 30% of patients receiving intravenous immunoglobulin at the discretion of the treating physician.[21]

Liso-cel is also a CD19-directed CAR T-cell product using a lentiviral vector and 4-1BB costimulation domain and is currently under review with the FDA for approval for commercial use. Compared with axi-cel and tisa-cel, which are both produced using bulk autologous T-cells, liso-cel manufacturing separately transduces and expands CD4+ and CD8+ CAR T-cells and administers them at a fixed 1:1 ratio that allows for precise dosing to every patient.[22] The TRANSCEND study was designed as a dose-escalation and dose-expansion study followed by a pivotal cohort in relapsed/refractory (R/R) DLBCL. Patients were treated at doses of 5 × 10^7 dose level (DL; DL1) or 1 × 10^8 (DL2) or 1.50 × 10^8 (DL3) CAR T-cells. Eligible patients had DLBCL, double-/triple-hit lymphoma, primary mediastinal B-cell lymphoma (PMBCL), FL grade 3b, and DLBCL transformed from indolent histologies. There was no minimal absolute lymphocyte count required for enrollment, though patients did have to exhibit adequate organ and bone marrow function similar to the other pivotal trials. Patients with both prior allo-HSCT off immune suppression and/or secondary CNS involvement with measurable systemic disease were allowed on trial. Eligibility included a minimum of two prior lines of therapy, and this protocol did allow bridging chemotherapy after apheresis before infusion of cells. LD chemotherapy consisted of 300 mg/m^2 of cyclophosphamide and 30 mg/m^2 of fludarabine for 3 days, followed 2 to 7 days later by liso-cel infusion.

Three hundred forty-four patients received leukapheresis; 269 patients received liso-cel (DL1, n = 51; DL2, n = 177; DL3, n = 41). Twenty-five patients received nonconforming product; product could not be manufactured for two patients. Thirteen percent of patients had double-/triple-hit lymphoma, and median prior lines of therapy was 3, with 67% of patients having chemo-refractory disease. The median age was 63 years and the oldest patient treated was age 86 years. Among patients evaluable for efficacy (n = 256), the best ORR was 73% with a best CR rate of 53%; and at 1 year, 58% of patients remained alive. At 12 months of follow-up, the median duration of response had not been reached, and 44% of patients were in ongoing remission.[12] The median PFS was 6.8 months, and median OS was 21.1 months. As with prior studies, durable responses were observed across all high-risk subsets, including double-/triple-hit lymphoma and chemo-refractory disease.

Toxicity and CRS was graded using the same criteria by Lee et al[20] that was used for axi-cel in Zuma 1; and in this study was 37% and occurred at a median of 5 days, with severe CRS observed only in one patient (1%). The rate of any neurologic toxicity was 23%, with 13% of patients experiencing severe neurologic toxicities. There were no deaths related to CRS or neurologic toxicities in the study. Tocilizumab and corticosteroids were administered to 17% and 21% of patients, respectively. Prolonged grade 3 or higher cytopenia (based on laboratory assessment at day 29) was reported in 37% of patients. The pivotal cohort of this study has completed accrual but has not yet been reported, and this product remains investigational pending FDA approval.

Given the outcomes of the pivotal trials, these three products—axi-cel, tisa-cel, and liso-cel—can all be considered effective treatments for patients with chemo-refractory DLBCL or transformed follicular lymphoma beyond second-line therapy. However, there are distinct differences among the products, which require appropriate treatment selection for a given patient. Axi-cel has proven to have the most rapid vein to vein time from apheresis to infusion, which is important for patients with rapid disease kinetics. Conversely, incidence of CRS and neurotoxicity seems to be higher with axi-cel than with either of the two 4-1BB costimulated products, tisa-cel and liso-cel, likely reflecting differences in the kinetics of T-cell expansion and proliferation conferred by the costimulation domains. Tisa-cel and liso-cel have lower overall rates of CRS

and neurologic toxicity and, overall, a later onset of these toxicities; therefore, centers often choose to administer this treatment in the outpatient setting.[23] Of note, toxicity grading scale selection was not standardized with the pivotal trials. Tocilizumab and steroids were received by 43% and 27% of patients treated with axi-cel and 14% and 10% of patients treated with tisa-cel, respectively, suggesting less toxicity with tisa-cel. Because of anticipated toxicity differences, axi-cel–treated patients received CAR T-cell therapy as an inpatient, whereas 61% of patients received tisa-cel as an outpatient.[24,25]

Two multicenter retrospective analyses evaluated the use of commercial axi-cel after FDA approval.[26,27] In these studies, patients often did not strictly meet the eligibility criteria of the pivotal trial but were treated in accordance with the FDA label. Most commonly, the difference was with the administration of bridging therapy after apheresis; however, patients were also older than those in the pivotal trial, with patients treated up to age 83 years. The study reported by Nastoupil et al included 295 patients, with 274 patients treated. The final CAR T-cell product did not meet FDA specifications in seven patients.

The median time from apheresis to start of LD chemotherapy was 21.5 days; however, the delivery of the product was approximately 15 to 16 days after apheresis. The time to initiation of LD was delayed awaiting count recovery because of bridging therapy, which a majority of patients received; this is in contrast to the ZUMA-1 trial, in which approximately 55% patients received any form of bridging therapy. General characteristics included a median age of 60 years (range, 21–83), stage III/IV in 83%, ECOG performance status (PS) 0–1 in 81%, three or more lines of therapy in 75% of cases, and relapsed post auto-HCT in 33%. Interestingly, 43% of patients (124/286) would not have been eligible for the ZUMA-1 trial per the trial eligibility criteria, yet overall efficacy was similar to the ZUMA-1 trial, with 3-month ORR and CR rates of 81% and 57%, respectively.[26] Jacobson et al reported on 108 patients who received axi-cel; of those, 104 were evaluable for efficacy. The median age was 63.8 years, ECOG PS 0–1 in 90% of cases, prior auto-HCT in 27%, and prior allo-HCT in 3%. About 52% of the evaluable patients received bridging chemotherapy after apheresis; 60% of patients would have not met criteria for the ZUMA-1 clinical trial. In the 95 patients evaluable for response, the best ORR and CR rates were 71% and 44%, respectively. Similarly, about 50% of patients who initially had a PR, achieved CR at a later time.[27] These studies highlight that response rates and toxicity profiles were similar to the pivotal trial while being inclusive of patients who would not fit within the highly restrictive parameters of clinical trials (Table 17–1).

TOXICITY AND SIDE EFFECTS

Distinct from chemotherapy-associated side effects, CAR T-cell–mediated toxicities are unique and potentially life threatening such as CRS and immune effector cell–associated neurotoxicity syndrome (ICANS, previously termed *CAR-T-cell–related encephalopathy syndrome*). Many of these effects are on target and reverse when the CAR T-cell expansion subsides.[28] CRS is caused by cytokine elevations as a result of immune activation of large numbers of lymphocytes, which can manifest as fever, hypotension, and/or hypoxia.[20,29] CRS typically occurs within the first week after CAR T-cell infusion and peak CAR T-cell levels and serum IL-6 levels have strongly correlated with the severity of CRS. Those at highest risk for adverse outcomes from severe CRS include patients with large tumor burdens, comorbidities, or development of early-onset CRS within three days of infusion.[30] Comparisons of CRS severity across CAR T studies is complicated by the use of different grading systems, which before the consensus guidelines, were product specific—ie, the Penn scale (tisa-cel)[31] and the Lee scale (axi-cel).[20] A consensus statement to standardize CRS grading was endorsed by American Society of Transplantation and Cellular Therapy (ASTCT) in 2019, which employs a grading scale using fever, and/or hypoxia, and hypotension (Table 17–2).[32]

Although many cases of CRS may be self-limited and treated with supportive care alone, the mainstay for treatment of severe CRS are tocilizumab and corticosteroids. Tocilizumab is an anti–IL-6 receptor antagonist approved by the FDA in August 2017 to treat CRS when the first CAR T-cell product was approved. It can induce a rapid reversal of CRS and has become the standard of care for this complication.[19,33] Corticosteroids are also effective in the management of toxicities after CAR T-cell therapies because they suppress inflammatory responses. Corticosteroids are often administered if the patient does not have a rapid response to IL-6 receptor blockade, and it can be given in a number of ways including with initial tocilizumab, concurrently with subsequent doses of tocilizumab if there is inadequate response, or as a single agent after tocilizumab. The general principle guiding steroids for treatment of CART toxicity is that they should be prescribed at the lowest effective dose for the shortest possible duration to limit the risk of abrogating CAR T-cell efficacy and persistence. However, as of this writing, the dose and duration of steroids required to irreversibly impair CAR T-cell efficacy is unknown. There are reports that early and prolonged use of high-dose corticosteroids are associated with early progression and death in patients treated with axi-cel.[34]

Table 17–1 Pivotal Trials for Anti-CD19 CAR T-Cell therapy Multicenter Trials in Aggressive B-Cell NHLs

Cell Product	Axi-cel	Tisa-cel	Liso-cel
Trial	ZUMA-1[19]	JULIET[21]	TRANSCEND[22]
Costimulatory and T-cell activation domains	CD28 and CD3ζ	4-1BB and CD3ζ	4-1BB and CD3ζ
Vector	Retrovirus	Lentivirus	Lentivirus
Number of cells infused	2×10^6 CAR T-cells per kg	$0.6–6.0 \times 10^8$ CAR T-cells	5×10^7 or 1×10^8 or 1.5×10^8 CD4:CD8 ratio = 1:1
Median prior LOT	3	3	3
LD regimen	Cy 500 mg/m²/day for 3 days Flu 30 mg/m²/day for 3 days	Cy 250 mg/m²/day for 3 days Flu 25 mg/m²/day for 3 days OR Bendamustine 90 mg/m² IV daily for 2 days	Cy 300 mg/m²/day for 3 days Flu 30 mg/m²/day for 3 days
Number enrolled (infused)	111 (101)	165 (111)	342 (268)
Number response-evaluable	101	93	256
Lymphoma subtypes	DLBCL, TFL, PMBCL	DLBCL, TFL	DLBCL, HGBCL, DLBCL transformed from FL, CLL and MZL, PMBCL and FL3B
Best ORR (CR)	83% (58%)	52% (40%)	73% (53%)
Median DoR	11.1 months after median follow-up of 27.1 mo	Not reached after median follow-up of 14 mo	Not reached after median follow-up of 12 mo
12-month PFS	44%	31%	44%
12-month OS	59%	49%	58%
FDA Approval Status	Approved	Approved	Under review
Toxicity			
CRS All grades	93%	58%	42%
CRS grade ≥3	13%	22%	2%
NT all grades	64%	21%	30%
NT grade ≥3	28%	12%	10%

LOT, lines of therapy; NR, not reached; NT, neurotoxicity.

Neurologic toxicity is the second clinically significant adverse event associated with CAR T-cell therapy. Early descriptions often combined CRS and ICANS under the overarching term CRS, but growing understanding of these toxicities suggest they are distinct entities with different pathophysiology and management recommendations. ICANS typically occurs after the peak of CRS (often >3 days later) and rarely occurs without antecedent CRS, and peak symptoms occur on days 5 to 9. ICANS may be affected by patient-specific factors including disease type, disease burden, treatment history, and patient age, as well as product-specific factors such as CAR design, cell manufacturing conditions, CAR T-cell dose, preconditioning regimen, and product potency.[33] Anecdotal data indicate that the IL-1 antagonist, anakinra, may be effective in patients with severe CRS and ICANS,[35] and it is being explored in clinical trials to assess its role in mitigation of CRS and ICANS.

Common clinical manifestations of ICANS are expressive aphasia or language disturbance, impairments of attention, cognitive processing, and changes in handwriting. However, symptoms can be diverse and include encephalopathy (confusion or delirium), motor weakness, tremor, headache, seizures, depressed level of consciousness, and, rarely, diffuse cerebral edema.[36,37] In both ICANS and CRS, there is likely overlap in the pathophysiology of toxicity in which it is suggested that endothelial activation is the driving mechanism. ICANS is characterized by increased blood-brain barrier (BBB) permeability, capillary leak, and disseminated intravascular coagulation, with increased inflammatory cytokines, CAR T-cells, and myeloid cells in cerebrospinal fluid.[38] The ASTCT

Table 17–2 ASTCT CRS Consensus Grading[32]

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[a]	Temperature ≥38 °C	Temperature ≥38 °C	Temperature ≥38 °C	Temperature ≥38 °C
WITH				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
AND/OR[b]				
Hypoxia	None	Requiring low-flow nasal cannula[c] or blow-by	Requiring high-flow nasal cannula,[c] facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

[a]Fever is defined as temperature ≥38 °C not attributable to any other cause.
[b]CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause.
[c]Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.
BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure.

consensus guidelines for grading ICANS uses an updated encephalopathy screening tool, the Immune Effector Cell Encephalopathy (ICE) score, in addition to assessment of level of consciousness, seizure, motor findings, and elevated intracranial pressure/cerebral edema (Tables 17–3 and 17–4).

In contrast to CRS, tocilizumab is not effective for ICANS as a single agent, which is likely both a function of the multifactorial pathogenesis of ICANS, in addition to the inability of tocilizumab to cross the BBB.[37] Most centers are using corticosteroids as first-line therapy for isolated ICANS with the addition of tocilizumab to corticosteroids given for ICANS that develops concurrently with CRS.

Steroid recommendations are based on clinical trial experience because no randomized trial data are available and the absolute benefit is unknown. Different corticosteroids are used depending on institutional standards, although dexamethasone use is most common because it has excellent CNS penetration, whereas high-dose methylprednisolone is used in the more severe cases of ICANS based on experience with fulminant neuroinflammatory disorders.[38] Prophylactic anticonvulsants are largely standard, although the data supporting their use are lacking.

Table 17–3 ASTCT ICE Assessment Tool for Encephalopathy in Adults

Orientation	Orientation to year, month, city, hospital: 4 points
Naming	Ability to name 3 objects: 3 points
Following Commands	Ability to follow simple commands: 1 point
Writing	Ability to write a standard sentence: 1 point
Attention	Ability to count backwards from 100 by 10: 1 point

Grading by score:
Grade 1: 7–9 points
Grade 2: 3–6 points
Grade 3: 0–2 points
Grade 4: unarousable, unable to complete assessment

In addition to CRS and ICANS, there are CAR T-cell–associated side effects as well as organ-specific toxicity associated with CAR T-cell therapy. Cytopenias have been commonly documented after CAR T-cell infusion with grade 3–4 anemias, thrombocytopenia, or leukopenia reported beyond 28 days in more than 30% of patients.[21,39] Although not life threatening, hypogammaglobulinemia as a result of prolonged B-cell aplasia can lead to infectious complications. Some centers routinely administer intravenous immunoglobulin, whereas others restrict usage to patients who have repeated infections. In severe CRS, a cytokine signature mirroring that of hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) can occur, with optimal treatment still to be defined although high-dose steroids, tocilizumab, and sometimes anakinra have been used with success.[6,40]

Most patients who receive CAR T-cell immunotherapy have poor immune function caused by the effects of their malignancy, prior cytotoxic treatment, and management for CRS and ICANS, including steroids, which can cause further immune suppression. Data on infectious complications are still preliminary, but there is a suggestion that prolonged neutropenia and higher-grade CRS, which may be a surrogate for prolonged corticosteroid

Table 17–4 ASTCT ICANS Consensus Grading for Adults[32]

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7–9 points	3–6 points	0–2 points	0 Unarousable
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure	NA	NA	Any clinical seizure, focal or Generalized, that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	NA	NA	NA	Deep focal motor weakness such as hemiparesis or paraparesis
Raised ICP/cerebral edema	NA	NA	Focal/local edema with or without hemorrhage on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing triad

EEG, electroencephalogram; ICP, intracranial pressure.

use, increase the risk of all infections (viral, bacterial, and fungal.) The increased risk for invasive fungal infections in patients who have a history of prior auto- or allo-HCT or development of life-threatening CRS and/or neurotoxicity has led most centers to broaden fungal prophylaxis in these high-risk patients.[41] At our center, patients receive prophylaxis for *Pneumocystis jiroveci* pneumonia, herpes zoster, and herpes simplex infection from time of CAR infusion to at least 12 months post infusion. Fungal prophylaxis is divided into low risk and high risk, with mold coverage for high-risk patients continuing at least 30 days after completion of steroids or the time point when high-risk features were identified. High risk is defined as history of leukemia, recipient of auto- or allo-HCT, history of mold infection, neutropenia lasting more than 14 days, grade 3 or 4 CRS/ICANS, receipt of more than 3 days of steroids, or history of HLH/MAS.

RELAPSE AND FAILURE OF CAR T-CELL THERAPY

Despite the success with CAR T-cell therapy, treatment failure remains a major challenge. Although the exact mechanisms causing tumor escape remain unknown, relapse after CAR T-cell therapy that targets the CD19 antigen can be categorized broadly as (1) antigen loss, (2) lack of CAR T-cell persistence, or (3) host-specific factors.

A well-characterized mechanism of resistance in patients with ALL is the loss of tumor expression of the extracellular CD19 epitope, to which the CAR binds. This can occur because of alterations in CD19 secondary to acquired mutations and loss of heterozygosity.[42,43] Patients treated on ZUMA-1 with DLBCL who received axi-cel demonstrated a loss of tumor CD19 as evaluated by immunohistochemistry or flow cytometry by local pathologic evaluation and was described in 3 of 11 (27%) patients with biopsies at relapse after CAR T-cell therapy.[19] Approaches to overcome antigen loss include multispecific CAR T-cells to target more than one antigen, coadministration of two separate CAR T-cell products, or even a mixed product with heterogeneous CAR T-cells.[44]

Lack of persistence has been attributed to T-cell exhaustion. CAR T-cell exhaustion may arise from factors before chemotherapy, alterations in the tumor microenvironment, contributions from circulating cells, or it could be associated with variations in the manufacturing process. "Exhausted" CAR T-cells are less proliferative, have a higher number of inhibitory receptors (ie, programmed death 1 [PD-1]), and are

less potent/cytotoxic than nonexhausted T-cells. T-cell exhaustion is a complex phenomenon and is accompanied by an upregulation of inhibitory receptors, such as PD-1, TIM-3, and LAG-3.[45] Multiple environmental and T-cell–intrinsic mechanisms contribute toward the acquisition of an exhausted phenotype and, as a result, these cells have poor effector cell function and reduced efficacy.[25] Off-label use of the PD-1–blocking antibodies, pembrolizumab and nivolumab, has resulted in clinical responses with evidence for enhanced CAR T-cell function and antitumor activity through the re-expansion and restored antitumor activity of exhausted CAR T-cells.[25] The phase 1 results of ZUMA-6, which adds PD-L1 blockade with atezolizumab after axi-cel infusion, has shown a manageable safety profile with CRS and neurotoxicity rates that are not significantly increased, despite a suggestion for greater CAR T-cell expansion compared with ZUMA-1. The expansion cohort is currently under investigation.[46] In addition to T-cell exhaustion, regulatory T-cells and myeloid-derived suppressor cells may suppress CAR T-cell proliferation and cytokine production, leading to a dampening of the antitumor response. It is important to note that persistence has not been correlated directly with the presence or lack of durable long-term response. Long-term follow-up from ZUMA-1 demonstrates that 75% of patients with ongoing responses had B-cell recovery, and data from JULIET showed no link between expansion, T-cell concentration, and clinical outcomes.

Host factors driving CART efficacy continue to be defined. The depth of lymphodepletion before CAR T-cell infusion has been shown to impact treatment outcomes. Data comparing fludarabine/cyclophosphamide as LD conditioning versus cyclophosphamide alone LD conditioning showed the former was associated with increased CAR T-cell expansion, persistence, and improved response rates, indicating that lymphodepletion is an important driver of response.[18] Tumor burden may also correlate to outcomes; patients with ALL with less than 5% blasts demonstrated a superior OS compared with those with a higher disease burden in multiple reports.[47] Locke et al reported data from ZUMA-1 suggesting that high tumor volumes are associated with inferior durable responses in DLBCL.[48] Although bridging therapy was not allowed on the initial ZUMA-1 trial, when CAR T-cell therapy is used in the real-world setting, often bridging chemotherapy is used to control disease until the time of cell infusion. Pinnix et al reported patients who received subsequent axi-cel infusion with or without bridging therapy (BT) and reported that those who received BT had a worse PFS and OS when compared with those who did not receive BT. In this study, BT consisted of chemotherapy, radiation, or a combination of both. Patients who received bridging were more likely to have adverse factors at leukapheresis, including worse PS, international prognostic index (IPI) score of at least 3, bulky disease, and elevated lactate dehydrogenase. Of note, while in this group of 124 patients, BT was administered to 50%, the patients who received radiation as BT had an apparent increased CR rate (82%) compared with those treated with chemotherapy alone (38%), without any increase in CAR T-cell–related toxicity.[49]

INDOLENT LYMPHOMAS

Early trials with CAR T-cells initially commenced with enrollment of indolent NHLs (iNHL); however, the first-generation anti-CD19 CAR T-cells (without costimulation) reported no clinical efficacy in FL cases.[50] Turtle et al reported on 8 FL patients treated with the 4-1BB CAR T-cell construct (1:1 CD4/CD8 ratio),7 of 8 patients achieved CR rates with all ongoing at a median follow-up of 24 months.[51] The largest single-institution data in CAR T-cell therapy for the treatment of FL to date come from the analysis of tisa-cel from the University of Pennsylvania that included 14 FLs. These FL patients had relapsed within 24 months of initial diagnosis and remained refractory to at least two lines of therapy.[52,53] Patients received a variety of conditioning regimens and included FL patients with poor prognosis features, including prior multiple therapies (median of 5), relapsed post auto-HCT (21%) and allo-HCT (1 patient). The updated analysis showed a 3-month ORR and CR of 79% (11/14) and 71% (10/14), respectively. The median PFS was not reached, and 70% of patients with FL were disease free at a median follow-up of 28.6 months.[53]

Interim results from ZUMA-5, a phase 2, multicenter study of axi-cel in patients with R/R iNHL, was reported in abstract form earlier this year. The trial eligibility included R/R FL (grades 1–3a) or MZL (nodal or extranodal) after at least two lines of therapy, and ECOG PS of 0–1. Patients received LD chemotherapy followed by axi-cel infusion at 2×10^6 CAR T-cells/kg. To date, 96 pts (80 FL; 16 MZL) received axi-cel with a median follow-up of 12.8 months (range, 1.9–28.8). These patients had a median age of 63 years (range, 34–79), 49% of patients were male, 52% had stage IV disease, 51% had follicular lymphoma IPI of at least 3, and 49% had high tumor bulk. This was a heavily pretreated population with a median 3 prior lines of therapy, and 54% of patients had progressed less than 2 years after initial anti-CD20 monoclonal antibody (mAb)-containing therapy (POD24), whereas 73% were refractory to the last prior treatment. Of 96 patients evaluable for efficacy, ORR was 93% (80% CR rate). Patients with FL (n = 80) had an ORR of 95% (81% CR rate). Patients with MZL (n = 16) had an ORR of 81% (75% CR rate). Overall, 68% of FL patients

had ongoing responses as of the data cutoff. The rate of grade 3 or higher CRS was 8%, whereas grade 3 or higher ICANS was 17%.[54] These data support anti-CD19 CAR T-cell therapy as a promising therapy in iNHL, and there are a number of trials that are ongoing in this patient population.

CENTRAL NERVOUS SYSTEM LYMPHOMA

The early CAR T-cell trials excluded patients with primary (PCNSL) or secondary CNS (SCNSL) lymphoma because of the concern of increased risk of neurotoxicity. In general, CNS lymphoma is challenging to treat because of the limited penetration of chemotherapy and immunotherapy through the BBB. Although there are reports of documented CNS penetration of CAR T-cells in leukemia, small studies have only recently shown active CAR T-cells in lymphoma.[55–57] There have now been a number of reports that have shown efficacy of commercial CAR T-cell therapy without a significant increase in ICANS in patients with SCNSL. Fifteen patients with a recent history or active SCNSL treated with axi-cel reported an ORR of 75% (including two achieving CR with active SCNSL) without a significant difference in toxicity compared with patients without CNS involvement.[58] In another series, eight patients with CNS involvement were treated with tisagenlecleucel. Two of eight patients had systemic disease in addition to CNS involvement at the time of infusion. All patients received CNS-directed therapy for refractory disease up until lymphodepletion. No patients required tocilizumab or high-dose steroids for the management of CRS and/or ICANS, with durable responses noted in a small minority of patients.[55] This experience is echoed by Siddiqi et al, who report on an ongoing phase 1 trial investigating an autologous CD19-specific, hinge-optimized, CD28 costimulatory CAR with a truncated estimated glomerular filtration rate, which does not exclude patients with PCNSL or SCNSL. Three patients with PCNSL and four with SCNSL were treated without any grade 3 or higher CRS or ICANS and an ORR of 57%.[59] Further data are needed to qualify the long-term durable response of autologous CD19–directed CAR T-cell therapy in CNS lymphoma, but there are ample data that confirm no increase above baseline in terms of toxicity, specifically neurotoxicity.

T-CELL LYMPHOMA

TCLs are associated with an overall poor prognosis and do not have as many treatment options as B-cell lymphomas. Because of shared antigen expression between normal, malignant, and therapeutic T-cells, CAR T-cell therapy targeting T-cell malignancies can potentially lead to CAR T-cell fratricide (self-killing) and prolonged T-cell aplasia.[60,61] CD5 and CD7 have been identified as potential targets, with significant antitumor activity seen in preclinical models.[62] The phase 1 results were reported in abstract form of a CD5 CAR T-cell trial for treatment of CD5-positive T-cell malignancies in five patients at two dose levels (1×10^7 and 5×10^7 CAR T-cells/m^2) with a median of four prior lines of therapy (range, 2–8). CRS occurred in three of five patients (all at DL2); however, the highest-grade CRS or ICANS observed was grade 2. On disease reevaluation 4 to 8 weeks post-CD5 CAR T-cell infusion, three of five evaluable patients obtained an objective response (one on DL1 and two on DL2). Two patients achieved CR and a third had a mixed response and then responded to an additional infusion. All of the patients who achieved a response then proceeded to allo-HCT.[63] Although this is a small series, it shows efficacy targeting CD5 as an antigen for CAR T-cell therapy. Larger studies with longer follow-up are needed to assess whether this is a pathway that could be feasible, devoid of the allogeneic transplant as consolidation.

CD30 is almost universally expressed in anaplastic large-cell lymphomas (ALCL), and in a proportion of other T-cell lymphoma types, including cutaneous T-cell lymphomas. CD30 is an excellent candidate for immune-based therapies because of its restricted expression on tumor cells, with limited expression on a small subset of activated normal (nonmalignant) lymphocytes, leading to low risk for off-tumor, on-target toxicity.[64] Two trials of CD30-directed CAR T-cells published have included T-cell lymphomas in addition to other CD30-expressing disease. The largest series reported on 18 patients with R/R CD30+ lymphoma (17 with HL and one with cutaneous ALCL) with an anti-CD30 CAR,[65] which utilized the 4-1BB costimulatory endodomain and a lentiviral vector for T-cell engineering. The patient population was heavily pretreated and there was no CRS observed; however, the responses were modest, with seven patients attaining a PR and six patients with stable disease. There were no CRs and the ORR was 39%. The median PFS was 6 months.

Using a different construct, Ramos et al reported the results of nine patients with R/R CD30+ lymphoma (six with HL, two with ALCL, and one with DLBCL evolved to HL). For this trial, the CD30 CAR included a CD28 costimulatory endodomain and was delivered into T-cells via a gamma retroviral vector. These patients exhibited mild CRS and three patients attained CR, whereas another three had stable disease; notably, those who attained CR had prolonged disease-free time periods.[66]

There are a number of clinical trials investigating CD30 as a target for CAR T-cell therapy, both with autologous and allogeneic constructs.[67]

MANTLE CELL LYMPHOMA

Mantle cell lymphoma (MCL) comprises about 5% of newly diagnosed NHL, and the median age at diagnosis is about 68 years, with a subset of patients who do exceptionally poorly based on histology, TP53 gene mutation, and factors that define the mantle cell international prognostic index.[68,69] MCL is uniformly CD19 positive and amenable to CD19-directed immunotherapies or cellular immunotherapies. Preliminary data from the TRANSCEND study, using liso-cel, in nine heavily pretreated MCL patients (all with prior Bruton tyrosine kinase inhibitor exposure, three with prior auto-HCT) showed an encouraging ORR of 78%. In the pivotal ZUMA-2 trial, KTE-X19 product (brexucabtagene autoleucel) was tested in patients with R/R MCL.[70] KTE-X19 is an anti-CD19 CAR T-cell therapy produced in a manufacturing process that removes circulating CD19-expressing malignant cells for use in patients with leukemia or MCL. The removal of these cells reduces the possible activation and exhaustion of anti-CD19 CAR T-cells during the ex vivo manufacturing process. Brexucabtagene autoleucel has just recently received commercial approval based on the results of the ZUMA-2 pivotal trial. Conditioning chemotherapy consisted of fludarabine at a dose of 30 mg/m^2 per day, and cyclophosphamide at a dose of 500 mg/m^2 per day was administered on days –5, –4, and –3 before a single intravenous infusion of brexucabtagene autoleucel (brexu-cel) was administered at a dose of 2 × 10^6 CAR T cells/kg on day 0. There was no phase 1 study because the dose was determined on the basis of studies of axi-cel in patients with large B-cell lymphoma and of KTE-X19 in patients with ALL.[19,71] In contrast to the ZUMA-1 trial, before conditioning and after apheresis, patients who had a high disease burden could receive BT. The choice was at the investigator's discretion—glucocorticoid, ibrutinib, or acalabrutinib (or a combination of glucocorticoid plus ibrutinib or acalabrutinib)—with the intent of BT to keep the disease stable during the manufacturing period. Seventy-four patients were enrolled and product was manufactured for 71 patients and administered to 68; 96% of the patients had a dose successfully manufactured, with KTE-X19 delivered to the site in a median of 16 days after apheresis. The efficacy analysis showed 85% had an objective response and 59% had a CR. At a median follow-up of 12.3 months, 57% of the 60 patients in the primary efficacy analysis were in remission, whereas the 12-month PFS and OS were 61% and 83%, respectively. In terms of toxicity, 26% of patients had grade 3 or higher cytopenias lasting beyond 90 days after the administration of brexucel. Overall, any grade CRS occurred in 91% of the patients and most cases were grade 1 or 2 (in 76% of patients), whereas 15% were grade 3 or higher. A total of 63% of patients had neurologic events without any deaths attributed to ICANS. ICANS grade 1 or 2 occurred in 32% of the patients and events of grade 3 or higher occurred in 31%. The median duration of a neurologic event was 12 days, with events fully resolving in 37 of 43 patients (86%). There were two deaths associated with infection. Given these results, we will likely see a shift in paradigm as with DLBCL in timing of transplantation for MCL.

HODGKIN LYMPHOMA

HL is characterized by Reed-Sternberg cells that are CD19 negative and CD30 positive within an immunosuppressive tumor microenvironment containing CD19+ B cells. Studies using autologous anti-CD30 CAR[65] with the 4-1BB costimulatory endodomain and a lentiviral vector have recently reported the outcomes of 41 patients with R/R HL treated at two independent centers. Documented CD30 expression by immunohistochemistry was required, but there was no specific cutoff. Bridging chemotherapy was allowed before lymphodepletion, and LDC consisted of either cyclophosphamide 500 mg/m^2 per day and fludarabine 30 mg/m^2 per day for 3 days (flu/cy); bendamustine alone at 90 mg/m^2 per day for 2 days or bendamustine 70 mg/m^2 per day and fludarabine 30 mg/m^2 per day for 3 days (flu/benda). The cell dose at the expansion level was 2 × 10^8 cells/m^2. The bendamustine-alone arm did not have any patients who responded, whereas the flu/cy arm had an ORR of 65% with a CR rate of 47%, and the flu/benda arm had an ORR of 80% and CR rate of 73%. The 1-year PFS for patients with measurable disease was 41% for all patients who received fludarabine-based lymphodepletion and 61% for those who achieved CR as initial response.[72] Given these results, a planned phase 2 trial is pending using the flu/benda regimen for lymphodepletion.

ALLOGENEIC CAR T-CELLS

To overcome the cumbersome and expensive process of manufacturing patient-specific autologous CAR T-cells, there are also efforts ongoing to develop allogeneic off-the-shelf CAR T-cell therapy approaches, which allows generation of about 100 doses from each apheresis product and therefore could lower

the cost of this therapy. Allogeneic CAR T-cells have many potential advantages, such as a decreased cost as a result of the implementation of industrialized and scaled-up production pathways. "Off-the-shelf" allogeneic CAR T-cells are premanufactured from third-party healthy donors and expanded in high numbers before treatment to be made available to patients on demand and therefore may provide potential solutions to the delays faced by the autologous CAR T-cell therapy including: (1) Time to manufacturing, (2) need for interim bridging therapies, (3) risk of malignant contamination, (4) T-cell variability, (5) risk of insufficient T-cell expansion, (6) T-cell dysfunction, and (7) limited opportunity for redosing. However, certain unique challenges arise as a function of the allogenic cell source, including graft-versus-host disease (GVHD) and the durability of the injected cells.

Most of the allogeneic CAR T-cell candidates utilize cellular gene-editing approaches to ensure complete removal of the TCR. Transcription activator–like effector nucleases (TALEN) were the first technology to be used in patients for αβTCR removal,[73] including for ALLO-501 (described below). There are a number of gene-editing technologies currently being used preclinically in addition to those in clinical trials for allogeneic CARs. These include clustered, regularly interspaced, short palindromic repeat (CRISPR), as well as antigen receptor complex (ARC) – editing mega-nucleases for genome engineering which is the incorporation of the DNA-binding domain from transcription activator–like effectors into hybrid nucleases (mega-transcription activator–like effectors) and zinc fingers.[74]

Of note, ALLO-501 is an investigational anti-CD19 CAR T-cell product that has been genetically modified to eliminate TCRα expression, with the goal of reducing the risk of GVHD. ALLO-647 is an investigational mAb that selectively targets and binds CD52 on T-cells, triggering a host immune response that depletes CD52-positive T-cells. The ALLO-501 CAR T-cell product is also genetically engineered to remove the CD52 cell surface protein. When the anti-CD52 mAb is administered during lymphodepletion, the patient's CD52-positive T-cells are targeted. This strategy supports the persistence and expansion of the donor CAR T-cells. The multicenter, open-label, phase 1 ALPHA study examined the safety and efficacy of sequential treatment with ALLO-647 and ALLO-501 in 22 patients with R/R DLBCL or FL who were treated with at least two prior lines of therapy, including an anti-CD20 mAb.[75] Among 19 patients evaluable for efficacy, the ORR was 63% and the CR rate was 37%. Although numbers are small, higher ALLO-647 doses during lymphodepletion were thought to be associated with deeper responses, with 27% and 50% of patients in the ALLO-647 39 mg and ALLO-647 90 mg groups, respectively, achieving a CR.

An alternative strategy for allogeneic CAR T-cell therapy is to use a different cell type such as NK cells, NK T-cells, or γδ T-cells, which are not known to cause GVHD and therefore do not require the additional gene editing such as knocking out the TCR. Indeed, in a small phase 1 study of 11 patients with B-cell malignancies, administration of allogeneic anti-CD19 CAR NK cells with NK cells–derived cord blood induced CR in eight patients with no CRS, ICANS, or GVHD.[76] These early data are highly encouraging regarding the safety, feasibility, and short-term efficacy of allogeneic CAR T-cell therapy. However, longer follow-up is needed to determine the durability of the responses.

NOVEL CAR DESIGNS

Empowering CAR T-cells to be able to recognize a combination of antigens on the cell surface of the tumor may help avoid antigen escape and/or reduce toxicity. These next-generation CARs, including multitargeted CAR configurations, include the following.

"OR"-gate CARs, where the binding of either CAR to its cognate antigen is enough to drive full T-cell activation. This strategy is to overcome tumor resistance. These include:

- Dual CARs[77]: coexpress two different CARs in one cell
- Tandem CARs[78]: contain two different single-chain variable fragments in a single CAR molecule that can either be stacked in a series or as a looped structure

The major advantage resides in the fact that the presence of *both* targets allows for an enhanced T-cell function, which makes them more efficient than a pooled combination of CAR T-cells at inducing antitumor responses.[79,80] However, such a strategy of targeting two antigens may result in increased risk for toxicity, especially when treating solid tumors.

"AND" -gate CARs, where CAR T-cells are fully activated only when antigen A *and* antigen B are recognized.[81] This strategy is to minimize toxicities.

These include:

- Combinatorial CARs[82]: combine two constructs where one bears the CD3z signaling motif and the other bears the costimulatory signaling domain. In this split-signal approach, recognition of a single antigen, which may happen in normal cells, leads to suboptimal T-cell activation and limited killing of normal cells. In tumors where both antigens may be expressed, full T-cell activation is achieved after engagement of both single-chain variable fragments (scFvs) to their cognate antigens.
- Synthetic notch (synNotch) receptor CARs that induce the transcription of a CAR after antigen recognition of their cognate antigen.[81] Activation of

one receptor (synNotch) induces the expression of a second receptor (CAR) that induces T-cell activation after antigen recognition. Full T-cell activation and tumor elimination occur only when both antigens are expressed. However, tumor escape of CAR T-cells through loss of the first antigen targeted by the synNotch receptor is a major limitation of this strategy.

On-switch CARs[83], which remain inactive until specific activating agents are added, assembling a fully functional receptor. These are designed as fragmented CAR receptors, where the extracellular antigen-binding module is dissociated from the intracellular signaling components. Assembly of these two receptors in the presence of a heterodimerizing small molecule, such as tacrolimus-based analogs, leads to CAR T-cell activation. The magnitude of responses depends on the dosage of the drug, which allows for titratable control.

Inhibitory CARs (iCARs),[84] which inhibit T-cell activation after antigen recognition in normal cells. This is a strategy to limit toxicity. This includes the coexpression of a classic CAR with an antigen-specific iCAR bearing the signaling domain of an immunoinhibitory receptor (ie, CTLA-4 or PD-1). Engagement of iCARs to antigens in normal cells can constrain T-cell functions, which can be resumed in the absence of the iCAR-targeted antigen and after antigen recognition by the activating CAR. One of the challenges of this approach is the identification of cell surface antigens that are expressed in normal cells but absent in tumor cells, a problem that is complementary to the obstacle of identifying tumor-specific antigens absent in normal tissues.

Universal or switchable CAR T-cells, which remain inactive until antibody-based molecules targeting a tumor antigen are supplied to reconstitute a fully active CAR construct. A different strategy that could simultaneously address antigen escape while mitigating toxicities is the utilization of so-called "universal CARs." Instead of engineering T-cells with fixed-antigen specificities, these CAR therapies are composed of two parts:

1. An antibody-based molecule that recognizes a tumor antigen and is modified to express a "switch"; and
2. A universal CAR T-cell without tumor specificity by itself, which contains a construct with an extracellular portion that binds to the switch and is linked to the intracellular signaling domains.

In a first approach, universal CAR T-cells were designed to bind to:

a. biotinylated antigen-specific molecules[85];
b. small-molecule fluorescein isothiocyanate[86]; and
c. short peptide in the antibody-based switch, allowing activation of the corresponding switchable CAR T-cells after tumor recognition by the antibody switch.[86,87]

In a more recent approach, universal CAR T-cells are designed where the split-CAR system named "SUPRA CAR" combines zipCAR T-cells containing an extracellular leucine zipper with an scFv domain fused to a second leucine zipper (zipFv).[88]

These versatile systems allow for the combination of universal CAR T-cells with zipFvs targeting different antigens to avoid tumor escape. At the same time, modulating the dose or affinity of the antibody-based switches may control toxicities. In the case of SUPRA CAR T-cells, T-cell activation can be prevented when necessary by the addition of a competitive zipFv that can bind with high affinity to the zipFv with tumor specificity.[88]

FUTURE DIRECTIONS

Although CAR T-cell therapy is among the most dynamic therapies developed for lymphoma over the past few decades, further work is needed to improve its safety, efficacy, and affordability. Several reports indicate that altering the design of the CAR molecule could improve the safety profile without affecting the efficacy. Ghorashian and colleagues showed that lowering the binding affinity of the scFv by having a similar on-rate but faster off-rate to the CD19 target lowers the incidence of severe CRS without affecting efficacy in patients with B-cell ALL.[89] Ying et al demonstrated that altering the length of the hinge and transmembrane domain of the CAR molecule confers different properties, such as different cytokine profiles with preserved cytolytic activity.[90] In a phase 1 trial in 25 patients with B-cell lymphoma, an optimized hinge and transmembrane domain resulted in a 55% CR rate with only grade 1 CRS and no ICANS.[90] As discussed previously, the 4-1BB costimulatory domain appears to induce lower toxicity rates compared with the CD28 costimulatory domain.[19,81,92] Preclinical studies also indicate that the CD3ζ signaling domain could be modified to favor better persistence of the CAR T-cells while reducing inflammation.[93]

Preclinical and correlative studies from clinical trials suggest that the functional phenotype of the T-cells in the apheresis and CAR T-cell products could affect safety and efficacy. In patients with lymphoma, the polyfunctionality of the CAR T-cells was associated with both response and toxicity.[94] In patients with CLL, apheresis products with higher frequency of early memory CD8+ T-cells defined by CD27+CD45RO– resulted in better-quality CAR T-cell products and better clinical efficacy.[95] Deng and colleagues demonstrated that a higher frequency of memory phenotype in the CAR T-cell product was associated with better

durability of response, whereas a higher frequency of exhausted phenotype was associated with inferior outcome.[96] Together, these results indicate that the safety and efficacy of CAR T-cell therapy could be improved by transducing the CAR gene into specific subsets of T-cells. Other strategies to improve efficacy of CAR T-cell therapy include targeting multiple antigens simultaneously to overcome antigen escape, which has been reported in around 30% of patients after anti-CD19 CAR T-cell therapy in DLBCL.[19,26] CAR T-cells targeting other pan–B-cell antigens such as CD20, CD22, CD79b, and BAFF-R are in various stages of preclinical and clinical development, either as CARs against single targets or CARs against multiple antigens targeted simultaneously.[97–100]

In summary, three anti-CD19 CAR T-cell therapy products have been approved for the treatment of R/R LBCL and/or MCL. These products are now being evaluated in other subtypes of NHL, and randomized trials are ongoing to directly compare CAR T-cell therapy with SCT at first relapse in patients with DLBCL. In additional, use of CAR T-cell therapies against novel targets in B-cell lymphoma and HL and T-cell lymphomas are in development. The high efficacy of CAR T-cell therapy together with the appeal of a single infusion to induce durable remission and possible cure suggests that this may be the beginning of a paradigm shift on how the management of lymphomas is likely to evolve in the future.

MD ANDERSON PRACTICE TIPS

- Current data suggest that CAR T-cell therapy is preferred over allo-SCT as the first choice in patients whose disease has relapsed after auto-SCT in most clinical situations. Allogeneic transplant should be reserved for patients who either have no CAR therapy options or have had disease relapse after CAR T-cell therapy.
- Delivering CAR T-cell therapy requires a comprehensive multidisciplinary approach with highly specialized medical teams, including subspecialty medicine and emergency and critical care groups that quickly evaluate and treat patients for complications. At MDACC, we have a core group of hematologic malignancy, stem cell transplant, critical care, neurology, emergency medicine, cardiology, infectious disease, pulmonary, renal, psychiatry, physiatry, and palliative medicine specialists who take part in the care of patients.
- It is vital to appreciate that patients may exhibit toxicity at variable time points after infusion of cells. CRS generally develops within the first week after infusion, whereas ICANS occurs after the peak of CRS (often >3 days later), with peak symptoms occurring during days 5 to 9. Upon standard treatment with high-dose steroids, ICANS is mostly transient, with a median duration of 5 to 11 days, but can follow a prolonged course in individual patients. Correctly identifying CRS and ICANS is imperative for appropriate treatment with IL-6 antagonists and corticosteroids.
- More than 20% of CD19 CAR T-cell–treated patients have protracted or recurrent neutropenia and/or thrombocytopenia beyond 4 weeks after infusion. Our standard procedure is for patients to remain on viral and *Pneumocystis* pneumonia prophylaxis for one year post infusion of CAR T-cells.
- In the relapsed/refractory setting, patients with lymphoma continue to have a poor prognosis, and these patients should be referred to high-volume centers where clinical trials are available

REFERENCES

1. Tang J, Hubbard-Lucey VM, Pearce L, et al. The global landscape of cancer cell therapy. *Nat Rev Drug Discov.* 2018;17:465-466.
2. Gross G, Waks T, Eshhar Z. Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity. *Proc Natl Acad Sci U S A.* 1989;86:10024-10028.
3. van der Stegen SJ, Hamieh M, Sadelain M. The pharmacology of second-generation chimeric antigen receptors. *Nat Rev Drug Discov.* 2015;14:499-509.
4. Maus MV, Grupp SA, Porter DL, June CH. Antibody-modified T cells: CARs take the front seat for hematologic malignancies. *Blood.* 2014;123:2625-2635.
5. Weinkove R, George P, Dasyam N, McLellan AD. Selecting costimulatory domains for chimeric antigen receptors: functional and clinical considerations. *Clin Transl Immunology.* 2019;8:e1049.
6. Freyer CW, Porter DL. Advances in CAR T therapy for hematologic malignancies. *Pharmacotherapy.* 2020;40(8):741-755.
7. Timmers M, Roex G, Wang Y, et al. Chimeric antigen receptor-modified T cell therapy in multiple myeloma: beyond B cell maturation antigen. *Front Immunol.* 2019;10:1613.
8. Zhang C, Liu J, Zhong JF, Zhang X. Engineering CAR-T cells. Biomark Res 2017;5:22.
9. Brentjens RJ, Curran KJ. Novel cellular therapies for leukemia: CAR-modified T cells targeted to the CD19 antigen. *Hematology Am Soc Hematol Educ Program.* 2012;2012:143-151.
10. Ajina A, Maher J. Strategies to address chimeric antigen receptor tonic signaling. *Mol Cancer Ther*. 2018;17:1795-1815.
11. Maus MV, June CH. Making better chimeric antigen receptors for adoptive T-cell therapy. *Clin Cancer Res.* 2016;22:1875-1884.
12. Abramson JS, Lunning M, Palomba ML. Chimeric antigen receptor T-cell therapies for aggressive B-cell lymphomas: current and future state of the art. *Am Soc Clin Oncol Educ Book.* 2019;39:446-453.
13. Kansagra AJ, Frey NV, Bar M, et al. Clinical utilization of chimeric antigen receptor T cells in B cell acute lymphoblastic leukemia: an expert opinion from the European Society for Blood and Marrow Transplantation and the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant.* 2019;25:e76-e85.
14. Klebanoff CA, Khong HT, Antony PA, et al. Sinks, suppressors and antigen presenters: how lymphodepletion enhances T cell-mediated tumor immunotherapy. *Trends Immunol.* 2005;26:111-117.
15. Lowe KL, Mackall CL, Norry E, et al. Fludarabine and neurotoxicity in engineered T-cell therapy. *Gene Ther.* 2018;25:176-191.
16. Turtle CJ, Hanafi LA, Berger C, et al. CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. *J Clin Invest.* 2016;126:2123-2138.
17. Turtle CJ, Maloney DG. Clinical trials of CD19-targeted CAR-modified T cell therapy; a complex and varied landscape. *Exp Rev Hematol*. 2016;9:719-721.
18. Turtle CJ, Hanafi LA, Berger C, et al. Immunotherapy of non-Hodgkin's lymphoma with a defined ratio of CD8+ and CD4+ CD19-specific chimeric antigen receptor-modified T cells. *Sci Transl Med.* 2016;8:355ra116.
19. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med.* 2017;377:2531-2544.
20. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood.* 2014;124:188-195.
21. Schuster SJ, Investigators J. Tisagenlecleucel in diffuse large B-cell lymphoma. Reply. *N Engl J Med.* 2019;380:1586.
22. Abramson JS, Gordon LI, Palomba ML, et al. Updated safety and long term clinical outcomes in TRANSCEND NHL 001, pivotal trial of lisocabtagene maraleucel (JCAR017) in R/R aggressive NHL. *J Clin Oncol.* 2018;36(suppl 15):7505.
23. Abramson JS, Siddiqi T, Garcia J, et al. Burden of cytokine release syndrome (CRS) and neurologic events (NE) in patients (Pts) with relapsed/refractory non-Hodgkin lymphoma (NHL) receiving lisocabtagene maraleucel (Liso-cel; JCAR017) in TRANSCEND NHL 001. *J Clin Oncol.* 2019;37(suppl 15):6637.
24. Riedell PA, Walling C, Nastoupil LJ, et al. A Multicenter retrospective analysis of outcomes and toxicities with commercial axicabtagene ciloleucel and tisagenlecleucel for relapsed/refractory aggressive B-cell lymphomas. *Biol Blood Marrow Transplant.* 2020;26:S41-S42.
25. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. *Lancet Oncol.* 2019;20:31-42.
26. Nastoupil LJ, Jain MD, Feng L, et al. Standard-of-care axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma: results from the US Lymphoma CAR T Consortium. *J Clin Oncol.* 2020;JCO1902104.
27. Jacobson CA, Hunter BD, Redd R, et al. Axicabtagene ciloleucel in the non-trial setting: outcomes and correlates of response, resistance, and toxicity. *J Clin Oncol.* 2020;JCO1902103.
28. June CH, Sadelain M. Chimeric antigen receptor therapy. *N Engl J Med.* 2018;379:64-73.
29. Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy—assessment and management of toxicities. Nat Rev Clin Oncol 2018;15:47-62.
30. Teachey DT, Lacey SF, Shaw PA, et al. Identification of predictive biomarkers for cytokine release syndrome after chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. *Cancer Discov*. 2016;6:664-679.
31. Porter D, Frey N, Wood PA, et al. Grading of cytokine release syndrome associated with the CAR T cell therapy tisagenlecleucel. *J Hematol Oncol*. 2018;11:35.
32. Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant.* 2019;25:625-638.
33. Santomasso B, Bachier C, Westin J, et al. The other side of CAR T-cell therapy: cytokine release syndrome, neurologic toxicity, and financial burden. *Am Soc Clin Oncol Educ Book*. 2019;39:433-444.
34. Strati P, furqan f, Westin J, et al. Prognostic impact of dose, duration, and timing of corticosteroid therapy in patients with large B-cell lymphoma treated with standard of care axicabtagene ciloleucel (Axi-cel). *J Clin Oncol.* 2020;38:8011-8011.
35. Strati P, Ahmed S, Kebriaei P, et al. Clinical efficacy of anakinra to mitigate CAR T-cell therapy-associated toxicity in large B-cell lymphoma. *Blood Adv.* 2020;4:3123-3127.
36. Gust J, Ishak GE. Chimeric antigen receptor T-cell neurotoxicity neuroimaging: more than meets the eye. *AJNR Am J Neuroradiol.* 2019;40:E50-E51.
37. Gust J, Taraseviciute A, Turtle CJ. Neurotoxicity associated with CD19-targeted CAR-T cell therapies. *CNS Drugs*. 2018;32:1091-1101.
38. Santomasso BD, Park JH, Salloum D, et al. Clinical and biological correlates of neurotoxicity associated with CAR T-cell therapy in patients with B-cell acute lymphoblastic leukemia. *Cancer Discov*. 2018;8:958-971.
39. Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. *Blood.* 2016;127:3321-3330.
40. Ahmed S, furqan f, Strati P, et al. Haemophagocytic lymphohistiocytosis (HLH) in patients with large B-cell lymphoma treated with standard of care (SOC) axicabtagene ciloleucel (Axi-cel). *J Clin Oncol.* 2020;38:8057-8057.

41. Hill JA, Li D, Hay KA, et al. Infectious complications of CD19-targeted chimeric antigen receptor-modified T-cell immunotherapy. *Blood.* 2018;131:121-130.
42. Fischer J, Paret C, El Malki K, et al. CD19 isoforms enabling resistance to CART-19 immunotherapy are expressed in B-ALL patients at initial diagnosis. *J Immunother.* 2017;40:187-195.
43. Byrne M, Oluwole OO, Savani B, et al. Understanding and managing large B cell lymphoma relapses after chimeric antigen receptor T cell therapy. *Biol Blood Marrow Transplant.* 2019;25:e344-e351.
44. Lesch S, Benmebarek MR, Cadilha BL, et al. Determinants of response and resistance to CAR T cell therapy. *Semin Cancer Biol.* 2020;65:80-90.
45. Long AH, Haso WM, Shern JF, et al. 4-1BB costimulation ameliorates T cell exhaustion induced by tonic signaling of chimeric antigen receptors. *Nat Med.* 2015;21:581-590.
46. Jacobson CA, Locke FL, Miklos DB, et al. End of phase 1 results from Zuma-6: axicabtagene ciloleucel (Axi-Cel) in combination with atezolizumab for the treatment of patients with refractory diffuse large B cell lymphoma. *Blood.* 2018;132.
47. Park JH, Riviere I, Gonen M, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. *N Engl J Med.* 2018;378:449-459.
48. Locke FL, Ghobadi A, Jacobson CA, et al. Durability of response in patients with refractory large B cell lymphoma treated with axicabtagene ciloleucel in the pivotal phase 2 study, ZUMA-1. *Clin Lymphoma Myeloma Leuk*. 2018;18:S277-S278.
49. Pinnix CC, Gunther JR, Dabaja BS, et al. Bridging therapy prior to axicabtagene ciloleucel for relapsed/refractory large B-cell lymphoma. *Blood Adv.* 2020;4:2871-2883.
50. Kochenderfer JN, Somerville RPT, Lu T, et al. Long-duration complete remissions of diffuse large B cell lymphoma after anti-CD19 chimeric antigen receptor T cell therapy. *Mol Ther.* 2017;25:2245-2253.
51. Hirayama AV, Gauthier J, Hay KA, et al. High rate of durable complete remission in follicular lymphoma after CD19 CAR-T cell immunotherapy. *Blood.* 2019;134:636-640.
52. Schuster SJ, Svoboda J, Nasta SD, et al. Sustained remissions following chimeric antigen receptor modified T cells directed against CD19 (CTL019) in patients with relapsed or refractory CD19+ lymphomas. *Blood.* 2015;126.
53. Chong EA, Svoboda J, Nasta SD, et al. Chimeric antigen receptor modified T cells directed against CD19 (CTL019) in patients with poor prognosis, relapsed or refractory CD19+ follicular lymphoma: prolonged remissions relative to antecedent therapy. *Blood.* 2016;128.
54. Jacobson CA, Chavez JC, Sehgal AR, et al. Interim analysis of ZUMA-5: a phase II study of axicabtagene ciloleucel (axi-cel) in patients (pts) with relapsed/refractory indolent non-Hodgkin lymphoma (R/R iNHL). *J Clin Oncol.* 2020;38:8008-8008.
55. Frigault MJ, Dietrich J, Martinez-Lage M, et al. Tisagenlecleucel CAR T-cell therapy in secondary CNS lymphoma. *Blood.* 2019;134:860-866.
56. Rheingold SR, Chen LN, Maude SL, et al. Efficient trafficking of chimeric antigen receptor (CAR)-modified T cells to CSF and induction of durable CNS remissions in children with CNS/combined relapsed/refractory ALL. *Blood.* 2015;126.
57. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med.* 2014;371:1507-1517.
58. Bennani NN, Maurer MJ, Nastoupil LJ, et al. Experience with axicabtagene ciloleucel (Axi-cel) in patients with secondary CNS involvement: results from the US Lymphoma CAR T Consortium. *Blood.* 2019;134.
59. Siddiqi T, Wang X, Palmer J, et al. CD19-targeting CAR-T cell therapy in CNS lymphoma. *Blood.* 2019;134:4075-4075.
60. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood.* 2016;127:2375-2390.
61. Mamonkin M, Mukherjee M, Srinivasan M, et al. Reversible transgene expression reduces fratricide and permits 4-1BB costimulation of CAR T cells directed to T-cell malignancies. *Cancer Immunol Res.* 2018;6:47-58.
62. Gomes-Silva D, Srinivasan M, Sharma S, et al. CD7-edited T cells expressing a CD7-specific CAR for the therapy of T-cell malignancies. *Blood.* 2017;130:285-296.
63. Hill L, Rouce RH, Smith TS, et al. CD5 CAR T-cells for treatment of patients with relapsed/refractory CD5 expressing T-cell lymphoma demonstrates safety and anti-tumor activity. *Biol Blood Marrow Transplant.* 2020;26: S237-S238.
64. Hombach A, Heuser C, Sircar R, et al. An anti-CD30 chimeric receptor that mediates CD3-xi-independent T-cell activation against Hodgkin's lymphoma cells in the presence of soluble CD30. *Cancer Res.* 1998;58:1116-1119.
65. Wang CM, Wu ZQ, Wang Y, et al. Autologous T cells expressing CD30 chimeric antigen receptors for relapsed or refractory Hodgkin lymphoma: an open-label phase I trial. *Clin Cancer Res.* 2017;23:1156-1166.
66. Ramos CA, Ballard B, Zhang H, et al. Clinical and immunological responses after CD30-specific chimeric antigen receptor-redirected lymphocytes. *J Clin Invest.* 2017;127:3462-3471.
67. Grover NS, Savoldo B. Challenges of driving CD30-directed CAR-T cells to the clinic. *BMC Cancer*. 2019;19:203.
68. Armitage JO. Management of mantle cell lymphoma. *Oncology (New York).* 1998;12:49-55.
69. Hanel W, Epperla N. Emerging therapies in mantle cell lymphoma. *J Hematol Oncol.* 2020;13.
70. Wang MH, Munoz J, Goy A, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. *N Engl J Med.* 2020;382:1331-1342.
71. Lee DW, Wayne AS, Huynh V, et al. Updated results from Zuma-4: a phase 1/2 study of Kte-C19 chimeric antigen receptor (Car) T cell therapy in pediatric and adolescent patients with relapsed/refractory acute lymphoblastic leukemia. *Haematologica.* 2017;102:346-347.
72. Ramos CA, Grover NS, Beaven AW, et al. Anti-CD30 CAR-T cell therapy in relapsed and refractory Hodgkin lymphoma. *J Clin Oncol.* 2020;JCO2001342.
73. Sunder-Plassmann R, Lialios F, Madsen M, et al. Functional analysis of immunoreceptor tyrosine-based activation motif (ITAM)-mediated signal transduction: the two YxxL segments within a single CD3zeta-ITAM are functionally distinct. *Eur J Immunol.* 1997;27:2001-2009.
74. Chmielewski M, Abken H. CAR T cells transform to trucks: chimeric antigen receptor-redirected T cells engineered to deliver inducible IL-12 modulate the tumour stroma to combat cancer. *Cancer Immunol Immunother.* 2012;61:1269-1277.
75. Neelapu SS MJ, Locke FL, et al. First- in-human data of ALLO-501 and ALLO-647 in relapsed/refractory large B-cell or follicular lymphoma (R/R LBCL/FL): ALPHA study. *J Clin Oncol.* 2020;38(suppl 15):8002.
76. Liu E, Marin D, Banerjee P, et al. Use of CAR-transduced Natural Killer Cells in CD19-positive lymphoid tumors. *N Engl J Med.* 2020;382:545-553.
77. Ruella M, Barrett DM, Kenderian SS, et al. Dual CD19 and CD123 targeting prevents antigen-loss relapses after CD19-directed immunotherapies. *J Clin Invest.* 2016;126:3814-3826.
78. Grada Z, Hegde M, Byrd T, et al. TanCAR: a novel bispecific chimeric antigen receptor for cancer immunotherapy. *Mol Ther Nucleic Acids*. 2013;2:e105.
79. Hegde M, Mukherjee M, Grada Z, et al. Tandem CAR T cells targeting HER2 and IL13Ralpha2 mitigate tumor antigen escape. *J Clin Invest.* 2016;126:3036-3052.

80. Hegde M, Corder A, Chow KK, et al. Combinational targeting offsets antigen escape and enhances effector functions of adoptively transferred T cells in glioblastoma. *Mol Ther.* 2013;21:2087-2101.
81. Roybal KT, Rupp LJ, Morsut L, et al. Precision tumor recognition by T cells with combinatorial antigen-sensing circuits. *Cell.* 2016;164:770-779.
82. Kloss CC, Condomines M, Cartellieri M, et al. Combinatorial antigen recognition with balanced signaling promotes selective tumor eradication by engineered T cells. *Nat Biotechnol.* 2013;31:71-75.
83. Wu CY, Roybal KT, Puchner EM, et al. Remote control of therapeutic T cells through a small molecule-gated chimeric receptor. *Science.* 2015;350:aab4077.
84. Fedorov VD, Themeli M, Sadelain M. PD-1- and CTLA-4-based inhibitory chimeric antigen receptors (iCARs) divert off-target immunotherapy responses. *Sci Transl Med.* 2013;5:215ra172.
85. Urbanska K, Lanitis E, Poussin M, et al. A universal strategy for adoptive immunotherapy of cancer through use of a novel T-cell antigen receptor. *Cancer Res.* 2012;72:1844-1852.
86. Rodgers DT, Mazagova M, Hampton EN, et al. Switch-mediated activation and retargeting of CAR-T cells for B-cell malignancies. *Proc Natl Acad Sci U S A.* 2016;113:E459-468.
87. Ma JS, Kim JY, Kazane SA, et al. Versatile strategy for controlling the specificity and activity of engineered T cells. *Proc Natl Acad Sci U S A.* 2016;113:E450-458.
88. Cho JH, Collins JJ, Wong WW. Universal chimeric antigen receptors for multiplexed and logical control of T cell responses. *Cell.* 2018;173:1426-1438, e1411.
89. Ghorashian S, Kramer AM, Onuoha S, et al. Enhanced CAR T cell expansion and prolonged persistence in pediatric patients with ALL treated with a low-affinity CD19 CAR. *Nat Med.* 2019;25:1408-1414.
90. Ying Z, Huang XF, Xiang X, et al. A safe and potent anti-CD19 CAR T cell therapy. *Nat Med.* 2019;25:947-953.
91. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med.* 2019;380:45-56.
92. Abramson JS PM, Gordon LI, et al. Pivotal safety and efficacy results from Transcend NHL 001, a multicenter phase 1 study of lisocabtagene maraleucel (liso-cel) in relapsed/refractory (R/R) large B cell lymphomas. *Blood.* 2019;134(suppl 1):241.
93. Feucht J, Sun J, Eyquem J, et al. Calibration of CAR activation potential directs alternative T cell fates and therapeutic potency. *Nat Med.* 2019;25:82-88.
94. Rossi J, Paczkowski P, Shen YW, et al. Preinfusion polyfunctional anti-CD19 chimeric antigen receptor T cells are associated with clinical outcomes in NHL. *Blood.* 2018;132:804-814.
95. Fraietta JA, Lacey SF, Orlando EJ, et al. Determinants of response and resistance to CD19 chimeric antigen receptor (CAR) T cell therapy of chronic lymphocytic leukemia. *Nat Med.* 2018;24:563-571.
96. Deng Q, Guangchun H, Puebla-Osorio N, et al. Characteristics of anti-CD19 CAR T-cell infusion products associated with efficacy and toxicity in patients with large B-cell lymphomas. *Nat Med*. 2020;26(12)1878-1887.
97. Lee SY, Olsen P, Lee DH, et al. Preclinical optimization of a CD20-specific chimeric antigen receptor vector and culture conditions. *J Immunother.* 2018;41:19-31.
98. Fry TJ, Shah NN, Orentas RJ, et al. CD22-targeted CAR T cells induce remission in B-ALL that is naive or resistant to CD19-targeted CAR immunotherapy. *Nat Med.* 2018;24:20-28.
99. Ormhoj M, Scarfo I, Cabral ML, et al. Chimeric antigen receptor T cells targeting CD79b show efficacy in lymphoma with or without cotargeting CD19. *Clin Cancer Res.* 2019;25:7046-7057.
100. Qin H, Dong Z, Wang X, et al. CAR T cells targeting BAFF-R can overcome CD19 antigen loss in B cell malignancies. *Sci Transl Med.* 2019;11(511):eaaw9414.

This page intentionally left blank

Section III

Stem Cell Transplantation

Section Editor: Elizabeth J. Shpall

18 Autologous Hematopoietic Progenitor-Cell Transplantation

19 Allogeneic Transplantation

20 Alternative Donor Transplants: Cord Blood Transplant

21 Alternative Donor Transplants: Haploidentical Hematopoietic Stem Cell Transplantation

22 Cellular Therapy in Allogeneic Hematopoietic Cell Transplantation

This page intentionally left blank

18 Autologous Hematopoietic Progenitor-Cell Transplantation

Neeraj Saini
Yago Nieto

Key Concepts

- The use of autologous hematopoietic progenitor-cell transplant (AHPCT) overcomes myelotoxicity of high-dose chemotherapy (HDC). Therefore, drugs with a markedly myelosuppressive side effect profile and a steep dose-response effect are preferred. The most common nonhematologic regimen-related toxicity (RRT) is oropharyngeal mucositis, which is rarely life threatening. The most common among the potentially severe extramedullary RRT are interstitial pneumonitis and veno-occlusive disease of the liver.
- HDC with AHPCT has been the standard of care for chemosensitive, relapsed diffuse large B-cell lymphoma (DLBCL) for the last three decades. However, the results remain suboptimal in patients whose disease relapses less than one year after completion of frontline chemoimmunotherapy (eg, R-CHOP).
- In follicular lymphoma, HDC with AHPCT should be considered for high-risk relapses occurring within two years of completing frontline therapy (POD24) or second or more advanced relapses.
- Management of relapsed or primary refractory Hodgkin lymphoma in patients should be a salvage strategy using one or more lines of therapy, including regimens such as bendamustine/brentuximab vedotin or ifosfamide/carboplatin/etoposide aiming at a positron emission tomography–negative remission before AHPCT. Patients with a high-risk for disease relapse should be considered for post-AHPCT maintenance with brentuximab vedotin.
- Modern treatment of newly diagnosed myeloma should include induction with a proteasome inhibitor and an immunomodulatory drug (eg, bortezomib/lenalidomide/dexamethasone [VRD]) followed by melphalan-based HDC and AHCPT, and consolidation and/or maintenance with drugs like lenalidomide, with the goal of achieving a minimal residual disease-negative remission.
- Tandem cycles of carboplatin-containing HDC with AHPCT should be considered for any patient with a germ-cell tumor in the second or later relapse. Their role in the first relapse is still undetermined.

BASIC CONCEPTS

High-dose chemotherapy (HDC) with autologous hematopoietic progenitor-cell transplant (AHPCT) is an effective treatment modality for a variety of hematologic malignancies and selected solid tumors. This chapter reviews its current role in the treatment of cancer, outlining future directions of progress.

Doses of radiation and chemotherapy are limited by toxicity to normal tissues and, particularly, the bone marrow. However, the doses of certain chemotherapeutic agents and radiation can be substantially escalated, exploiting their dose-response effect, when followed by autologous or allogeneic transplantation of HPCs to restore hematopoiesis. Pluripotent HPC progenitors present in the graft proliferate and differentiate into the mature blood and immune cells. AHPCT involves the collection, cryopreservation, and infusion of the patient's own HPCs.

GENERAL PROCEDURES FOR AUTOLOGOUS TRANSPLANTATION

Figure 18–1 shows the different procedures related to autologous transplantation.

Preceding Standard-Dose Chemotherapy

Standard-dose chemotherapy is usually given to cytoreduce the tumor before proceeding to AHPCT. In general, the best outcomes are seen in patients with chemosensitive disease in complete remission, or with minimal tumor burden at the time of transplantation.

Peripheral Blood Progenitor Cell Collection

Peripheral blood progenitor cells (PBPCs) should be collected while the patient's marrow is normocellular and uninvolved by the malignancy. PBPCs are normally present in very low numbers in the blood but are mobilized into the blood at postchemotherapy recovery with granulocyte colony-stimulating factor (G-CSF). PBPCs are collected using apheresis with continuous-flow cell separation. The minimal and optimal CD34+ cell doses for an autologous HPC transplant are 2×10^6/kg and 5×10^6/kg, respectively. The collected PBPCs are cryopreserved until infusion to the patient.

Multiple factors have been shown to predict poor success in mobilization and collection, including advanced age, amount of preceding chemotherapy, presence of marrow-infiltrating disease, history of pelvic radiation, prior exposure to certain drugs such as melphalan, carmustine or bendamustine, low premobilization platelet counts, short interval from last chemotherapy cycle to mobilization, inadequate chemotherapy mobilizing regimens and/or low-dose G-CSF,[1] and previous treatment with multiple cycles of lenalidomide.[2] A count of CD34+ cells greater than 10/mL in peripheral blood is highly predictive of an adequate collection. Plerixafor is a useful second PBPC-mobilizing agent, which acts synergistically with G-CSF and is effective in patients predicted or shown to be "poor mobilizers."[3]

High-Dose Therapy

Autologous transplants are most effective in diseases where a several-fold dose escalation of myelosuppressive drugs leads to a markedly increased cytotoxic effect on the malignancy. Given their steep dose-response effect, alkylating agents constitute the backbone of HDC regimens. The activity of alkylating agents depends on the extent of DNA damage and repair. Thus, drugs that inhibit DNA damage repair, such as the nucleoside analogs fludarabine or clofarabine for leukemia, or gemcitabine for lymphomas, have been combined with alkylating agents, with resulting synergy and improved clinical results.[4,5]

The optimal HDC regimen is specific to each disease. The most common cause of failure after AHPCT is relapse of the underlying malignancy as a result of insufficient antitumor effect of HDC. Venues to improve the activity of HDC include the incorporation of novel chemotherapy agents (such as gemcitabine or clofarabine), monoclonal antibodies (such as rituximab for CD20+ lymphomas), or epigenetic modulators (such as vorinostat or azacitidine).[6,7] The use of sequential cycles of HDC has been thoroughly evaluated in myeloma and is usual practice in treating germ-cell tumors. A major pitfall of efforts to improve the efficacy of established HDC is that merely increasing the total dose of antineoplastic drugs may improve the tumor response but will certainly increase the severity of side effects. Thus, novel HDC regimens must have a solid pharmacologic rationale, with careful consideration of scheduling, and be developed in well-designed clinical trials aiming for the optimal therapeutic index.

Reinfusion of Collected Stem Cells

Stem cells are infused intravenously after HDC is cleared from the patient's bloodstream, usually 1 to 3 days after completion of this treatment. The cells circulate transiently and then home to the bone marrow. Hematopoiesis is restored within a few weeks.[8] Neutrophils recover typically in 7 to 10 days and platelets recover in 10 to 21 days after infusion.

Supportive Care

Patients usually receive G-CSF or other hematopoietic growth factors to accelerate neutrophil recovery. Patients are routinely prescribed a prophylactic antibiotic, antiviral, and antifungal therapy for the prevention of infection during the initial phase of marrow engraftment and hematologic recovery.

AUTOLOGOUS VERSUS ALLOGENEIC HPC TRANSPLANTS

The relative role of autologous versus allogeneic transplants varies for each hematologic malignancy. AHPCT is a process that carries less overall morbidity and mortality because the reinfused cells are neither subject to immunologic rejection nor will produce graft-versus-host disease. On the other hand, there is a potential risk of tumor contamination of the autologous graft, particularly in patients with bone marrow tumor involvement. In vivo bone marrow purging with monoclonal antibodies preceding PBPC mobilization and apheresis in particular, rituximab for CD20+ B-cell lymphomas, has be shown to be effective. Finally, there is no evidence that the immune-mediated graft-versus-tumor effect associated with allogeneic HPC transplantation occurs with AHPCT.

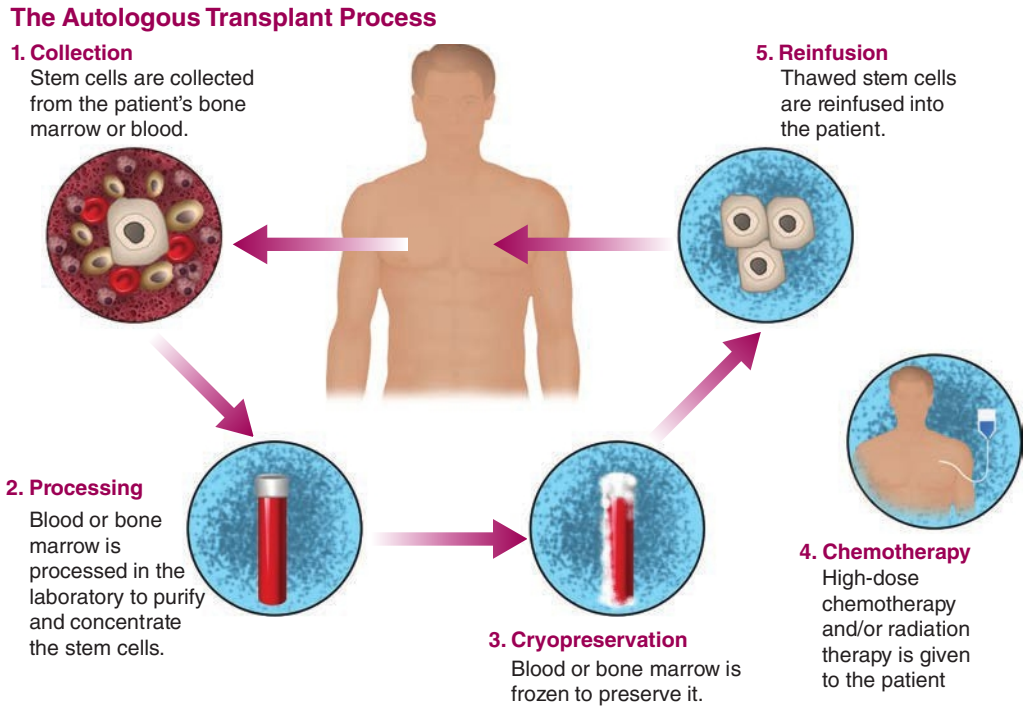


FIGURE 18–1 **Autologous hematopoietic progenitor-cell transplantation process.**

COMPLICATIONS OF HIGH-DOSE CHEMOTHERAPY

HDC produces profound pancytopenia that usually lasts from 7 to 10 days. Infectious complications can occur during the neutropenic period (ranging from uncomplicated neutropenic fever to life-threatening sepsis) and up to 6 months or more post-transplant in the case of *Pneumocystis jiroveci*, fungal infections or zoster reactivation. Antibacterial prophylaxis with a fluoroquinolone, antiviral prophylaxis with acyclovir/valacyclovir, and antifungal prophylaxis with fluconazole are generally started at the time of stem cell infusion and continued throughout neutropenia. *Pneumocystis jiroveci* pneumonia prophylaxis (eg, trimethoprim/sulfamethoxazole) is usually started at 3 to 4 weeks post-transplant for at least 6 months. Antiviral prophylaxes (acyclovir, valacyclovir) are given for 6 to 12 months.[9]

Regimen-related toxicity (RRT) are the side effects of HDC in nonhematopoietic tissues, which depend on the specific regimen. The oral mucosa and the gastrointestinal tract are the most sensitive tissues to these effects. Several agents have shown some efficacy in randomized clinical trials in the prevention of mucositis (such as amifostine, palifermin, topical glutamine, or laser therapy), whereas many others in common use have not been shown to be effective (such as steroids, sucralfate, "magical mouthwash," or topical anesthetics).

The lungs, heart, liver, brain, and kidneys are less commonly affected, generally in heavily pretreated patients or in those with comorbid conditions. Overall, 1% to 4% of patients die from RRT or infections, which makes AHPCT substantially safer than allogeneic transplantation.

Toxic interstitial pneumonitis can occur in up to 40% of patients receiving HDC. It has been described with several different chemotherapy agents, such as carmustine, busulfan, and total-body irradiation.[10] It is particularly common in patients previously treated with mediastinal radiotherapy. Prompt diagnosis is essential, and steroids are usually effective in its treatment.

Cardiac toxicity is uncommon. It can be seen after high doses of cyclophosphamide or melphalan. Prior radiation therapy to the mediastinum or left chest wall, as well as advanced age are also predictors of an increased risk of cardiac complications.[11] Central nervous system complications are rare, but dementia and leukoencephalopathy have been described, particularly from drugs that penetrate the cerebrospinal fluid, such as carmustine or thiotepa.[12] Hypothyroidism and hypoandrogenism are frequent and occur 6 months to 2 years after transplant.[13] Hemorrhagic cystitis, after high-dose cyclophosphamide or ifosfamide, is uncommon and can be effectively prevented with mesna.[14]

Sinusoidal obstruction syndrome (SOS) (formerly known as venoocclusive disease) of the liver is clinically characterized by fluid retention (despite

optimal use of diuretics), rising direct hyperbilirubinemia, and hepatomegaly that can be painful.[15] Its severity depends on the presence of multiorgan failure and the velocity of bilirubin rise. Although mild cases are often self-limited, severe cases can be fatal in more than 80% of patients. Several factors predisposing to SOS include prior liver impairment, older age, and iron overload. The use of oral busulfan and total-body irradiation has been most commonly associated with SOS, particularly if it is used with cyclophosphamide.[16] Recently, the introduction of new calicheamicin immunotoxin conjugated drugs, inotuzumab ozogamicin,[17] and gemtuzumab ozogamicin, in treatment of leukemia before transplant has contributed to increased incidence of SOS. Andersson et al at MDACC have pioneered the use of intravenous busulfan, which effectively addressed the issue of intrapatient dose-to-dose variability of oral busulfan and substantially decreased the risk of SOS compared with its oral formulation.[18] This group also developed the pharmacokinetic-guided dosing of intravenous busulfan, which corrects interpatient variability and further decreases the incidence of SOS. Systemic anticoagulant and thrombolytic therapies have been shown to be ineffective and are associated with major bleeding complications. The only FDA-approved drug for the treatment of SOS is defibrotide. In a phase 3 trial, the day +100 complete response (CR) rate was 25.5% for the defibrotide group compared with 12.5 % for the historical control group.[19] Defibrotide was associated with significant improvement in day +100 CR and overall survival (OS) rate. Supportive care also plays a crucial role, using diuretics and sodium restriction, avoidance of hepatotoxins, oxygen support, and renal replacement therapy if needed.

Finally, therapy-related MDS (t-MDS) and therapy-related acute myeloid leukemia (t-AML) are potentially devastating complications of AHPCT, with a cumulative probability that ranges from 1.1% at 20 months to 23% at 4 years.[20] With improvement in the management of post-AHCPT infections and RRT, t-MDS/t-AML have emerged as the main cause of nonrelapse mortality after AHPCT. There are two main types of t-MDS/t-AML: those related to alkylating agents or radiation, and those related to topoisomerase II inhibitors. The former group appears 4 to 7 years post-AHPCT, with two-thirds of patients presenting with MDS and one-third with AML with myelodysplastic features. There is a high incidence of abnormalities of chromosomes 5 (-5/del(5q)) and 7 (-7/del(7q)). In contrast, topoisomerase II inhibitor–related AML often appears as overt acute leukemia without preceding MDS, with a shorter latency period of 6 months to 3 years. Most often, it is associated with translocations involving 11q23 or 21q22. Risk factors for t-MDS/t-AML include older age at transplant, pre-HDC exposure to alkylating agents, topoisomerase II inhibitors and radiotherapy, use of etoposide to mobilize the PBPC, use of total-body irradiation as part of the AHPCT conditioning, infusion of lower numbers of CD34+ cells, and multiple transplantations (as in myeloma or germ-cell tumors). The prognosis for t-MDS/t-AML is poor, and the only potentially curative treatment is an allogeneic stem cell transplant (SCT).

RESULTS OF AUTOLOGOUS TRANSPLANTATION

Non-Hodgkin Lymphoma

Autologous transplantation has been extensively studied in patients with non-Hodgkin lymphoma (NHL), either as frontline consolidation or in patients who are refractory to firstline therapy or in relapse.

Diffuse large B-cell lymphoma

HDC and AHPCT has been for several decades the standard of care for patients with chemosensitive relapsed diffuse large B-cell lymphoma (DLBCL) (Fig. 18-2).[21] Factors such as resistance to salvage chemotherapy, increased lactic dehydrogenase at the time of relapse or progression, prior CR of less than 12 months, and secondary international prognostic index (IPI) (ie, at the time of relapse or progression) score higher than 1 are adverse predictors of survival in patients receiving HDC. In the modern era of exposure to rituximab as part of firstline therapy (R-CHOP), the CORAL study has shown 3-year event-free survival (EFS) rates of around 25% in patients with chemosensitive relapsed disease who are undergoing autologous SCT.[22]

In contrast to relapsed disease, the efficacy of HDC as frontline consolidation for DLBCL patients in first CR has not been demonstrated after many randomized trials, especially when patients previously receive R-CHOP instead of CHOP.[23] Thus, AHPCT is not indicated as consolidation of the first remission for DLBCL patients.

Follicular Lymphoma

The role of AHPCT in the treatment of patients with chemosensitive relapsed follicular lymphoma (FL) remains unclear. The classical regimen of high-dose cyclophosphamide/total-body irradiation has been largely abandoned because of its high risk of t-MDS/t-AML. Historically, a major challenge has been contamination of the autologous graft by malignant cells.[24] More recently, systemic treatment with rituximab has

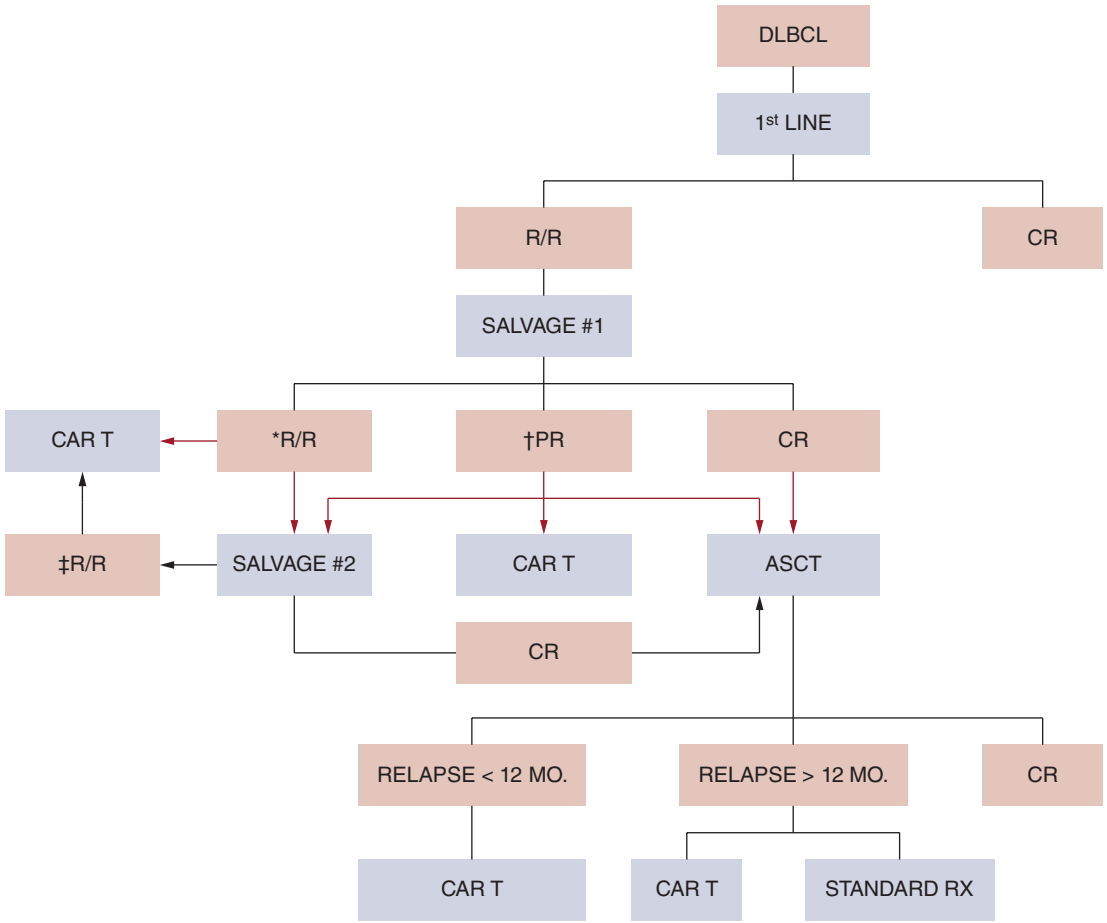


FIGURE 18–2 **Algorithm for treatment of DLBCL: stepwise description of DLBCL treatment approach and the role of autologous and allogeneic progenitor-cell transplantation after relapse. ASCT, allogeneic stem cell transplant.**

reduced the numbers of circulating lymphoma cells, thus yielding effective in vivo purging with high likelihood polymerase chain reaction–negative tumor-free PBPC grafts.[25] A European randomized trial showed improved PFS and OS after HDC for chemosensitive relapsed FL.[26] However, that study was conducted in the prerituximab era and is not entirely applicable to modern patients.

Approximately 20% of patients with FL develop progression of disease within 2 years (POD24) after completing frontline chemoimmunotherapy. This subset of patients has a poor prognosis (5-year OS ~50%). In a retrospective combined registry analysis of CIBMTR and National Lymphocare database, early AHPCT within a year of relapse was associated with a decreased risk of mortality (HR = 0.63, P = .02) in POD24 FL patients.[27,28] Also, subset analyses from two German prospective randomized trials in FL confirmed the OS benefit of early AHPCT in POD24 FL patients, with a 5-year OS rate of 77% with transplant versus 59% with no transplant (HR = 0.54, P = .03).[29]

HODGKIN LYMPHOMA

Most patients with Hodgkin lymphoma (HL) are cured with firstline therapy. However, 20% of patients will not respond to firstline chemotherapy and approximately 30% will have relapse after an initial response. HDC has been proven to be beneficial in those two settings with expected long-term EFS of 30% to 40% for patients with primary refractory tumors that subsequently respond to salvage therapy, and of 30% to 65% for patients with chemosensitive relapsed HL (Fig. 18-3).[30,31]

Unfavorable prognostic features for AHPCT include a first CR shorter than 1 year, extranodal relapse, B symptoms at the time of relapse or progression, bulky (>5 cm) lesions at relapse, and relapse within a prior radiation field. Patients with no unfavorable prognostic features have a long-term EFS of around 70% at 4 years, compared with 20% or less in patients with adverse features. PET scan uptake at the time of HD has emerged as the main prognostic factor.[32] Therefore,

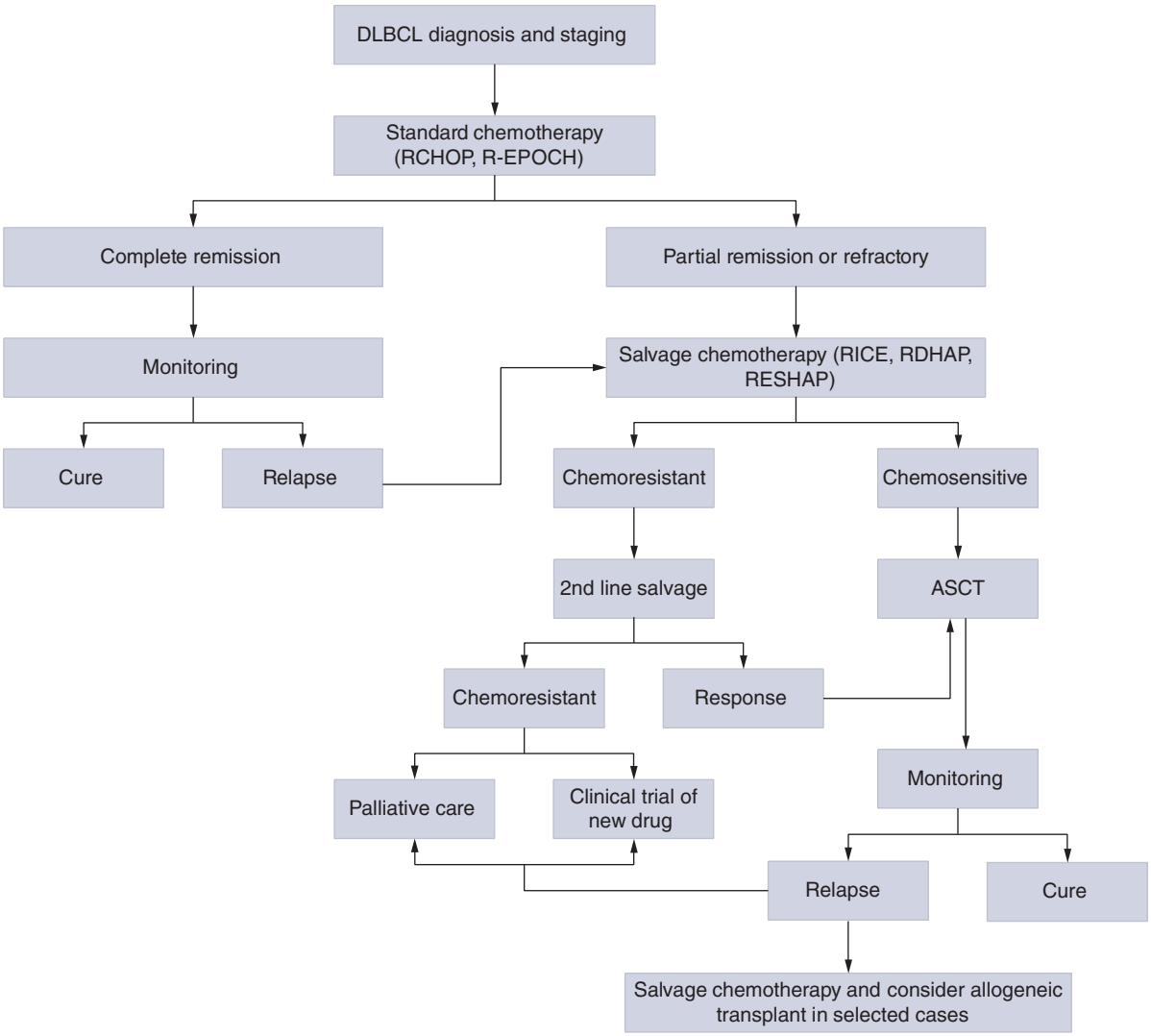


FIGURE 18–3 Algorithm for treatment of HL: stepwise description of HL treatment approach and the role of autologous and allogeneic progenitor-cell transplantation after relapse.

PET-adapted salvage therapy aiming at a PET-negative CR before transplant using non–cross-resistant lines of therapy has been shown to result in improved post-AHPCT outcomes.[33,34] Approaches to improve survival outcomes and prevent relapses after autologous SCT have included the development of more effective HDC regimens and/or post-AHPCT maintenance treatment. The combination of gemcitabine/busulfan/melphalan, developed at MDACC, resulted in improved 2-year PFS (65% vs 51%, $P < .01$) and OS (89% vs 73%; $P < .001$) when compared with matched-pair historical patients treated with BEAM, the standard HDC regimen in HL.[35,36]

In a phase 3 randomized trial, the use of post-AHPCT maintenance brentuximab vedotin for 16 cycles in patients with primary refractory disease or high-risk relapse (defined as prior CR1 shorter than 1 year or extranodal disease at the start of pretransplant salvage chemotherapy) resulted in a significant PFS advantage (59% vs 41% at 5 years), but without OS differences, compared with placebo.[37,38] In a small phase 2 trial, maintenance pembrolizumab led to 18-month PFS and OS rates of 82% and 100%, respectively.[39]

MULTIPLE MYELOMA

HDC with AHPCT is an established treatment for multiple myeloma (MM) (Fig. 18–4). In the era preceding the introduction of novel antimyeloma agents, AHPCT showed significantly superior PFS and OS rates compared with standard-dose chemotherapy (SDC) in several randomized trials.[40–42] Subsequently, the introduction of proteasome inhibitors (PI), immunomodulatory drugs

(IMiDs), and monoclonal antibodies in the up-front induction treatment led to significant improvement in the depth of response. In this modern setting, randomized trials have still shown benefit of AHPCT consolidation over nontransplant management including novel agents. In the randomized IFM 2009 trial, which included both PIs and IMiDs in frontline induction treatment, a higher CR rate (59% vs 48%; $P = .03$) and minimal residual disease negativity (79% vs 65%; $P < .001$) was observed among patients assigned to the frontline AHPCT arm, which translated into a significant PFS advantage (median 50 vs 36 months; $P < .001$) and no OS differences at short follow-up.[43]

Maintenance therapy post-transplant with lenalidomide has been shown to prolong EFS and perhaps OS, as shown in several randomized studies.[44,45] There is uncertainty about the optimal duration of lenalidomide treatment, because its use after ASCT has been associated with a small risk of secondary malignancies in the French, but not in the US, study. In the recent updates of the US trial, lenalidomide discontinuation at 3 years was associated with inferior PFS (80% vs 61%) and therefore, depending on patient preference and tolerability, our preference has been to continue maintenance therapy indefinitely. Some centers have adopted a risk-adapted maintenance approach in newly diagnosed myeloma with double-agent maintenance (PI + IMiD) in high-risk patients that has led to significant improvement in survival rates.

The use of a second course of high-dose melphalan ("tandem" transplants) has been compared with a single transplant in randomized trials in Europe and the US, which have shown conflicting results. In the European trial, patients who received a tandem AHPCT had greater 3-year PFS than patients who received a single AHPCT (73% vs 60%, respectively) and improved 3-year OS compared with single AHCT (89% vs 85%, respectively).[46] In contrast, in the US Intergroup study, the 3-year PFS rate was 58% for tandem AHPCT with maintenance lenalidomide, 58% for single AHPCT/consolidation with four cycles of bortezomib/lenalidomide/dexamethasone (VRD)/maintenance lenalidomide, and 54% for AHPCT/maintenance with lenalidomide.[47] Important differences in study design between both trials probably account for their differing results. Importantly, one group which appears to benefit from tandem transplant is that of patients with high-risk cytogenetics. Both in the European and the US trials, the subgroups with high-risk cytogenetics have shown superior PFS with tandem AHPCT compared with a single AHPCT.[46,48]

Role of Salvage or Second Transplant

Several retrospective analyses have demonstrated durable responses of a second salvage course of HDC with autologous SCT for patients with relapsed disease.[49] In general, the outcomes appear more favorable for patients who had relapse later than 12 months after a first AHPCT and who respond to subsequent salvage treatment.[50] A randomized controlled trial conducted in the UK comparing salvage AHPCT with salvage SDC showed superior PFS (median 19 months vs 11 months, HR 0.36; $P < .0001$) and OS (median 67 months vs 52 months, HR 0.56; $P = .01$) for the transplant arm.[51,52]

Newer HDC Regimens

For the past 40 years, the standard HDC regimen for AHPCT in MM has been high-dose melphalan (200 mg/m^2). The only regimen that has shown superiority over melphalan as frontline consolidation has been intravenous busulfan/melphalan (Bu/Mel) in a randomized trial conducted at MDACC, where Bu/Mel resulted in significantly better PFS (64 months vs 43 months, HR 0.53; $P = .02$), particularly in the subset of patients with high-risk cytogenetics.[53] Gemcitabine/busulfan/melphalan, a regimen built from Bu/Mel exploiting the inhibition by gemcitabine of DNA damage repair, showed in a phase 2 trial conducted at MDACC in patients with relapsed or refractory myeloma, significantly superior PFS and OS compared with matched-pair historical controls who received high-dose melphalan.[54] The combinations of PI with high-dose alkylators, which shows synergy when given in the correct sequence, has shown promising clinical results.[55–57]

Other promising new therapies under current investigation in myeloma that could be easily implemented in the post-AHCT setting include tumor vaccines[58] and cellular immunotherapy with chimeric antigen receptor T-cells.[59]

SOLID TUMORS

Germ-Cell Tumors

Testicular germ-cell tumors (GCTs) are the most common malignancy in young men between the ages of 20 and 35 years. GCTs are highly curable, even in patients with advanced disease. Frontline cisplatin-based SDC cures 90% of advanced good-risk patients, 80% of those with intermediate risk and 50% of those with poor risk. To study whether AHPCT could improve results in intermediate- and poor-risk patients, tandem cycles of HDC were compared with SDC in a US Intergroup trial, with no significant differences in EFS or OS.[60]

In patients with relapsed disease, the best approach for salvage therapy remains unsettled. Salvage cisplatin–based SDC regimens, such as paclitaxel/ifosfamide/

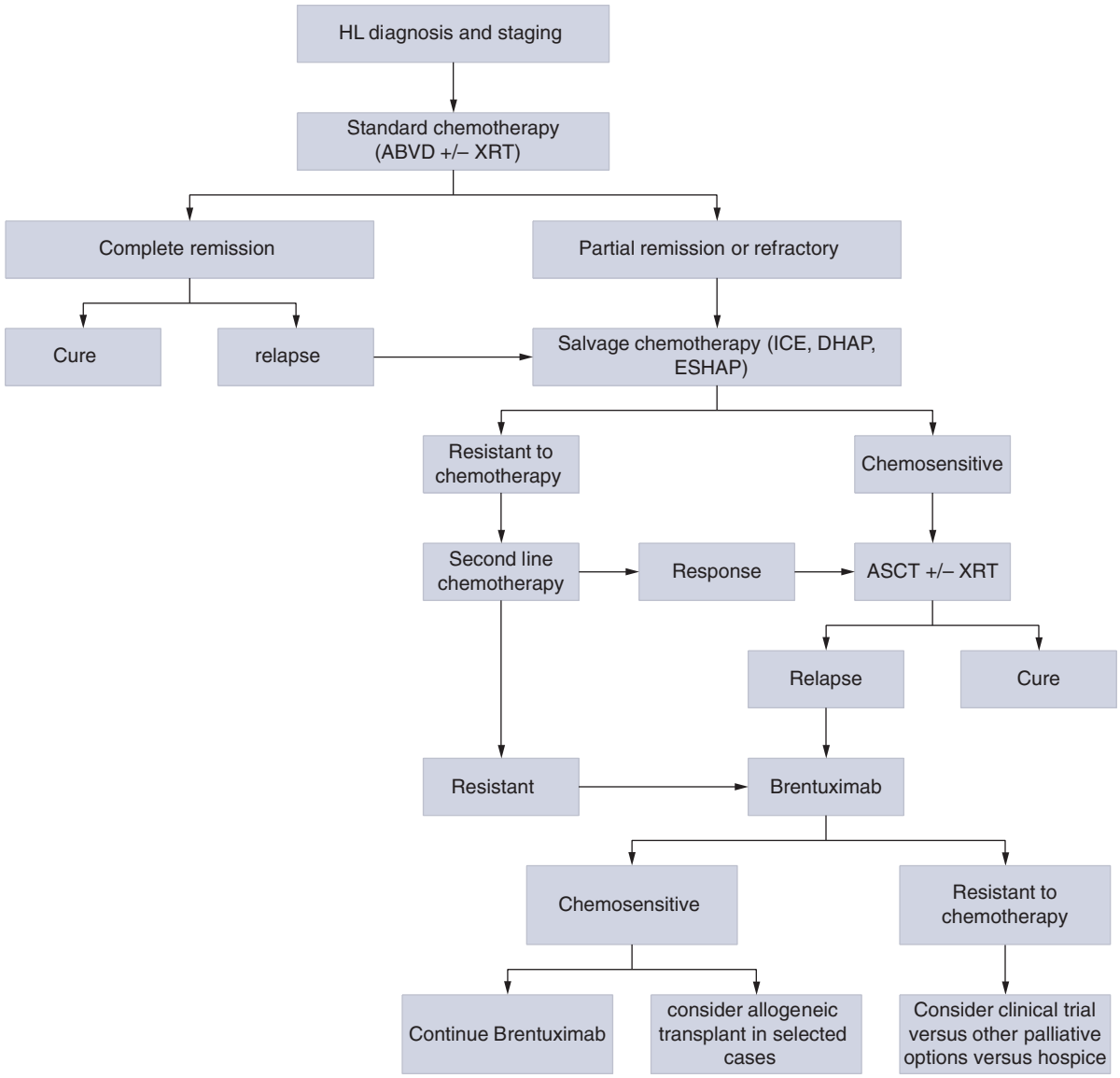


FIGURE 18–4 Algorithm for the treatment of MM: stepwise description of MM treatment approach and the role of autologous and allogeneic progenitor-cell transplantation after relapse.

cisplatin (TIP), result in CR rates of 50% to 60% and long-term EFS of 20% to 30%.[61] The use of tandem cycles of HDC with carboplatin and etoposide (CE) with AHPCT, developed at Indiana University, has shown efficacy. A retrospective analysis of a cohort of 364 patients transplanted with tandem CE in 2004 to 2014 showed that patients transplanted in the first relapse had better outcomes than those transplanted in the second or later relapse (2-year EFS of 63% and 49%, respectively).[62] The addition of a third drug, such as cyclophosphamide, ifosfamide, paclitaxel, or thiotepa, to CE, results in cure of 40% to 50% of patients with cisplatin-sensitive tumors, but only of 4% to 20% of those with refractory disease.[63–66]

Feldman et al tested the use of three cycles of HDC in 107 patients with relapsed disease and unfavorable prognostic features. Of them, 76% were transplanted at first relapse, 20% at second relapse, and 4% at third or later relapse; 76% were cisplatin refractory. These patients received two cycles of paclitaxel/ifosfamide followed by three cycles of high-dose CE, with 47% EFS at 5 years.[67] The EFS rates in patients in first relapse and second or later relapses were 55% and 23%, respectively.

Our group at MDACC focused on patients with a very poor prognosis for the development of more potent HDC seeking new synergistic interactions. Testing the potential synergy between bevacizumab and chemotherapy, we conducted a phase 2 trial of

tandem cycles of bevacizumab-HDC in patients with advanced refractory relapses.[68] In our initial report, 42 patients with heavily pretreated tumors (median 3 prior relapses), 87% of them cisplatin refractory, received a first HDC cycle with bevacizumab and gemcitabine/docetaxel/melphalan/carboplatin followed by a second AHPCT with bevacizumab + ifosfamide/carboplatin/etoposide. At a median follow-up of 46 months, the EFS and OS rates were 56% and 58%, respectively, clearly exceeding the expected outcomes in this population with very poor prognosis. Bevacizumab was subsequently omitted in a second cohort seeking to increase treatment tolerability.[69] At median follow-up of this second cohort of 26 months, the EFS and OS rates were 71% and 74%, respectively. These encouraging results, with or without bevacizumab, likely result from a synergistic interaction between gemcitabine and the other agents based on DNA damage repair inhibition through suppression of nucleotide excision repair, a major mechanism of cisplatin resistance in GCT cells.[70]

There is no consensus yet about whether HDC should be considered for all patients in first relapse. Two cycles of HDC seem more effective than a single cycle.[71] Results of tandem cycles of HDC as salvage treatment appear superior to those expected with SDC.[72] The randomized phase 3 TIGER trial is underway and addresses this important question, comparing TI-CE, with three cycles of HDC, with SDC (TIP × 4).[73]

In summary, the current data available from randomized trials do not support a standard role for HDC in frontline treatment of GCT. Further clarity in its role as part of salvage treatment in first relapse awaits completion of the ongoing randomized TIGER trial. Finally, HDC is widely accepted as an established treatment for patients in second or later relapse.

OTHER SOLID TUMORS

Initial phase 2 studies of HDC in patients with high-risk primary breast cancer (HRPBC) sparked enthusiasm by showing encouraging long-term PFS rates of 57% to 72% in patients with involvement of 10 or more axillary lymph nodes.[74,75] These results led to a significant increase in the number of transplantations performed in the 1990s and prompted randomized phase 3 trials. Fifteen randomized trials of HDC with AHPCT were conducted for HRPBC, defined as 4 or more positive nodes and, in some trials, 10 or more positive nodes. Although most trials showed EFS benefit, only two showed OS benefit. A meta-analysis of those trials (N = 6210) demonstrated at a median follow-up of 6 years a significant benefit in EFS (HR 0.87, $P < .001$) but no significant difference in OS (HR 0.94, $P = .13$).[76] More recently, a long-term report at 20-year follow-up of the largest of those randomized trials, conducted in the Netherlands, showed an improved OS for the subset of patients with very high risk (≥10 more involved nodes) in the HDC arm.[77]

Similar to HRPBC, the initial prospective HDC trials in metastatic breast cancer (MBC) showed very high response and CR rates and apparently improved long-term disease control. Those results led to randomized trials comparing HDC with SDC in chemosensitive MBC. Six of those eight trials demonstrated an EFS advantage for HDC, but only one showed OS benefit. A meta-analysis showed a statistically significant improvement in PFS (median 11 vs 8 months, HR 0.76; $P < .001$), however with no statistically significant OS benefit.[78]

In conclusion, randomized trials in the MBC and HRPBC settings have shown improvement in PFS but have largely failed to show OS benefit. The meta-analyses did detect a statistically significant 13% decrease in the risk of relapse in HRPBC and a 24% decrease in the risk of progression in MBC. Although there are still populations that might benefit from HDC, such as patients with 10 or more involved nodes,[77] inflammatory breast cancer,[79] or oligometastatic disease,[80] HDC has been largely abandoned as a treatment for breast cancer.

HDC has been evaluated in other chemosensitive solid tumors in adults, including ovarian cancer, small-cell lung cancer, melanoma, malignant gliomas, and sarcomas. Most of those studies were small and failed to show a survival benefit.[81]

CONCLUSIONS

In summary, HDC with AHPCT is a safe treatment that achieves major tumor cytoreduction and is curative for NHL, HL, MM, and GCT in a variety of settings. Current studies focus on improvement of current HDC regimens and post-transplant strategies to prevent regrowth of minimal residual disease.

MD ANDERSON PRACTICE TIPS

- As of this writing, there is no role of up-front autologous transplant in first remission in B-cell non-Hodgkin (except for selected patients with high-risk IPI aggressive lymphoma) and Hodgkin lymphomas. In contrast, most patients with T-cell lymphoma (except those with ALK-positive anaplastic large-cell lymphoma) seem to benefit from an up-front consolidation autologous transplant.
- A subset of patients with follicular lymphoma who have disease progression within 2 years after frontline chemoimmunotherapy have a poor prognosis, and early autologous transplantation is recommended in these patients.
- High-risk patients with MM benefit from dose intensification of conditioning chemotherapy. Patients with high-risk characteristics are offered a combination of intravenous busulfan and melphalan at our center.
- Maintenance with brentuximab vedotin after autologous transplant in HL has led to significant improvement in PFS and is routinely considered for patients with high-risk relapse at MDACC.
- The novel HDC regimen of vorinostat/gemcitabine/busulfan/melphalan for autologous transplant in Hodgkin and non-Hodgkin lymphomas has produced impressive outcomes in high-risk disease-relapsed patients. Patients with refractory diseases and high-risk features are offered this novel HDC regimen, preferably as part of a clinical trial, at MDACC.
- Relapsed GCTs are considered for tandem ASCT at MDACC. High-risk relapses or advanced (second or later) relapses are offered our tandem approach of gemcitabine/docetaxel/melphalan/carboplatin for the first ASCT and ICE for the second ASCT, which have shown results that appear to be superior to those with the more traditional tandem approach of carboplatin/etoposide × 2.

REFERENCES

1. Ikeda K, Kozuka T, Harada M. Factors for PBPC collection efficiency and collection predictors. *Transfus Apher Sci*. 2004;31(3):245-259.
2. Popat U, Saliba R, Thandi R, et al. Impairment of filgrastim-induced stem cell mobilization after prior lenalidomide in patients with multiple myeloma. *Biol Blood Marrow Transplant.* 2009;15(6):718-723.
3. Devine SM, Flomenberg N, Vesole DH, et al. Rapid mobilization of CD34 + cells following administration of the CXCR4 antagonist AMD3100 to patients with multiple myeloma and non-Hodgkin's lymphoma. *J Clin Oncol.* 2004;22:1095-1102.
4. de Lima M, Couriel D, Thall PF, et al. Once-daily intravenous busulfan and fludarabine: clinical and pharmacokinetic results of a myeloablative, reduced-toxicity conditioning regimen for allogeneic stem cell transplantation in AML and MDS. *Blood.* 2004;104(3):857-864.
5. Nieto Y, Thall P, Valdez B, et al. High-dose infusional gemcitabine combined with busulfan and melphalan with autologous stem-cell transplantation in patients with refractory lymphoid malignancies. *Biol Blood Marrow Transplant.* 2012;18(11):1677-1686.
6. Nieto Y, Valdez BC, Thall PF, et al. Vorinostat combined with high-dose gemcitabine, busulfan, and melphalan with autologous stem cell transplantation in patients with refractory lymphomas. *Biol Blood Marrow Transplant.* 2015;21(11):1914-1920.
7. Nieto Y, Valdez BC, Thall PF, et al. Double epigenetic modulation of high-dose chemotherapy with azacitidine and vorinostat for patients with refractory or poor-risk relapsed lymphoma. *Cancer.* 2016;122:2680-2688.
8. Ketterer N, Salles G, Raba M, et al. High CD34 (+) cell counts decrease hematologic toxicity of autologous peripheral blood progenitor cell transplantation. *Blood*. 1998;91(9):3148-3155.
9. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant.* 2009;15(10):1143-1238.
10. Cooke KR, Yanik GA. Lung injury following hematopoietic cell transplantation. In: Appelbaum FR, Forman SJ, Negrin RS, Blume KG, eds. *Thomas' Hematopoietic Cell Transplantation: Stem Cell Transplantation*. 4th ed. Wiley-Blackwell; 2009.
11. Nieto Y, Cagnoni PJ, Bearman SI, et al. Cardiac toxicity following high-dose cyclophosphamide, cisplatin, and BCNU (STAMP-I) for breast cancer. *Biol Blood Marrow Transplant.* 2000;6:198-203.
12. Openshaw H. Neurologic complications of hematopoietic cell transplantation. In: Appelbaum FR, Forman SJ, Negrin RS, Blume KG, eds. *Thomas' Hematopoietic Cell Transplantation: Stem Cell Transplantation*. 4th ed. Wiley-Blackwell; 2009.
13. Kandell FR. Endocrine complications following hematopoietic cell transplantation. In: Appelbaum FR, Forman SJ, Negrin RS, Blume KG, eds. *Thomas' Hematopoietic Cell Transplantation: Stem Cell Transplantation*. 4th ed. Wiley-Blackwell; 2009.
14. Hingorani S. Kidney and bladder complications of hematopoietic cell transplantation. In: Appelbaum FR, Forman SJ, Negrin RS, Blume KG, eds. *Thomas' Hematopoietic Cell Transplantation: Stem Cell Transplantation*. 4th ed. Wiley-Blackwell; 2009.
15. Bearman SI. The syndrome of hepatic veno-occlusive disease after marrow transplantation. *Blood.* 1995;85:3005-3020.
16. Strasser SI, McDonald GB. Gastrointestinal and hepatic complications. In: Appelbaum FR, Forman SJ, Negrin RS, Blume KG, eds. *Thomas' Hematopoietic Cell Transplantation: Stem Cell Transplantation*. 4th ed. Wiley-Blackwell; 2009.
17. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. *N Engl J Med.* 2016;375(8):740-753.
18. Andersson BS, Madden T, Tran HT, et al. Acute safety and pharmacokinetics of intravenous busulfan when used with oral busulfan and cyclophosphamide as pretransplant conditioning therapy: a phase I study. *Biol Blood Marrow Transplant.* 2000; 6:548-554.
19. Richardson PG, Riches ML, Kernan NA, et al. Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. *Blood*. 2016;127:1656-1665.
20. Bhatia S, Bhatia R. Secondary malignancies after hematopoietic cell transplantation. In: Appelbaum FR, Forman SJ, Negrin RS, Blume KG, eds. *Thomas' Hematopoietic Cell Transplantation: Stem Cell Transplantation*. 4th Edition. Wiley-Blackwell; 2009.
21. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med*. 1995;333(23):1540-1545.
22. Gisselbrecht C, Glass B, Mounier M, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol*. 2010;28(27):4184-4190.
23. Epperla N, Hamadani M, Reljic T, et al. Upfront autologous hematopoietic stem cell transplantation consolidation for patients with aggressive B-cell lymphomas in first remission in the rituximab era: a systematic review and meta-analysis. *Cancer.* 2019;125:4417-4425.
24. Gribben JG. Autologous hematopoietic transplantation for low-grade lymphomas. *Cytotherapy*. 2002; 4:205-215.
25. Ladetto M, Zallio F, Vallet S, et al. Concurrent administration of high-dose chemotherapy and rituximab is a feasible and effective chemo/immunotherapy for patients with high-risk non-Hodgkin's lymphoma. *Leukemia.* 2001;15:1941-1949.
26. Schouten HC, Qian W, et al. High-dose therapy improves progression-free survival and survival in relapsed follicular non-Hodgkin's lymphoma: results from the randomized European CUP Trial. *J Clin Oncol.* 21:3918-3927.
27. Casulo C, Friedberg J, Ahn KW, et al. Autologous transplantation in follicular lymphoma with early therapy failure: a national LymphoCare Study and Center for International Blood and Marrow Transplant Research Analysis. *Biol Blood Marrow Transplant*. 2018;24:1163-1171.
28. Smith S, Godfrey J, Ahn KW, et al. Autologous transplantation versus allogeneic transplantation in patients with follicular lymphoma experiencing early treatment failure. *Cancer*. 2018;124:2541-2551.
29. Jurinovic V, Metzner B, Pfreundschuh, et al. Autologous stem cell transplantation for patients with early progression of follicular lymphoma: a follow-up study of 2 randomized trials from the German Low Grade Lymphoma Study Group. *Biol Blood Marrow Transplant*. 2018; 24:1172-1179.
30. Linch DC1, Winfield D, Goldstone AH, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. *Lancet.* 1993;341:1051-1054.
31. Schmitz N, Pfistner B, Sextro M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial of the German Hodgkin's Lymphoma Study Group (GHSG) and the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation (EBMT). *Lancet.* 2002;359:2065-2071.
32. Moskowitz A, Yahalom J, Kewalramani T, et al. Pretransplantation functional imaging predicts outcome following autologous stem cell transplantation for relapsed and refractory Hodgkin lymphoma. *Blood.* 2010;116:4934-4937.
33. Moskowitz CH · Matasar MJ, Zelenetz AD, et al. Normalization of pre-ASCT, FDG-PET imaging with second-line, non-cross-resistant, chemotherapy programs improves event-free survival in patients with Hodgkin lymphoma. *Blood.* 2012;119:1665-1670.

34. Moskowitz AJ, Schöder H, Yahalom J. et al. PET-adapted sequential salvage therapy with brentuximab vedotin followed by augmented ifosamide, carboplatin, and etoposide for patients with relapsed and refractory Hodgkin's lymphoma: a non-randomised, open-label, single-centre, phase 2 study. *Lancet Oncol*. 2015;16:284-292.
35. Nieto Y, Popat U, Anderlini P, et al. Autologous stem cell transplantation for refractory or poor-risk relapsed Hodgkin's lymphoma: effect of the specific high-dose chemotherapy regimen on outcome. *Biol Blood Marrow Transplant* 2013;19:410-417.
36. Nieto Y, Thall PF, Ma J, et al. Phase II trial of high-dose gemcitabine/busulfan/melphalan with autologous stem cell transplantation for primary refractory or poor-risk relapsed Hodgkin lymphoma *Biol Blood Marrow Transplant*. 2018;24:1602-1609.
37. Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomized, double-blind, placebo-controlled phase 3 trial. *Lancet.* 2015;385:1853-62
38. Moskowitz CH, Walewski J, Nademanee A, et al. Five-year PFS from the AETHERA trial of brentuximab vedotin for Hodgkin lymphoma at high risk of progression or relapse. *Blood.* 2018;2639-2642.
39. Armand P, Chen Y-B , Redd RA, et al. PD-1 blockade with pembrolizumab for classical Hodgkin lymphoma after autologous stem cell transplantation. Blood. 2019;134:22-29.
40. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. *N Engl J Med*. 1996;335(2):91-97.
41. Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med.* 2003;348:1875-1883.
42. Palumbo A, Triolo S, Argentino C, et al. Dose-intensive melphalan with stem cell support (MEL100) is superior to standard treatment in elderly myeloma patients. *Blood*. 1999;94(4):1248-1253.
43. Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. *N Engl J Med*. 2017;376:1311-1320.
44. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med.* 2012;366:1782-1791.
45. McCarthy P, Owzar K, Hofmeister C, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med.* 2012;366:1770-1781.
46. Cavo M, Gay F, Beksac M, et al. Autologous haematopoietic stem-cell transplantation versus bortezomib-melphalan-prednisone, with or without bortezomib-lenalidomide-dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): a multicentre, randomised, open-label, phase 3 study. *Lancet Haematol.* 2020;7:e456-e468.
47. Stadtmauer EA, Pasquini MC, Blackwell B. Autologous transplantation, consolidation, and maintenance therapy in multiple myeloma: results of the BMT CTN 0702 Trial. *J Clin Oncol.* 2019;37:589-597.
48. Parameswaran Hari, Pasquini MC, Stadtmauer EA, et al. Long-term follow-up of BMT CTN 0702 (STaMINA) of post-autologous hematopoietic cell transplantation (autoHCT) strategies in the upfront treatment of multiple myeloma (MM). Presented at the 2020 ASCO Virtual Scientific Meeting. Accessed April 6, 2021. https://meetinglibrary.asco.org/record/186147/abstract
49. Shah N, Ahmed F, Bashir Q, et al. Durable remission with salvage second autotransplants in patients with multiple myeloma. *Cancer.* 2012;118(14):3549-3555.
50. WI Gonsalves, MA Gertz, MQ Lacy, et al. Second auto-SCT for treatment of relapsed multiple myeloma. *Bone Marrow Transplant.* 2013;48,568-573.
51. Cook G, Williams C, Brown JM et al. High-dose chemotherapy plus autologous stem-cell transplantation as consolidation therapy in patients with relapsed multiple myeloma after previous autologous stem-cell transplantation (NCRI Myeloma X Relapse [Intensive trial]): a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2014;15:874-885.
52. Cook G, Ashcroft AJ, Cairns DA, et al. The effect of salvage autologous stem-cell transplantation on overall survival in patients with relapsed multiple myeloma (final results from BSBMT/UKMF Myeloma X Relapse [Intensive]): a randomised, open-label, phase 3 trial. *Lancet Haematol.* 2016;3:e340-e351.
53. Bashir Q, Thall PF, Milton DR, et al. Conditioning with busulfan plus melphalan versus melphalan alone before autologous haemopoietic cell transplantation for multiple myeloma: an open-label, randomised, phase 3 trial. *Lancet Haematol.* 2019;6(5):e266-e275.
54. Nieto Y, Valdez BC, Pingali SR, et al. High-dose gemcitabine, busulfan, and melphalan for autologous stem-cell transplant in patients with relapsed or refractory myeloma: a phase 2 trial and matched-pair comparison with melphalan. *Lancet Haematol.* 2017;4(6):e283-e292
55. Rodriguez T, Hari P, Stiff PJ, et al. Busulfan, melphalan, and bortezomib versus high-dose melphalan as a conditioning regimen for autologous hematopoietic stem cell transplantation in multiple myeloma. *Biol Blood Marrow Transplant.* 2016;22:1391-1396
56. Roussel M, Moreau P, Huynh A, et al. Bortezomib and high-dose melphalan as conditioning regimen before autologous stem cell transplantation in patients with de novo multiple myeloma: a phase 2 study of the Intergroupe Francophone Du Myelome (IFM). *Blood.* 2010;115;32-37.
57. Lonial S, Kaufman J, Tighiouart M, et al. A phase I/II trial combining high-dose melphalan and autologous transplant with bortezomib for multiple myeloma: a dose- and schedule-finding study. *Clin Cancer Res.* 2010;16:5079-5086.
58. Rosenblatt J, Avivi I, Vasir B, et al. Vaccination with dendritic cell/tumor fusions following autologous stem cell transplant induces immunologic and clinical responses in multiple myeloma patients. *Clin Cancer Res.* 2013;19:3640-3648.
59. Garfall AL, Stadtmauer EA, Hwang W-T, et al. Anti-CD19 CAR T cells with high-dose melphalan and autologous stem cell transplantation for refractory multiple myeloma. *JCI Insight.* 2019;4(4):e127684.
60. Motzer RJ, Nichols CJ, Margolin KA, et al. Phase III trial of conventional-dose chemotherapy with or without high-dose chemotherapy and autologous hematopoietic stem-cell rescue as first-line treatment for patients with poor prognosis metastatic germ cell tumors. *J Clin Oncol*. 2007;25:247-256.
61. Kondagunta GV, Bacik J, Donadio A, et al. Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. *J Clin Oncol.* 2005;23:6549-6555.
62. Adra N, Abonour R, Althouse SK, et al. High-dose chemotherapy and autologous peripheral-blood stem-cell transplantation for relapsed metastatic germ cell tumors: the Indiana University experience. *J Clin Oncol.* 2017;35:1096-1102.
63. Siegert W, Beyer J, Strohscheer I, et al. High-dose treatment with carboplatin, etoposide and ifosfamide followed by autologous stem-cell transplantation in relapsed or refractory germ cell cancer: a phase I/II study. *J Clin Oncol.* 1994;12:1223-1231.
64. Motzer RJ, Mazumdar M, Bosl GJ, et al. High-dose carboplatin, etoposide, and cyclophosphamide for patients with refractory germ cell tumors: treatment results and prognostic factors for survival and toxicity. *J Clin Oncol.* 1996;14:1098-1105.

65. Margolin K, Doroshow JH, Ahn C, et al. Treatment of germ cell cancer with two cycles of high-dose ifosfamide, carboplatin, and etoposide with autologous stem-cell support. *J Clin Oncol.* 1996;14:2631-2637.
66. Margolin KA, Doroshow JH, Frankel P, et al. Paclitaxel-based high-dose chemotherapy with autologous stem-cell rescue for relapsed germ cell cancer. *Biol Blood Marrow Transplant.* 2005;11:903-911.
67. Feldman DR, Sheinfeld J, Bajorin DF, et al. TI-CE high-dose chemotherapy for patients with previously treated germ cell tumors; results and prognostic factor analysis. *J Clin Oncol.* 2010;28:1706-1713.
68. Nieto Y, Tu SM, Bassett R, et al. Bevacizumab/high-dose chemotherapy with autologous stem-cell transplant for poor-risk relapsed or refractory germ-cell tumors. *Ann Oncol.* 2015;26:2125-2132.
69. Nieto Y, Tu S-M, Campbell MT, et al. Infusional gemcitabine + docetaxel/melphalan/carboplatin (GemDMC) ± bevacizumab (BEV) as an effective high-dose chemotherapy (HDC) regimen for refractory of poor-risk relapsed germ-cell tumors (GCT). *J Clin Oncol.* 2017;35(suppl):abstract 4519.
70. Usanova S, Piée-Staffa A, Sied U, et al. Cisplatin sensitivity of testis tumour cells is due to deficiency in interstrand-crosslink repair and low ERCC1-XPF expression. *Mol Cancer*. 2010:9:248.
71. Kilari D, D'Souza A, Fraser R, et al. Autologous hematopoietic stem cell transplantation for male germ cell tumors: improved outcomes over 3 decades. *Biol Blood Marrow Transplant.* 2019;25:1099-1106.
72. Lorch A, Bascoul-Mollevi C, Kramar A, et al. Conventional-dose versus high-dose chemotherapy as first salvage treatment in male patients with metastatic germ cell tumors: evidence from a large international database. *J Clin Oncol.* 2011;29:2178-2184.
73. Feldman DR, Huddart R, Hall E, et al. Is high dose therapy superior to conventional dose therapy as initial treatment for relapsed germ cell tumors? The TIGER Trial. *J Cancer*. 2011;2:374-377.
74. Peters WP, Ross M, Vredenburgh JJ, et al. High-dose chemotherapy and autologous bone marrow support as consolidation after standard-dose adjuvant therapy for high-risk primary breast cancer. *J Clin Oncol.* 1993;11:1132-1143.
75. Gianni AM, Siena S, Bregni M, et al. Efficacy, toxicity, and applicability of high-dose sequential chemotherapy as adjuvant treatment in operable breast cancer with 10 or more involved axillary nodes: five-year results. *J Clin Oncol.* 1997;15:2312-2321.
76. Berry DA, Ueno NT, Johnson MM, et al. High-dose chemotherapy with autologous hematopoietic stem-cell transplantation in metastatic breast cancer: overview of six randomized trials. *J Clin Oncol.* 2011;29:3224-3231.
77. Steenbruggen TG, Steggink LC, Seynaeve CM, et al. High-dose chemotherapy with hematopoietic stem cell transplant in patients with high-risk breast cancer and 4 or more involved axillary lymph nodes: 20-year follow-up of a phase 3 randomized clinical trial. *JAMA Oncol.* 2020;6:528-534.
78. Berry DA, Ueno NT, Johnson MM, et al. High-dose chemotherapy with autologous hematopoietic stem-cell transplantation in metastatic breast cancer: overview of six randomized trials. *J Clin Oncol.* 2011;29:3224-3231.
79. Cagnoni PJ, Nieto Y, Shpall EJ, et al. High-dose chemotherapy with autologous hematopoietic progenitor-cell support as part of combined modality therapy in patients with inflammatory breast cancer. *J Clin Oncol.* 1998;16:1661-1668.
80. Nieto Y, Nawaz S, Jones RB, et al. Prognostic model for relapse after high-dose chemotherapy with autologous stem-cell transplantation for stage IV oligometastatic breast cancer. *J Clin Oncol*. 2002;20:707-718.
81. Nieto Y, Jones RB, Shpall EJ. Stem-cell transplantation for the treatment of advanced solid tumors. *Semin Immunopathol*. 2004;26:31-56.

This page intentionally left blank

19 Allogeneic Transplantation

Rohtesh S. Mehta
Chitra Hosing

KEY CONCEPTS

- The numbers of allogeneic hematopoietic stem cell transplantation (HCT) are increasing over time, with an increasing use of alternative donors, and with increasing use of reduced-intensity conditioning (RIC).
- Myeloablative conditioning (MAC) for HCT is associated with a lower risk of relapse compared with RIC, but it is also associated with a higher risk of nonrelapse mortality (NRM).
- Age, performance status, and HCT-specific comorbidity index are some of the predictors of NRM and are taken into consideration along with the risk of relapse of the underlying disease, when deciding about conditioning intensity.
- Relapse of the underlying disease is the leading cause of deaths after allogeneic HCT, while graft-versus-host disease (GVHD) and infections are the leading causes of NRM after allogeneic HCT.
- Risk of relapse may be reduced with the use of maintenance therapy after allogeneic HCT, which is an area of active investigation.
- Novel GVHD prophylaxis strategies are being explored to reduce the risk of GVHD and its associated morbidity and mortality.

Allogeneic hematopoietic stem cell transplantation (HCT) is a potentially curative approach for a variety of malignant and nonmalignant disorders. With the development of novel techniques of transplantation including the refinement of conditioning regimens and improved management of transplantation-associated toxicities, increasing numbers of patients with advanced age and/or comorbidities are now being transplanted. More than 9000 allogeneic HCTs were performed in the United States in 2018[1]; about 30% of patients were age 60 years or older and 6% were 70 years or older.[2] This chapter reviews the current state of the allogeneic HCT in general, with particular attention paid to strategies used at MDACC. The in-depth discussion of specific diseases and their indications for HCT can be found in their respective chapters.

HISTORICAL BACKGROUND

Research in the field of HCT intensified after the unfortunate events of nuclear bombing in 1945,[3] with one of the first HCT in humans performed in the late 1950s. The initial attempts at transplantation of bone marrow (BM) from fetal or adult cadavers in six patients with terminal conditions was unsuccessful without engraftment. However, it did provide important safety data about the infusion of BM with no case of pulmonary emboli.[4] A few years later, syngeneic BM transplantation (BMT) in two children with acute lymphoblastic leukemia (ALL) after lethal dose of total-body irradiation (TBI) led to successful engraftment, but the conditioning intensity was insufficient to prevent disease relapse.[5] Thereafter, modifications were made to intensify the conditioning regimen before transplantation. There was a vigorous interest in BMT in the early 1960s, with occasional success stories, but interest waned owing to extremely poor outcomes, engraftment in less than 40% of cases, and mortality in about 75% of patients.[6] This was partly related to the lack of knowledge about graft-versus-host disease (GVHD), which was not recognized until the mid-1960s,[7] and inadequate understanding of the human leukocyte antigen (HLA) system—the concept of which was

incorporated into the HCT setting in the late 1960s. The initial cases of successful "HLA-matched" sibling donor (MSD) HCTs were reported in 1968 in two children with nonmalignant hematologic disorders.[8,9] Of note, the HLA matching at that time was performed using historic serologic methods that detected antibodies in human serum that were capable of agglutinating human peripheral blood (PB) T-cells or B cells. With these successful cases, and with the mounting understanding of GVHD and the HLA system, the interest in BMT reemerged. Soon, the donor pool was expanded to involve unrelated donors, and the first successful HCT with an HLA-matched unrelated donor (MUD) was performed in 1973 on a 2-year-old boy with X-linked chronic granulomatous disorder.[10,11] Thereafter, successful cases of partially matched/mismatched haploidentical donor and umbilical cord blood (UCB) HCT were reported.

COMPONENTS OF ALLOGENEIC STEM CELL TRANSPLANTATION

The key components of allogeneic HCT include recipient, donor (related or unrelated), stem cell graft source (BM, PB, or UCB), HLA matching between the recipient and the donor (matched or mismatched), conditioning regimen intensity (myeloablative [MAC], nonmyeloablative [NMA], or reduced-intensity conditioning [RIC]), GVHD prophylaxis, and post-HCT supportive care. Each of these are discussed next individually.

Recipient

Allogeneic HCT is indicated for a variety of malignant (mostly hematologic and some solid tumors) and nonmalignant disorders (such as aplastic anemia, Fanconi anemia and other BM failure syndromes, hemophagocytic lymphohistiocytosis, severe combined immunodeficiency, Wiskott-Aldrich syndrome, sickle cell disease, thalassemia major, advanced autoimmune diseases, etc). However, for the purpose of brevity, this chapter will focus primarily on hematologic malignancies in adults, because acute myelogenous leukemia (AML), ALL, myelodysplastic syndrome (MDS), and myeloproliferative neoplasms (MPNs) are the most common indications that accounted for about 75% of all allogeneic HCTs performed in the United States in 2018.[1] Other hematologic malignancies, such as lymphoma, multiple myeloma, chronic lymphocytic leukemia, chronic myelogenous leukemia (CML), and nonmalignant diseases accounted for the rest.[1]

Given the risk of morbidity and mortality associated with allogeneic HCT, it is important to distinguish patients who are likely to do well without transplantation from those who will benefit the most from it while minimizing the risk of non-elapse mortality (NRM). Among several other elements, two patient-related factors that independently affect outcomes are (1) comorbidities, which determine the risk of NRM; and (2) disease risk, which impacts the risk of relapse and related mortality post-HCT.

One of the most commonly used tools to assess the risk of NRM is the HCT-specific comorbidity index (HCT-CI),[12] which is a combined score of several individual comorbidities, including cardiovascular, pulmonary, hepatic, or renal dysfunction, prior solid tumor, and diabetes, to name a few, each of which is assigned a distinct weighted score. Based on the total score, patients are divided into three risk categories—low (0), intermediate (1–2), and high (≥3), with corresponding NRM at 2 years of 14%, 21%, and 41%, respectively.[12] Subsequently, a composite scoring system incorporating age and HCT-CI was developed where one additional point was assigned for patients with 40 years or older. Patients with a score of 2 or lower had no increased increase of NRM compared with those with score 0, whereas those with a score of 3 or higher had a significantly higher risk. The risk of NRM varied by the conditioning intensity; it was significantly lower with NMA—but not after RIC—than with MAC. For patients with a score of 3 or 4, the incidence of NRM at 2 years was 17% (NMA), 36% (RIC), and 37% (MAC); and for patients with scores of 5 or above, it was 35% (NMA), 41% (RIC), and 49% (MAC).[13]

To determine disease risk, several systems can be used for prognostication that are either disease specific (eg, European LeukemiaNet [ELN] classification for AML,[14] Revised International Prognostic Scoring System [R-IPSS], for MDS[15]) or generic, such as the revised disease risk index (DRI).[16] The revised DRI (rDRI) classifies patients into one of the four risk groups based on the underlying disease and remission status at the time of HCT, with a 2-year overall survival (OS) of 66% (low risk), 51% (intermediate risk), 33% (high risk), or 23% (very high risk).[16] In general, patients with intermediate or high/very-high rDRI have an indication for transplantation, whereas low-risk patients benefit from nontransplantation approaches.

At MDACC, all patients undergo an extensive evaluation before transplantation to determine disease risk and to assess comorbidities. There is no specific age cutoff for transplantation, rather a patient's performance status, HCT-CI score, DRI, family and social support, and personal wishes are all taken into consideration. In addition, patients older than 60 years and those with poor performance status are also evaluated by a personalized, multidisciplinary team of the "Enhanced Recovery program," which includes HCT physicians, advanced care providers, nutritionists, physical and occupational therapists, pharmacists,

rehabilitation physicians, and geriatricians to assess and address patient frailty issues before HCT.

Donor

A majority of allogeneic HCTs in the United States are performed using an unrelated donor. The numbers of haploidentical HCT are increasing (21% of all HCT in 2018) and appear to be converging with that of MSD (25% of all HCT in 2018), whereas UCB transplantations have decreased over the past few years (Fig. 19–1).

The degree of HLA matching is one of the single most important determinants of GVHD and graft-versus-tumor (GVT) effect. Therefore, it is essential to have a thorough grasp of the topic. The major histocompatibility complex (MHC), called HLA in humans, is the most polymorphic gene cluster of the entire human genome, and encodes for a set of proteins on the cell surface that are responsible for antigen presentation to T-cells. The HLA complex is located on the short arm of chromosome 6 within the 6p21.3 region and contains more than 220 genes categorized into various classes. The class I includes three "classical" genes (HLA-A, B, C), three "nonclassical" genes (-E, -F, -G), and several pseudogenes (-H, -J, -K, -L, -N, -P, -S, -T, -U, -V, -W, -Y) with more than 19,000 alleles.[17] The HLA class I antigens are expressed on all nucleated cells (except those of the central nervous system) and on platelets, and its gene products present endogenous peptides to CD8+ T-cells. The class II genes include HLA-DR (-A, -B1 though -B9), -DQ (-A1, -A2, -B1), -DP (-A1, -A2, -B1, -B2), -DM (-A, -B), -DO (-A and -B) in humans, with more than 7000 alleles identified.[17] The HLA class II antigens are expressed on classical antigen-presenting cells (monocytes, macrophages, dendritic cells, Langerhans cells, and B lymphocytes) and others, including endothelial cells and thymic epithelial cells; and they encode proteins that display processed antigenic peptides for presentation to CD4+ T-helper cells. The HLA class III region includes genes involved in the inflammatory response and encode for proteins of the complement system, heat shock proteins, and tumor necrosis family genes.[18,19] Further, there are several minor histocompatibility antigens (miHAs), which may differ even when the donor and recipient are identical with regard to MHC genes.[20] These miHAs are further classified as either hematopoietic-restricted minor H antigens (crucial for GVT effects), or broadly-expressed minor H antigens (crucial for both GVT and GVHD).[20,21]

For HCT outside the context of clinical trials, only the classical HLA class I genes (A, B, C) and class II genes (DP, DQ, DR) are tested, whereas HLA class III genes and miHAs are not. The definition of "HLA matching" depends on which loci are tested. For example, a donor may be labeled as a 6/6-HLA match (matched at HLA-A, -B, and -DRB1), 8/8-HLA match (HLA-A, -B, -C, and -DRB1), 10/10-HLA match (HLA-A, -B, -C, -DRB1, and -DQB1) and 12/12-HLA match (HLA-A, -B, -C, -DRB1, -DQB1-, and -DPB1). In general, a HLA-identical sibling is considered the gold standard and is the preferred donor when available versus MUD because of a significantly lower risk of development of GVHD[22,23] and survival advantage noted in some studies in a subset of patients.[22,24] In the absence of a suitable MSD, MUD can lead to comparable outcomes,[25–28] especially because the techniques of HLA typing are becoming more sophisticated, and allele-level matching across several loci is now being routinely performed. Among patients who are 10/10-HLA matched with an unrelated donor, -DPB1 mismatch, which is further categorized as permissive or nonpermissive based on the T-cell epitope grouping,[29] is of added significance. For instance, nonpermissive -DPB1 mismatches are associated with an increased risk of NRM and severe acute

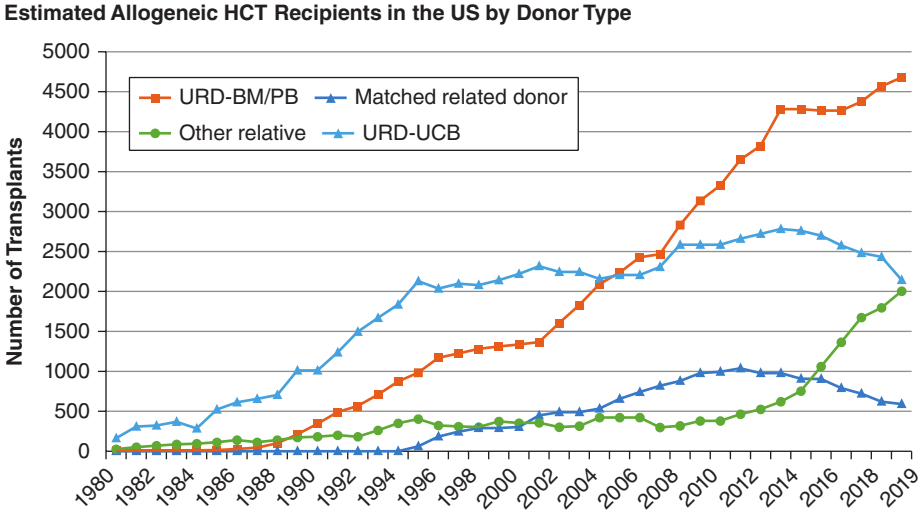


FIGURE 19–1 **Allogeneic HCT recipients in the United States by donor type. (Reproduced with permission from Phelan R, Arora M, Chen M: Current use and outcome of hematopoietic stem cell transplantation: CIBMTR US summary slides, 2020. https://www.cibmtr.org/ReferenceCenter/SlidesReports/SummarySlides/pages/index.aspx)**

GVHD, leading to poor OS compared with permissive -DPB1 mismatches. Compared with -DPB1–matched patient-donor pairs, permissive -DPB1 mismatches have a lower risk of relapse counterbalanced by a high risk of NRM, which leads to similar OS.[29] The current standard at MDACC is to test HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1 using high-resolution molecular methods, such as the polymerase chain reaction, sequence-based typing, or Sanger- or next-generation sequencing, in an attempt to find a donor matched at all loci ("12/12-HLA match"). The HLA matching requirements for UCB transplantation are somewhat different.

Although the terms *HLA-matched* and *HLA-identical* are often used interchangeably, especially with sibling donors, in its strictest sense, *HLA identity* means that the donor and recipient are matched for the entire amino acid sequence encoded by all HLA loci. Identity is assumed in the setting of related donor transplantation when segregation analysis demonstrates that the donor and recipient have inherited the same maternal and paternal haplotypes (genotypic HLA identity).[30] Otherwise, HLA identity can only be verified by sequencing all HLA loci (phenotypic HLA identity), which is impractical and rarely done. Because there is a strong linkage disequilibrium between HLA-B and -C genes and HLA-DRB1 and -DQB1 genes,[31] HLA matching in a sibling donor can generally be defined by HLA-A, -B, and -DRB1 typing ("6/6 HLA match"), because this would imply matching at HLA-C and -DQB1 as well ("10/10 HLA match"). However, there is a chance that the HLA-*matched* sibling may not be HLA-*identical*, even when they have inherited the same maternal and paternal haplotypes, although this is rare. One study using single-nucleotide polymorphism genotyping and full MHC genomic sequencing to estimate the level of the MHC identity in HLA-matched sibling HCT identified that only 4/255 (1.5%) "6/6-HLA-matched" pairs were mismatched at HLA-DPB1, and about 4% of the 6/6-HLA-matched sibling-patient pairs had large genomic differences in the MHC segment.[32]

Preparative/Conditioning Regimen

The goal of a conditioning regimen before stem cell infusion is (a) to eradicate or reduce tumor cell burden ("myeloablation," in the case of malignant disorders), and (b) to eradicate the recipient's cytotoxic lymphocytes ("lymphoablation"), thereby providing immunosuppression to prevent graft rejection. Conditioning regimens are categorized as either MAC, NMA, or RIC.[33] By definition, MAC regimens lead to prolonged and potentially irreversible pancytopenia without hematopoietic stem cell support, whereas NMA regimens cause minimal or no cytopenia and can thus be administered without stem cell infusion. The regimens that cannot be classified as either MAC or NMA are labeled as RIC regimens; these do cause cytopenia and require hematopoietic stem cell support.[33,34] Historically, all preparative regimens were myeloablative and included high doses of chemotherapy (generally alkylating agents) and/or TBI. However, older patients and those with high comorbidities were considered ineligible for allogeneic HCT because of significant regimen-related toxicities. Therefore, doses of radiation and/or chemotherapy in preparative regimens were inconsistently reduced to minimize these toxicities, and such regimens were arbitrarily labeled as either RIC, where, generally, the dose of alkylating agent(s) or TBI was generally reduced by at least 30%.[33,34] A few criteria were then proposed to establish uniformity in defining regimen intensity.[35] One of them, the "Champlin criteria," defined RIC as a regimen that "(1) results in reversible myelosuppression (usually within 28 days) when given without stem cell support; (2) results in mixed chimerism in a proportion of patients at the time of first assessment (usually 28–35 days post stem cell transplantation); and (3) it is associated with low rates of non-hematologic toxicity." A more concrete definition was formulated by an expert panel from the National Marrow Donor Program (NMDP)[36] and by the Center for International Blood and Marrow Transplantation Registry (CIBMTR).[1,37] This defined RIC as a regimen that consisted of: (a) <5 Gy TBI when given as a single fraction or ≤8 Gy if fractionated; (b) ≤9 mg/kg busulfan orally (or intravenous [IV] equivalent, 1.0 mg/kg oral Bu = 0.8 mg/kg IV Bu); (c) <10 mg/kg thiotepa; and (d) <140 mg/m^2 melphalan (or most recently ≤150 mg/m^2 melphalan),[37] generally with purine analogues such as fludarabine or cladribine (Fig. 19–2).

Common Conditioning Regimens in Acute Myelogenous Leukemia (AML) or Myelodysplastic Syndrome (MDS) Allogeneic HCT in the US, 2009-2019

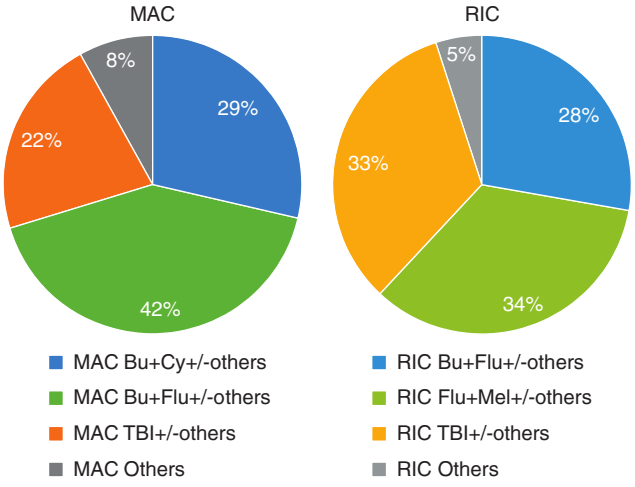


FIGURE 19–2 Common conditioning regimens in AML or MDS in allogeneic HCT in the United States from 2007-2017 (Reproduced with permission from Phelan R, Arora M, Chen M: Current use and outcome of hematopoietic stem cell transplantation: CIBMTR US summary slides, 2020. https://www.cibmtr.org/ReferenceCenter/SlidesReports/SummarySlides/pages/index.aspx)

Myeloablative Conditioning (MAC)

Myeloablative regimens can be broadly categorized as either chemotherapy based or TBI based, the latter used generally in conjunction with chemotherapy. The most commonly used chemotherapy drugs with high-dose TBI are cyclophosphamide (Cy/TBI)[38–42] and etoposide (TBI/Etoposide),[39,40] whereas others such as fludarabine (Flu/TBI),[43–45] cytarabine,[42,46] and melphalan,[43] are used less commonly. Increasing the total dose of TBI is associated with significantly lower risk of relapse, but it is offset by a higher NRM, leading to similar OS.[47,48–50] Hence, the concept of delivering TBI over multiple fractions each day was evaluated with a hypothesis that fractionated regimen would allow some recovery of normal tissues between the doses, thus theoretically lowering the toxicity while achieving satisfactory killing of malignant cells.[51–53]

Although efficacious, high-dose TBI is associated with a number of short- and long-term complications, including gastrointestinal (GI) and pulmonary toxicities, secondary malignancies, retarded growth, and/or intellectual development, cataracts, and endocrine dysfunction, to name a few. These concerns led to the development of radiation-free conditioning regimens. Of these, the combination of busulfan with either cyclophosphamide (Bu/Cy) or fludarabine (Bu/Flu) became the two most commonly used regimens. Busulfan was traditionally administered orally at a total dose of 16 mg/kg divided four times per day given over 4 consecutive days (1 mg/kg × 16 doses) followed by high-dose cyclophosphamide over 2 to 4 days (total dose about 120–200 mg/kg).[54,55] This was often complicated by excessive toxicities, including potentially fatal veno-occlusive disease (VOD)/sinusoidal obstruction syndrome (SOS) as a result of unpredictable intestinal absorption and erratic bioavailability of oral busulfan, especially when combined with an adverse interaction with cyclophosphamide,[56] because its metabolism varies considerably among individuals.[57] Further, the use of high-dose dual-alkylating agents, such as in the Bu/Cy regimen (both of which can deplete the liver of glutathione) can lead to overlapping toxicities.[58] Therefore, at MDACC, we substituted cyclophosphamide with fludarabine, which is as immunosuppressive as cyclophosphamide, has synergistic cytotoxicity with busulfan because it potentiates alkylator-induced cell killing through inhibition of DNA damage repair, and it does not cause SOS because it does not utilize the glutathione (GSH)/glutathione S-transferases (GST) and the hepatic CYP450-pathaways for metabolism. Moreover, replacement of oral busulfan with IV busulfan (0.8 mg/kg × 16 doses) led to dramatic reduction, but not elimination, of the risk of SOS and improved survival.[56] Intravenous busulfan has more predictable systemic drug exposure, especially when coupled with pharmacokinetic dose monitoring ("targeted-busulfan")[58] and allows for once-daily administration of both busulfan and fludarabine as a result of a long plasma half-life, which is much more practical and convenient.

With encouraging outcomes noted in multiple studies with the Bu/Flu regimen, this has become a standard MAC regimen both at MDACC[59,60] and at other major transplantation centers in North America.[61,62] In these Bu/Flu regimens, fludarabine is typically administered at a dose of 40–50 mg/m^2 on days –6 to –3, and each dose is followed immediately by IV busulfan on days –6 to –3, with the dose adjusted to achieve systemic exposure represented by an area under the curve (AUC) of an average 4000–6000 µmol/min per day, or total course AUC of 16,000–24,000 µmol/min. More recently, we developed a novel approach of delivering myeloablative doses of busulfan using a fractionated ("timed-sequential") regimen. Patients receive two doses of IV busulfan (80 mg/m^2 each) one to 2 weeks before HCT (either day –20 and –13, or days –13 and –12), followed by IV fludarabine and IV busulfan once daily on days –6 to –3. The dose of busulfan is guided by pharmacokinetic analysis, to achieve a total dose AUC of 16,000–20,000 ± 12% µmol/min.[63,64] With this approach, we have been able to safely administer MAC to patients up to 75 years of age and in those with significant comorbidities[63,64]—a population that would otherwise be deemed ineligible for MAC HCT.

Reduced-Intensity Conditioning/ Nonmyeloablative

The recognition of donor T-cell-mediated potent GVT effects emerged from studies in the late 1970s that noted inverse correlation between GVHD and leukemia relapse.[65–69] The hypothesis that GVT existed was further substantiated by the observations of a higher risk of relapse with syngeneic[70] than with allogeneic HCT, and higher risk of relapse with T-deplete than with T-replete grafts.[71] These findings collectively led to the origin of NMA/RIC regimens, where reduction in conditioning intensity was compensated by dependence on GVT effects, for patients who otherwise could not tolerate MAC.

Similar to MAC, NMA and RIC regimens can be chemotherapy and/or TBI-based. Preclinical work suggested that a TBI dose as low as 2 Gy was sufficient to allow engraftment of donor stem cells when used in conjunction with postgrafting immunosuppression.[72] Early studies from Fred Hutchinson Cancer Research Center used 2 Gy TBI as the sole conditioning regimen in patients with relative contraindications to MAC who underwent MSD HCT.[69] Donor lymphocyte infusions (DLI) were given post-HCT in patients with persistent malignancy and/or mixed chimerism. Although

20% failed to engraft, and relapse mortality was about 27%, the overall outcomes were encouraging, with about 67% survival as a result of low NRM (~7%).[69] Later, the addition of fludarabine to the regimen (Flu/TBI) improved donor chimerism and decreased graft rejection, but the rate of disease relapse/progression or related mortality remained significant.[73,74] Other studies added cyclophosphamide to fludarabine and low-dose TBI (Flu/Cy/TBI), a regimen popularly used in the setting of CBT[75,76] and haploidentical[77] HCT.

Among RIC, two that are commonly used at MDACC include fludarabine with an alkylating agent—either melphalan (Flu/Mel) or low-dose busulfan (Bu/Flu). Multiple studies from MDACC reported successful use of purine nucleoside analog-based regimens (mostly with fludarabine) and melphalan doses ranging from 100–180 mg/m^2, with or without other chemotherapy agents.[78–81] In the Bu/Flu-based RIC regimens, total dose of busulfan is 8 mg/kg orally (or 6.4 mg/kg IV) or lower. The so-called historical "FB2" regimen administered fludarabine with busulfan 3.2 mg/kg IV daily for 2 days (total dose 6.4 mg/kg IV) versus the traditional myeloablative "FB4" regimen, where busulfan 3.2 mg/kg IV daily was delivered for 4 days (total dose 12.8 mg/kg IV daily).[82,83] These definitions of FB2 versus FB4 are obsolete because a much lower dose of busulfan can also be delivered over 4 days (0.8 mg/kg IV daily × 4 days, with a total dose of 3.2 mg/kg IV).[84] Further, the concept of a fixed standard dose of busulfan is becoming outdated because the dosing is now routinely determined by the pharmacokinetic analysis, and the RIC regimens include doses that target total course AUC of 16,000 µmol/min or lower.[63,64,85]

Whenever possible, the standard at MDACC is to use MAC, at least for patients with myeloid malignancies, given the high risk of relapse and inferior survival with RIC regimens.[37] A phase 3 randomized trial conducted by the Blood and Marrow Transplantation Clinical Trials Network (BMT-CTN) compared RIC with MAC in patients up to 65 years of age with AML or MDS. The trial was stopped prematurely because of a significantly higher risk of relapse with RIC (48% vs 13%; $P < .001$), which translated to inferior disease-free survival (DFS) with RIC (47% vs 68%, $P < .01$) despite much lower NRM (4% vs 16%, $P = .002$) with RIC than with MAC, respectively.[37] Similar randomized trials are lacking patients with ALL, although many large retrospective studies suggested higher relapse and lower NRM with RIC, but similar survival between RIC and MAC.[86–88]

Sources of Hematopoietic Stem Cells

A separate chapter is dedicated to UCB transplantation, but this chapter will focus on BM- or PB-derived stem cells as the source of hematopoietic stem cells. The choice of stem cell/graft source has implications for both donor and recipient. Historically, hematopoietic stem cells were obtained through the harvest of BM from posterior superior iliac crests of normal donors. However, over the past decade, PB has become the most common graft source in adults undergoing MSD or MUD HCT, and more recently in the haploidentical HCT setting as well (Fig. 19–3).[1]

Bone marrow harvest is associated with a generally low incidence of complications for the donor and is usually performed on an outpatient basis.[89] Immediate complications of BM harvest (related to general anesthesia and intubation) are vomiting (about 10%), sore throat and hypotension (<10%). The most common complication is pain at the collection site, which requires analgesics (mostly non-narcotics), and occurs in about half of donors and can persist for up to 2 weeks (median 1 day).[90,91] The NMDP mandates that the duration of anesthesia be less than 150 minutes, duration of collection be less than 120 minutes, and allows for a maximum of 20 mL/kg (donor weight) of marrow to be aspirated, with a predicted median total nucleated cell (TNC) cell count/mL of 0.183 × 10^8/mL.[92,93] Unfortunately, the quality of BM harvest is declining over the years despite increased use of more optimal donors (eg, younger males).[93] This is concerning because the BM TNC dose is a significant prognostic factor for HCT outcomes. One study stratified patients into three groups based on the graft TNC dose: <2.5 × 10^8 cells/kg (low dose), 2.5–5 × 10^8 cells/kg (intermediate dose), and >5 × 10^8 cells/kg (high dose). Compared with low- and intermediate-dose groups, patients in the high-dose arm had significantly lower NRM (41%, 36%, and 28%, respectively; $P = .01$) and improved OS (45%, 51%, and 56%, respectively; $P = .0008$) in addition to faster and improved engraftment.[94]

Since the early 1990s, the use of PB-derived stem cells has become increasingly common; they are collected by using recombinant granulocyte colony-stimulating factor (G-CSF), given for 4 to 6 days at doses of 6–16 µg/kg per day. With this, the hematopoietic stem cells mobilize into the PB, where they may be collected by one or more leukapheresis procedures. A higher dose of CD34+ cells is required when using PB as the stem cell source than what can be achieved with BM graft. The typical dose of infused CD34+ cells ranges from about 2 × 10^6/kg to 10 × 10^6/kg, with about 4 × 10^6/kg being the standard at MDACC. Numerous studies including randomized control trials comparing PB with BM have now confirmed the efficacy and safety of this approach.[95–98] Studies suggest that an almost similar proportion of donors experience adverse events (AEs) with either PB (65%) or BM (57%) collection, most of which are transient and mild to moderate in severity, although the respective AE profiles are different. With PB stem cell collection, donors mostly have AEs related to either high-dose G-CSF (most commonly bone pain/myalgias, headaches or fatigue in

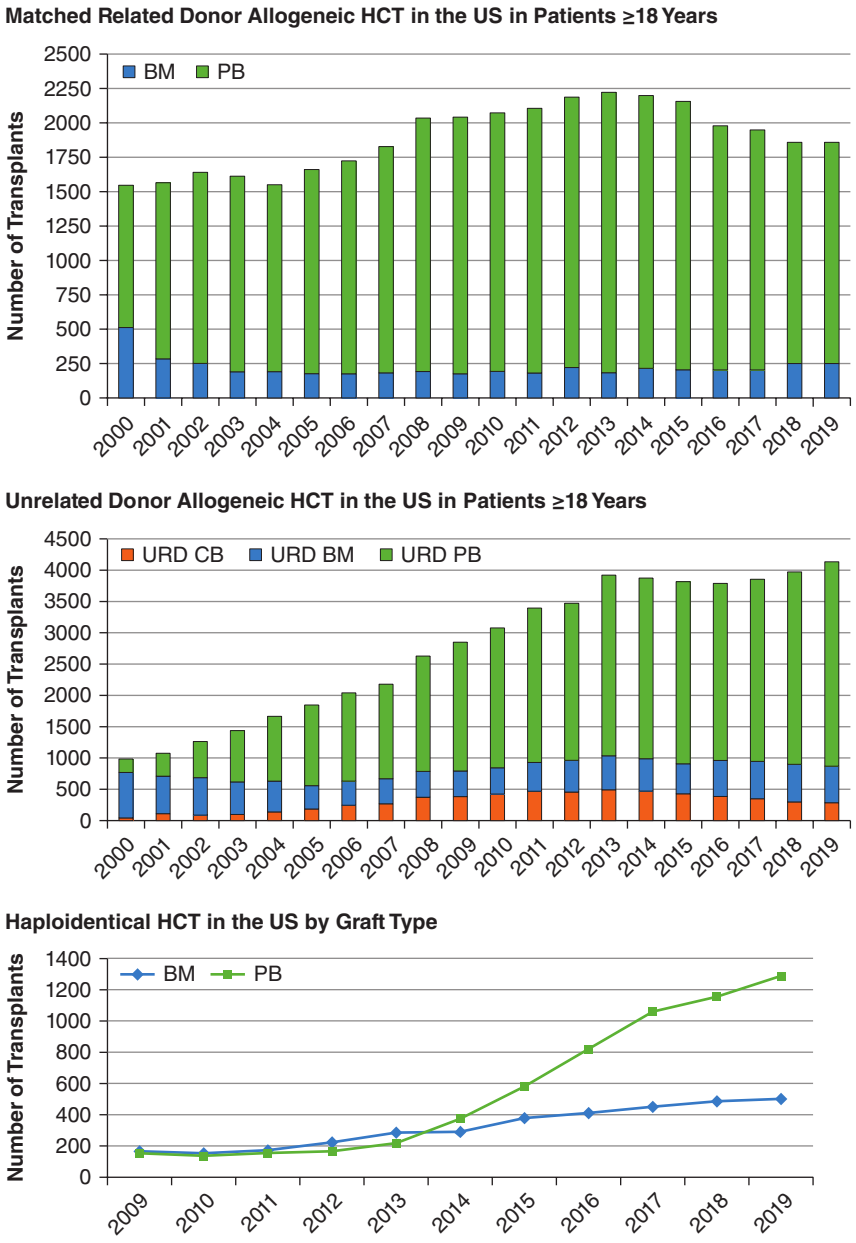


FIGURE 19–3 **Donors and recipients in allogeneic HCT (Reproduced with permission from Phelan R, Arora M, Chen M: Current use and outcome of hematopoietic stem cell transplantation: CIBMTR US summary slides, 2020. https://www.cibmtr.org/ReferenceCenter/SlidesReports/SummarySlides/pages/index.aspx)**

~70% of cases), or related to leukapheresis (tingling, numbness, carpal-pedal spasm, etc, caused by citrate administration, nausea [20%], problems with access [IV-line infiltration, hematomas, poor flow, etc, in ~20%]). Other rare leukapheresis-related AEs include chest pain, headaches, hypotension, syncope, and hypocalcemia-related tetany.[99]

Multiple studies evaluated patient outcomes after BM or PB graft in both MSD and MUD setting. In recipients of MUD HCT, a large phase 3 multicenter randomized controlled trial showed significantly higher risk of chronic GVHD (cGVHD), but not acute GVHD (aGVHD) after PB versus BM grafts (53% vs 41%, P = .01), with no difference in relapse, NRM, DFS, or OS. However, the incidence of graft failure was higher in the BM (9%) than in the PB group (3%), P = .002.[100] In the setting of MSD HCT, a randomized trial of PB versus BM showed significantly higher risk of cGVHD with PB than with BM (73% vs 56%, respectively; P = .021), without any differences in OS (49% vs 57%, respectively) or DFS (13% vs 28%, respectively, for ALL; 62% vs 47%, respectively, for AML; and 40% vs 48%, respectively, for CML).[101] Another study confirmed high risk of cGVHD (61% vs 45% at 6 years)

with no difference in risk of relapse with PB versus BM graft. However, NRM and DFS differed between PB and BM by disease and stage. For example, NRM was similar with PB or BM graft in patients with early leukemia and advanced CML, but higher with PB in early CML, and higher with BM in advanced leukemia. Compared with PB, BM was associated with higher DFS in early CML (41% vs 61%, respectively) but it led to lower DFS in those with advanced CML (33% vs 25%, respectively).[102] Individual patient data meta-analysis of nine randomized trials[103] showed significantly higher risk of grade III–IV aGVHD (odds ratio [OR] 1.39; 95% CI, 1.03–1.88), overall cGVHD (68% vs 52% at 3 years; OR 1.92; 95% CI, 1.47–2.49; $P < .000001$) and extensive cGVHD (47% vs 31% at 3 years; OR 1.89; 95% CI, 1.47–2.42; $P < .000001$), but also with significantly lower risk of relapse (21% vs 27% at 3 years; OR 0.71; 95% CI, 0.54–0.93; $P = .01$) with PB than with BM, respectively, and no differences in NRM. In patients with late-stage disease, OS (46% vs 31% at 3 years; OR 0.64; 95% CI, 0.46–0.90; $P = .01$) and DFS (41% vs 27% at 3 years; OR 0.63; 95% CI, 0.45–0.87; $P = .01$) were significantly superior with PB grafts.[103]

At MDACC, the graft source of choice for adult patients with MSD is PB (except certain diseases such as aplastic anemia and other bone marrow failure syndromes), and BM for patients with MUD except in those with highly advanced/refractory disease, prolonged cytopenias, myelofibrosis with splenomegaly, or other situations where rapid engraftment is necessary.

CHAPTER 19

Graft-Versus-Host Disease Prophylaxis

In a very broad sense, GVHD is an attack on recipient tissues by the donor's immune cells and most commonly involves the skin, GI tract, and liver in an acute setting. The pathophysiology of GVHD starts with the damage to host tissues from the preparative regimen, or even before, as a result of underlying disease itself or infections, resulting in substantial proinflammatory changes in endothelial and epithelial cells. The inflammatory cytokines then activate host antigen-presenting cells and upregulate adhesion molecules and several major and minor histocompatibility antigens, which leads to enhanced recognition by mature (infused) donor T-cells that secrete cytokines that mediate GVHD.[104] Approaches to reduce the risk of GVHD are targeted predominantly toward elimination or inhibition of donor T-cells, and include T-cell depletion (TCD) that can be done ex vivo (CD34+ selected or T-cell-depleted grafts) or in vivo (serotherapy with either antithymocyte globulin [ATG] or alemtuzumab), or by using post-transplantation immunosuppression with agents, such as methotrexate (MTX), calcineurin inhibitors (CNI, such as tacrolimus or cyclosporine), mycophenolate mofetil (MMF), sirolimus, or post-transplantation cyclophosphamide (PTCy).

Although the use of ex vivo TCD raises concerns about increased risk of graft failure[105] and relapse, at least in patients with CML,[106,107] it can reduce the risk of GVHD dramatically. In a study of 44 patients with AML who received TBI-based MAC followed by CD34-enriched, T-cell-depleted allografts from MSD, the incidence of aGVHD grade II–IV was about 23% without any post-transplantation GVHD prophylaxis.[108] The addition of in vivo TCD reduced the risk of aGVHD further, as shown in a study of 102 patients with MDS who received CD34-selected PB HCT after MAC with ATG. The cumulative incidence of grades II–IV aGVHD was about 10% at day 100 and about 16% at day 180. However, the use of T-cell-depleted grafts is plagued by slow and poor immune reconstitution that leads to significant risk of infections and consequent NRM.[109] To circumvent these issues, novel techniques of selective lymphocyte depletion such as CD3+/CD19+ and αβ T-cells/CD19 depletion are being evaluated.[110–112]

In vivo TCD is achieved with the use of serotherapy with either ATG[113,114] or alemtuzumab.[115,116] A variety of schedules and formulations of these have been tested for GVHD prophylaxis. Alemtuzumab is a humanized monoclonal antibody against CD52 that is expressed on a multitude of immune cells, including T-cells, B cells, natural killer cells, monocytes, macrophages, and some granulocytes and eosinophils. Antithymocyte globulin contains polyclonal antibodies generated in animals by inoculation with human thymocytes (developing T-cell progenitors that migrate from the BM to thymus for maturation). These antibodies bind to a variety of human T-cell receptors including CD2, CD3, CD4, CD8, CD25, CD45, and many HLA class I and II molecules, thus depleting lymphocytes from circulation. Two formulations approved by the FDA are equine ATG (ATGAM, Pfizer) and rabbit ATG (Thymoglobulin, Genzyme). Another rabbit ATG formulation is the ATG-Fresenius, which is used in many European studies and is not approved by the FDA. The immunosuppressive effects and doses of ATG vary significantly from one preparation to another.[117] In patients with severe aplastic anemia, immunosuppressive therapy with horse ATG (40 mg/kg/day for 4 days) plus cyclosporine as an alternative to HCT leads to superior survival than with rabbit ATG (3.5 mg/kg/day for 5 days) plus cyclosporine.[118] However, no such direct data about the superiority of one or the other formulation exist in the context of HCT. In contrast to horse ATG, rabbit ATG is more immunosuppressive and cytotoxic, depletes lymphocytes more efficiently, and induces the development of regulatory T-regulatory cells, which have added benefits for GVHD prevention.[118]

Therefore, rabbit ATG continues to be the preferred agent at many centers, including MDACC for GVHD prophylaxis, especially for patients with an unrelated donor. Serotherapy (ATG or alemtuzumab) is generally given before transplantation in conjunction with the conditioning regimens. However, because of long half-lives, their lymphodepleting effects last several days beyond the day of transplantation. This reduces the risk of GVHD by inhibiting donor T-cells, but also interferes with the recovery of donor-derived antiviral lymphocytes, leading to increased risk of cytomegalovirus and Epstein-Barr virus, adenovirus, and other viral reactivation, and may potentially interfere with the GVT effects. Because of the almost ubiquitous presence of CD52 on immune cells and significantly longer half-life, alemtuzumab leads to more intense immunosuppression, delayed immune reconstitution (with CD4 leukopenia lasting almost up to 3 years[119]), and higher risk of infections than with ATG.[120]

The history of using methotrexate (MTX) for GVHD prophylaxis dates back to the late 1950s when preclinical studies suggested that "mice which would normally succumb to a homograft reaction following lethal, total-body X irradiation and homologous marrow inoculation, may be spared if they are treated with folic acid antagonist, A-methopterin."[121] Thus, A-methopterin (methotrexate) became one of the earliest drugs used for GVHD prophylaxis.[122] It was used as a single agent dosed at 15 mg/m^2 on day +1, and 10 mg/m^2 on days +3, +6, and +11 and then weekly through day +102.[122] Subsequent adaptations included the addition of a CNI with a shorter course of methotrexate dosed at 15 mg/m^2 on day +1 and 10 mg/m^2 on days +3, +6, and +11,[123] or an even lower-dose regimen of 5 mg/m^2 on days +1, +3, +6, and +11 ("mini-methotrexate" regimen) used at MDACC.[124]

As of this writing, CNI is the most commonly used class of drugs for GVHD prophylaxis, generally in combination with either MTX or MMF. Both cyclosporine and tacrolimus bind to a cytoplasmic-receptor protein called immunophilin (cyclophilin and FKBP-12, respectively) and form a complex that binds to calcineurin and inhibits Ca2+-stimulated dephosphorylation of the cytosolic component of the nuclear factor of activated T-cells (NFAT). Upon T-cell receptor activation, calcineurin-induced dephosphorylation of NFAT is required to induce a number of cytokine genes, including interleukin-2 (IL-2). With the inhibition of dephosphorylation of NFAT by the calcineurin inhibitor/immunophilin complex, the activation of T-cells is thus inhibited.[125]

The combination of CNI and MTX is superior in reducing the risk of GVHD compared with either alone.[126,127] Which of the two CNIs (tacrolimus or cyclosporine) is superior was addressed in two large phase 3 randomized clinical trials.[123,128] One trial compared tacrolimus/methotrexate (Tac/MTX) with cyclosporine/MTX in patients who underwent MSD BMT. Patients in the cyclosporine arm had significantly higher incidences of grade II–IV aGVHD (44% vs 32%, respectively; $P = .01$) and extensive cGVHD ($P = .03$) than those in the tacrolimus arm, but with similar rates of grade III–IV aGVHD (17% vs 13%, respectively), overall cGVHD (50% and 56%, respectively), and relapse. Yet, patients in the cyclosporine arm also had a superior 2-year DFS (50% vs 40%; $P = .01$) and OS (57% vs 47%; $P = .02$) than the tacrolimus arm, respectively. This was likely related to a significantly higher proportion of patients with advanced disease in the tacrolimus arm (41% vs 29%; $P = .02$).[123] A subsequent phase 3 trial in patients undergoing MSD or MUD BMT also showed significantly higher risk of grade II–IV aGVHD in the cyclosporine versus the tacrolimus arm (48% vs 18%, respectively; $P < .0001$), but with no differences in cGVHD, relapse, or OS. However, one unexplained finding was that among recipients of MSD, relapse was noted to be significantly higher in the tacrolimus than in the cyclosporine group (31% vs 4%, respectively; $P = .01$).[128]

In contrast to CNI, sirolimus inhibits T-cell activation and proliferation downstream of IL-2. Although sirolimus also binds with an immunophilin (FKBP-12), the sirolimus/FKBP-12 complex does not affect calcineurin activity; rather it binds to and inhibits mammalian target of rapamycin (mTOR), which halts cell-cycle progression at the G1→S phase transition.[125] Studies also suggest that it promotes tolerance by expansion of CD4+CD25+FOXP3+ T-regulatory cells (Tregs) as well as dendritic cells.[129,130] Compared with Tac/MTX, the tacrolimus/sirolimus (Tac/Siro) combination has profound immunosuppressive effects, as suggested by higher Treg:Tcon ratio, and significantly lower absolute lymphocyte count, CD3+ cell, CD4+ cell, and conventional T-cell (Tcon) counts in the first 3 months after HCT, and delayed B-lymphocyte immune reconstitution.[131] Nevertheless, in the BMT-CTN randomized phase 3 clinical trial[132] comparing Tac/MTX with Tac/Siro in patients with MSD PB HCT, who received myeloablative TBI-based conditioning (Cy/TBI or TBI/etoposide), no differences were noted in the probability of day 114 grade II–IV aGVHD-free survival (67% vs 62%; $P = .38$), grades II–IV aGVHD (26% vs 34%; $P = .48$), cGVHD, DFS, or OS. Both tacrolimus and sirolimus were started at day −3 to maintain trough serum concentration of 5–10 ng/mL for tacrolimus and 3–12 ng/mL for sirolimus. Patients in the Tac/Siro arm experienced significantly higher incidence of elevation of creatinine, had a trend toward a higher risk of SOS/VOD (11% vs 5%; $P = .06$), and a higher incidence of thrombotic microangiopathy (TMA; 5% vs 1%; $P = .09$) than in the Tac/MTX arm. Also, of note, the

myeloablative Bu/Cy arm was stopped prematurely because of excessive risk of SOS,[132] which was seen in other studies as well.[133]

Another immunosuppressant commonly used with CNI is a purine metabolism inhibitor, MMF. It undergoes rapid metabolism to its active drug mycophenolic acid, which is a selective, reversible inhibitor of inosine monophosphate (IMP) dehydrogenase, an enzyme in the pathway of guanine nucleotide synthesis, critical for B and T lymphocyte proliferation. The combination of CNI/MMF is generally used in the setting of RIC or NMA HCT, and in those with MSD HCT,[134] but it may be a suboptimal approach in the setting of MAC and unrelated donor HCT.[135] It has also been used effectively with CNI or sirolimus in the setting of CBT[136,137] or haploidentical HCT with PTCy.[77]

Another novel approach to GVHD prophylaxis includes the use of the post-transplantation cytotoxic drug cyclophosphamide. The efficacy of cytotoxic drugs, including methotrexate, 6-mercaptopurine (6-MP), mechlorethamine, and cyclophosphamide to prevent GVHD was assessed as early as the 1960s.[138–140] In elegantly conducted experiments, Santos and Owen noted that cyclophosphamide, when given on days +2, +3, and +5 post-HCT, but not beyond day +7, significantly reduced the risk of GVHD.[139] However, because of concerns about its myelotoxicity when used after transplantation, its use as a GVHD prophylaxis strategy fell out of favor until late the 1990s/early 2000s, when this concept was revisited by investigators from the Johns Hopkins University in the setting of haploidentical HCT. Because of its unique pharmacology, cyclophosphamide can induce maximal immunosuppression without myeloablation, because it targets cells that express low levels of aldehyde dehydrogenase (such as B and T lymphocytes and natural killer cells), while sparing cells with a high level of this enzyme, such as the hematopoietic stem cells.[141] The safety and efficacy of using cyclophosphamide for prevention of both graft rejection and GVHD was demonstrated in a pivotal trial by O'Donnell et al,[142] where patients received T-cell-replete haploidentical BMT with NMA conditioning (Flu/TBI with or without Cy 14.5 mg/kg/day × 2 days pre-HCT), followed by single dose of Cy 50 mg/kg IV on day +3 post-HCT. Because CNI inhibits Cy-induced immunologic tolerance,[143] tacrolimus and MMF were added starting at day +4. Because the risk of graft failure and severe GVHD was still high (~60% at 6 months), the regimen was modified and patients received PTCy either on day +3 (50 mg/kg, n = 28) or on days +3 and +4 (50 mg/kg on each day, n = 40), followed by tacrolimus and MMF starting one day after PTCy.[77] Graft rejection occurred in 13%, and grades II–IV and III–IV aGVHD by day 200 were noted in 34% and 6% of patients, respectively. Although the risks of aGVHD, relapse, and NRM were similar among patients who received one or two doses of PTCy, the incidence of extensive cGVHD at one year was significantly lower in those who received two doses of PTCy than those who received a single dose (5% vs 25%, respectively; $P = .05$).[77]

The efficacy of PTCy was also tested in the setting of MSD or MUD HCT after RIC, in the BMT-CTN 1203 multicenter 1:1:1 randomized phase 2 clinical trial that evaluated three novel GVHD prophylaxis regimens—(1) PTCy/Tac/MMF (n = 92), (2) Tac/MTX with bortezomib (n = 89), and (3) Tac/MTX with maraviroc (n = 92).[144] Each study group was also compared separately with a contemporary control group of Tac/MTX (n = 224). Of these, the PTCy arm was found to be the most promising and led to statistically significant improvement in the primary end point (GVHD-free, relapse-free survival; GRFS: hazard ratio (HR) 0.72, 90% CI 0.54–0.94; $P = .044$) compared with controls. The incidence of grade II–IV aGVHD was not different among the arms, but that of grade III–IV was significantly lower only in the PTCy arm than in the controls (2% vs 13%; $P = .008$). Similarly, the risk of cGVHD (28% vs 38%; $P = .069$), and especially the cGVHD requiring immunosuppression (22% vs 37%; $P = .037$), were lower only in the PTCy arm. The risk of relapse, NRM, and DFS were similar among all groups, but viral infections appeared to be more common and occurred in about one-third of patients in the PTCy arm than other arms (20%–22%).[144]

MD ANDERSON CANCER CENTER APPROACH FOR GVHD PROPHYLAXIS

A combination of Tac/MTX is still considered the standard of care among recipients of sibling (without ATG) or unrelated (with ATG) donor HCT. However, PTCy/Tac/MMF, which is the standard for all haploidentical HCTs, is being used more commonly across all types of donor transplantations excluding CBT, where the standard is Tac/MMF with ATG. In the Tac/MTX regimen, tacrolimus is initiated on day –2, whereas it is started on day +5 in patients receiving PTCy. Tacrolimus is started at 0.015–0.03 mg/kg per day via continuous IV infusion with a target level of 7–12 ng/mL. In rare certain situations where tacrolimus cannot be used, cyclosporine is used to a target level of 300–400 ng/mL at least for the first 60 days post-HCT. Sirolimus is typically reserved for patients who are unable to tolerate tacrolimus, such as those with severe renal dysfunction or those with tacrolimus-related neurotoxicity. Methotrexate 5 mg/m^2 IV per dose is given on days +1, +3, +6, and +11. MMF is dosed at 15 mg/kg IV/by mouth every 8 hours (with a max of 1 g/dose).

POST-TRANSPLANTATION COMPLICATIONS

At least mild (grade I) toxicity related to the conditioning regimen will develop in almost all patients, whereas potentially life-threatening or fatal (grades III–IV) complications are relatively rare.[64,145] A detailed description of these complications is beyond the scope of this chapter. Some of the most commonly encountered nonhematologic toxicities include oral stomatitis (management reviewed by Keefe et al[146]), GI (nausea, vomiting, and diarrhea), and febrile neutropenia that occurs in more than 80% of patients, with documented infections noted in only about 25% to 50%[147,148] (management reviewed by the Infectious Diseases Society of America [IDSA][149] and the American Society for Blood and Marrow Transplantation [ASBMT][150]). Other regimen-related complications (besides GVHD) can be difficult to diagnose because similar presentation can be caused by several other factors. These include hepatic toxicities (drug-induced or infectious hepatitis or cholestatic disorders, iron overload, VOD/SOS; reviewed by Arai et al[151]); cardiovascular (hypertension, arrhythmias, cardiomyopathy, fluid volume overload; reviewed by Tichelli et al[152] and Blaes et al[153]); pulmonary (pulmonary edema, diffuse alveolar hemorrhage (DAH), idiopathic pneumonia syndrome; reviewed by Yen at al[154]); bladder (hemorrhagic cystitis,[155–158] which could be related to PTCy of infections such as BK virus and adenovirus); renal (acute or chronic kidney injury, thrombotic microangiopathy[159,160]); and CNS toxicity[161–163] (posterior reversible encephalopathy syndrome [PRES], seizures, hemorrhage, infections, encephalopathy), to name a few. The most common causes of death within the first 100 days of HCT are relapse of the underlying disease (20%–35%), infections (20%–30%), organ failure (20%–25%), and GVHD (~15%). The leading cause of death beyond 100 days of HCT is the relapse of the underlying disease (50%–60%), whereas infections (10%–15%), organ failure (~10%), GVHD (~15%), and others contribute to the rest (Fig. 19–4).

Infectious Disease Prophylaxis

We use fluoroquinolone (levofloxacin or ciprofloxacin) for antibacterial prophylaxis during the phase of neutropenia as recommended by the IDSA guidelines,[149] or cefpodoxime or azithromycin in case of quinolone allergies/contraindications. Patients also receive prophylaxis against *Candida* (per IDSA: fluconazole, itraconazole, voriconazole, posaconazole, or echinocandins are all acceptable options) and select patients (especially those with prior history of invasive mold infection, mismatched HCT, and those receiving in vivo TCD) also receive prophylaxis against invasive *Aspergillus* infections with either posaconazole[149] or voriconazole. Antifungal prophylaxis is generally continued until at least 2 months from when immunosuppression

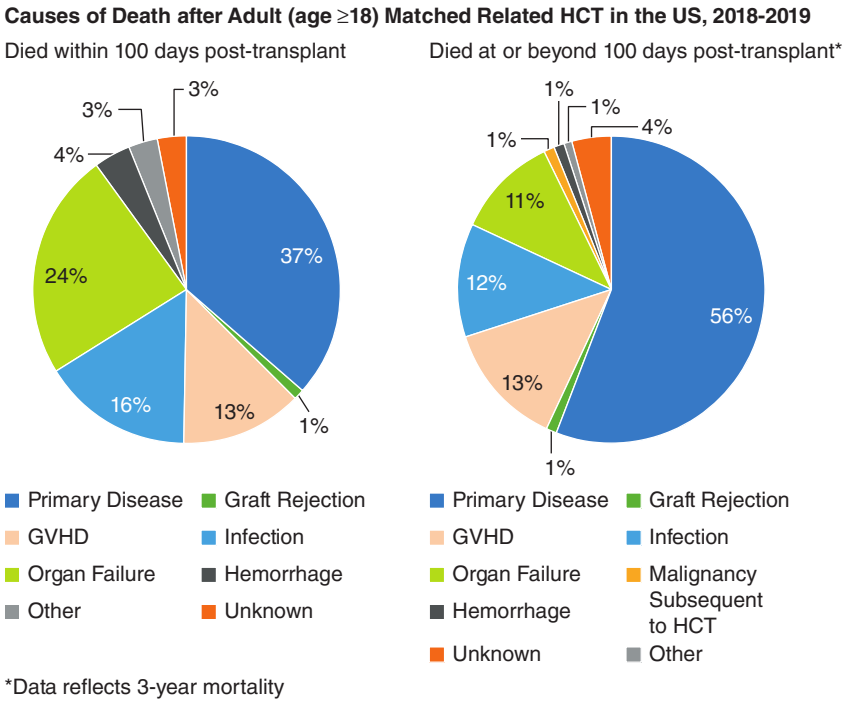


FIGURE 19–4 **Causes of death in matched sibling and unrelated donor HCT in 2016-2017 (Reproduced with permission from Phelan R, Arora M, Chen M: Current use and outcome of hematopoietic stem cell transplantation: CIBMTR US summary slides, 2020. https://www.cibmtr.org/ReferenceCenter/SlidesReports/SummarySlides/pages/index.aspx)**

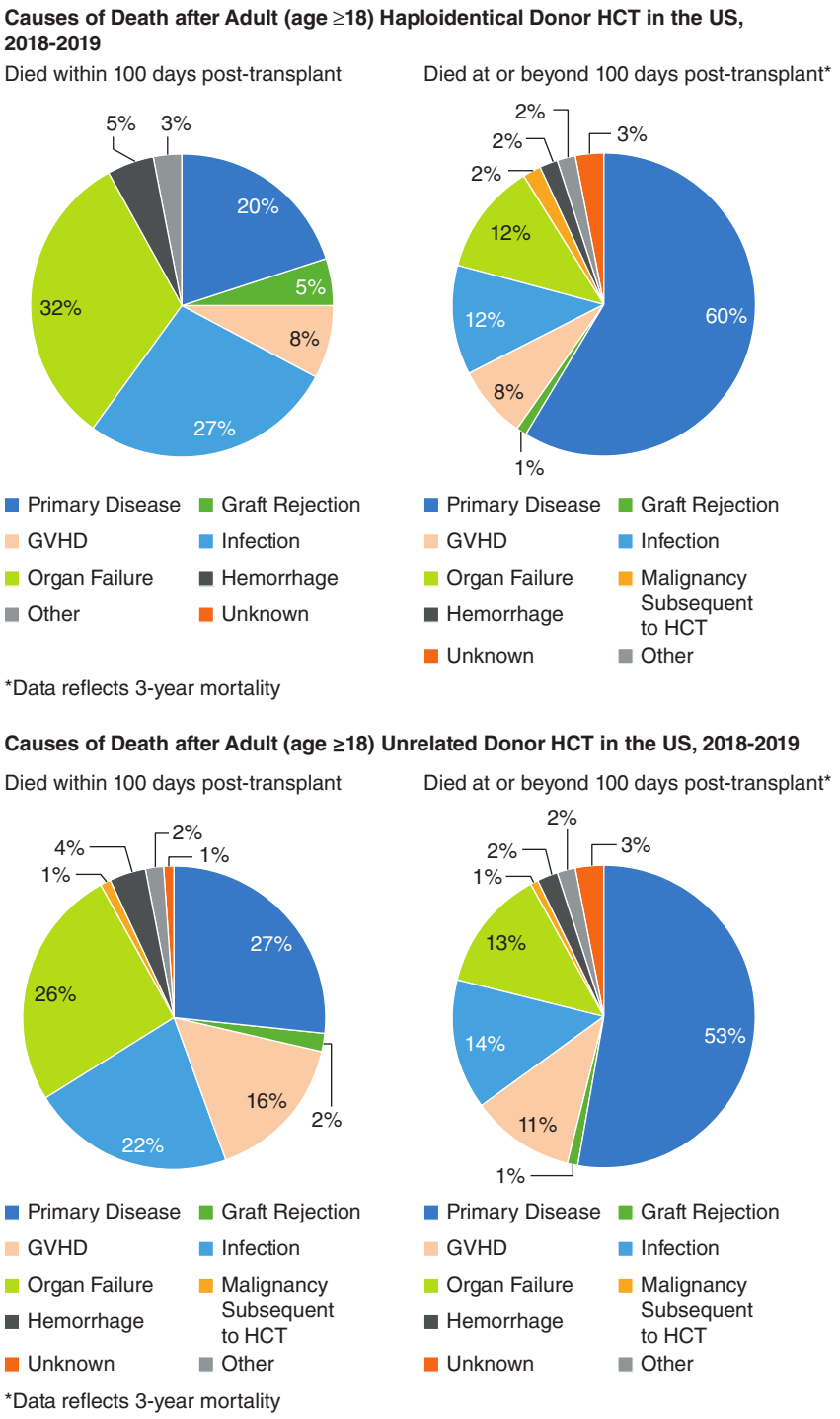


FIGURE 19–4 (*Cont.*)

is discontinued. Antiviral prophylaxis against varicella zoster virus/herpes simplex virus is provided with valacyclovir. All cytomegalovirus-seropositive patients receive prophylaxis with letermovir 480 mg by mouth/IV daily starting on day +5, which is continued through day +100.[164] Another infection against which prophylaxis is routinely used is *Pneumocystis jiroveci* pneumonia (PJP). Although its incidence appears to be decreasing in the modern era (<1% of allogeneic HCT patients), it is still associated with high mortality.[165] Half of PJP infections occur between 2 and 9 months post-HCT, with the rest being distributed equally before and after this period.[165] For prophylaxis against PJP, we prefer trimethoprim/sulfamethoxazole over atovaquone, pentamidine, or dapsone because it provides additional coverage against *Toxoplasma gondii*, *Nocardia*, *Stenotrophomonas*, and other susceptible bacteria. Trimethoprim/sulfamethoxazole is used as a

double-strength tablet (800/160 mg) once daily three times per week, or a single-strength tablet (400/80 mg) once daily. For patients with contraindications, alternative regimens include pentamidine 4 mg/kg IV every 21 days (or 300 mg inhaled every 28 days), dapsone 100 mg orally daily, or atovaquone 1500 mg orally daily. Of these, only atovaquone has activity against toxoplasmosis. Prophylaxis against PJP is usually started about 3 to 4 weeks post-HCT and is continued for a minimum of 12 months, or at until 2 months after discontinuation of immunosuppression, whichever is later

In addition, to shorten the duration of severe neutropenia, all patients receive recombinant granulocyte colony-stimulating factor (G-CSF),which is continued through neutrophil engraftment—defined as the first of 3 consecutive days on which the absolute neutrophil count is greater than or equal to 0.5×10^9/L. Multiple phase 2/3 clinical trials demonstrated the safety and efficacy of G-CSF in reducing the period of severe neutropenia by about one week, which reduces the risks of infections and aids in earlier discharge from the hospital.[166]

Hepatic Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome

The term VOD was used originally to describe a clinical syndrome of hepatomegaly, ascites, and jaundice, which was thought to be related to ingestion of certain toxic chemicals that led to fibrosis and occlusion of small hepatic venules. Description of its histologic findings can actually be traced back to reports from the 1920s describing it as "Senecio disease," related to ingestion of plants known as *Senecio ilicifolius* and *Senecio burchellii* that grew as weeds in wheat fields.[167] It has also been associated with pyrrolizidine alkaloids–induced liver toxicity.[168,169] At least in the context of HCT, when it was subsequently recognized that sinusoidal endothelial cells were the primary site of the toxic injury, the name was changed to SOS to adequately reflect its underlying pathophysiology.[170] Yet, both VOD and SOS continue to be used interchangeably, and will be referred to as VOD/SOS in this chapter.

Hepatic VOD/SOS is one of the most serious complications that can occur within the first few weeks of HCT, with an expected mortality exceeding 75% to 80%.[171] The reported incidence of VOD ranges from 0 to more than 60%, with a mean incidence of about 14% as reported by an analysis of 135 published studies.[171] The wide range in incidence across studies is likely related to the heterogeneity of the study population, type of transplantation, and conditioning regimen used. Risk factors include the use of MAC (especially high-dose TBI and oral or high-dose busulfan-based regimens), unrelated donor, HLA-mismatched donor, older age at HCT, poor performance status, females using norethisterone, advanced disease, genetic factors (GSTM1 polymorphism, C282Y allele, MTHFR 677CC/1298CC haplotype), prior history of liver disease/hepatitis, iron overload, abdominal or hepatic irradiation, and previous use of gemtuzumab ozogamicin or inotuzumab ozogamicin, to name a few.[172–175] The pathophysiology involves damage to endothelial cells and hepatocytes by high-dose conditioning, which leads to necrosis of hepatocytes in zone 3 of the liver acinus, engorgement of sinusoids with hepatocytes and red blood cells, and perivenular fibrosis, leading to obstruction of blood flow through hepatic capillaries and venules.[172–176]

The diagnosis of VOD is based purely on clinical presentation. Although radiographic findings and histology may help, they are never relied on primarily to make or exclude the diagnosis. Early initiation of treatment is crucial, because progressive disease, especially when associated with multiorgan failure, is almost universally fatal. Two most commonly used diagnostic criteria include the Seattle criteria, which was originally reported by McDonald et al in 1984[175] and subsequently revised in 1993 (the modified Seattle criteria),[173] and the Baltimore Criteria reported by Jones et al in 1987.[174] Most recently, the European Group for Blood and Marrow Transplantation (EBMT) criteria were reported in 2016[172] and include the classic VOD criteria based on the Baltimore Criteria that occurs within 21 days of HCT, and a distinct entity of late-onset VOD that can occur beyond 3 weeks, in which case hyperbilirubinemia is not mandatory for the diagnosis (Table 19–1). To grade the severity of VOD, the EBMT criteria categorize it as mild, moderate, severe, or very severe based on time to onset of VOD, degree and kinetics of hyperbilirubinemia, transaminases, weight gain, and renal function (Table 19–2).[172]

Treatment of VOD involves aggressive supportive care, with management of fluid and sodium balance with cautious use of diuretics, minimizing exposure to hepatotoxic agents, and pain/volume control with narcotics and paracentesis, or hemodialysis in patients with severe renal dysfunction or refractory fluid overload, and the use of defibrotide. Defibrotide is a "complex mixture of oligonucleotides derived from the controlled depolymerisation of porcine intestinal mucosal DNA."[177] The exact mechanism of its action is unclear but broadly involves two processes: (1) protection of endothelial cells and (2) restoration of the thrombotic-fibrinolytic balance as a result of its antithrombotic, profibrinolytic, and antiinflammatory properties.[177] In a multicenter phase 3 trial that included patients with VOD/SOS and advanced multiorgan failure (n = 102), defibrotide was given IV at 25 mg/kg per day in four divided doses (6.25 mg/kg IV every 6 hours), for a minimum of 21 days, and continued until

Table 19–1 Veno-Occlusive Disease (VOD)/Sinusoidal Obstruction Syndrome (SOS)

Seattle Criteria	Modified Seattle Criteria	Baltimore Criteria	EBMT Criteria	
Within **30 days** of HCT	Within **20 days** of HCT	Within **21 days** of HCT	Classical SOS/VOD in the first 21 days after HCT	Late-onset SOS/VOD >**21 days** after HCT
Any two of the following:	Any two of the following:			Classical VOD/SOS beyond day 21, OR
Hyperbilirubinemia (total serum bilirubin >2 mg/dL)	hyperbilirubinemia (total serum bilirubin >2 mg/dL)	hyperbilirubinemia ≥2 mg/dL **PLUS** at least 2 of 3 other findings	Bilirubin ≥2 mg/dL PLUS at least 2 of 3 other findings	Histologically proven SOS/VOD, OR
Hepatomegaly or right upper quadrant pain	Hepatomegaly or right upper quadrant pain	Hepatomegaly	Painful hepatomegaly	at least 2 of 3 other findings Bilirubin ≥2 mg/dL (or 34 µmol/L) Painful hepatomegaly Weight gain >5% Ascites
		Ascites	Ascites	
Sudden weight gain (>2% of baseline body weight)	Sudden weight gain (>2% of baseline body weight)	≥5% weight gain	>5% weight gain	AND Hemodynamic and/or ultrasound evidence of SOS/VOD

Table 19–2 EBMT Criteria for Severity Grading of Suspected SOS/VOD in Adults

	Mild[a]	Moderate[a]	Severe	Very Severe Multiorgan Dysfunction[b]
Time since first clinical symptoms of SOS/VOD[c]	>7 days	5–7 days	≤4 days	Any time
Bilirubin (mg/dL)	≥2 and <3	≥3 and <5	≥5 and <8	≥8
Bilirubin (µmol/L)	≥34 and <51	≥51 and <85	≥85 and <136	≥136
Bilirubin kinetics			Doubling within 48 hours	
Transaminases	≤2× normal	>2 and ≤5× normal	>5 and ≤8× normal	>8× normal
Weight increase	<5%	≥5% and <10%	≥5 % and <10%	≥10%
Renal function	<1.2× baseline at transplant	≥1.2 and <1.5× baseline at transplant	≥1.5 and <2× baseline at transplant	≥2× baseline at transplant or other signs of MOD/MOF

Patients belong to the category that fulfills two or more criteria. If patients fulfill two or more criteria in two different categories, they must be classified in the most severe category. Patient's weight increase ≥5% and <10% is considered by default as a criterion for severe SOS/VOD; however, if patients do not fulfill other criteria for severe SOS/VOD, weight increase ≥5 % and <10% is therefore considered a criterion for moderate SOS/VOD.
[a]In the case of the presence of two or more risk factors for SOS/VOD, patients should be in the upper grade.
[b]Patients with multiorgan dysfunction must be classified as very severe.
[c]Time from the date when the first signs/symptoms of SOS/VOD began to appear (retrospectively determined) and the date when the symptoms fulfilled SOS/VOD diagnostic criteria.

resolution of VOD/SOS or until patient discharge.[178] Treatment with defibrotide resulted in a significantly higher complete remission (CR) rate at day 100 (25% vs 12.5%; $P = .016$) and improved OS at day 100 (38% vs 25%; $P = .01$) than in historical controls, respectively. The incidence of adverse effects including DAH (12% and 16%) and GI bleeding (8% and 9%) were similar.[178] Despite similar rates of hemorrhagic complications, the EBMT guidelines suggest that patients treated with defibrotide should receive platelet transfusions to keep platelets above 30×10^9/L. Defibrotide has a short half-life (<2 hours), so it can

be held for about 2 hours before and after any invasive procedure that may be required.

Among several agents attempted for prophylaxis against VOD/SOS, including unfractionated heparin or low-molecular-weight heparin,[179] anti-thrombin III,[180] prostaglandin E1,[181,182] and pentoxifylline,[183,184] ursodeoxycholic acid (UDCA)[185] appears to be the most promising, with a very favorable toxicity profile. In a systematic review of four randomized clinical trials and two historically controlled studies, compared with no prophylaxis, UDCA was associated with significant reduction of VOD/SOS (relative risk [RR], 0.34; 95% CI, 0.17–0.66) and significant reduction in the risk of transplant-related mortality (RR, 0.58; 95% CI, 0.35–0.95), with no effect on aGVHD, relapse, or OS.[185] In a randomized trial comparing UDCA (n = 123) versus controls (n = 119),[186] UDCA was started at 12 mg/kg per day from a day before conditioning and continued until day +90 post-HCT. Use of UDCA was associated with significantly reduced risk of grade III–IV aGVHD; liver, GI, and severe skin GVHD, lower NRM (19% vs 34%), and improved survival (71% vs 55%) at 1 year.[186,187]

Similar to VOD/SOS, it has been hypothesized that many other complications in the early post-HCT period may have an endothelial origin as well. These complications include capillary leak syndrome, engraftment syndrome, transplant-associated microangiopathy (TMA), DAH, and idiopathic pneumonia syndrome.[188] Pathophysiology and management of these are reviewed elsewhere.[189]

ACUTE GRAFT-VERSUS-HOST DISEASE

Diagnosis and Classification

Although GVHD was traditionally classified as acute (aGVHD) or chronic (cGVHD) based on the timing of onset (before or after 100 days), the distinction is predominantly based on clinical presentation. The organs involved by aGVHD, in frequency of involvement, are skin (maculopapular rash), upper GI tract (anorexia, nausea, vomiting), lower GI tract (diarrhea, abdominal pain, bleeding), and liver (elevations of *total* serum bilirubin). Two most commonly used systems for staging and grading of aGVHD are (1) the modified Glucksberg GVHD staging system based on the 1994 Consensus Conference on Acute GVHD Grading held in Keystone,[190] and (2) the Mount Sinai Acute GVHD International Consortium (MAGIC) staging system reported by Harris et al in 2016 (Table 19–3).[191]

The differential diagnosis of skin rash post-HCT is broad and includes conditioning regimen-related rash, adverse drug-reaction, viral exanthema, cutaneous eruption of lymphocyte recovery, or GVHD. Therefore, skin biopsy is often performed to help with the diagnosis. Similar to clinical staging and grading, histopathologic findings are also graded based on the degree of injury noted by the pathologist. One histologic grading system reported by Lerner et al in 1974 ("Lerner grading system") includes changes of basal cell layer vacuolization often surrounded by lymphocytes, commonly called as satellitosis (grade I); grade II includes grade I changes plus focal spongiosis, single necrotic keratinocyte/dyskeratotic epidermal cell; grade III includes additional changes of formation of dermal-epidermal junction cleft; and grade IV is the complete loss of epidermis.[192] The utility of histologic confirmation for GVHD in confirming the diagnosis is controversial because many findings can also be seen in entities other than GVHD.[193–196] One study noted that 25% of GVHD and non-GVHD samples showed no basal vacuolization at all. Similarly, necrotic keratinocytes were noted in both GVHD and non-GVHD cases, although the GVHD cases trended to exhibit more necrotic keratinocytes. Further, more than half (55%) of the GVHD cases and about three-quarters (72%) of non-GVHD biopsies showed no or fewer than three necrotic keratinocytes per 4-mm biopsy.[195] Nevertheless, biopsies can be helpful in excluding other possibilities, especially infections, and confirming the diagnosis in the context of strong clinical suspicion.

In the GI tract, epithelial cell apoptosis (>1 per piece) in the crypts is the most important and the minimal pathologic criteria for histologic diagnosis of GVHD, as recommended by the GVHD consensus National Institutes of Health (NIH) Pathology Working Group—categorizing the findings as negative, possible, or likely GVHD.[197] Apart from this, there is no universally accepted grading system for histologic classification, and many are modified from what was originally described by Lerner et al in 1974.[192,198] One of these modified criteria and the one used at MDACC describes grade 1 histologic changes as the presence of increased apoptotic epithelial cells without crypt loss; grade 2: isolated crypt loss or micro-abscess; grade 3: 2 or more contiguous crypt loss; and grade 4: extensive crypt loss with mucosal denudation.[199] It is important to realize that histologic grade does not correlate well with clinical grade or prognosis, and even "mild" grade 1 histologic changes (which are the most common findings in a majority of biopsy specimens) are associated with significantly higher risk of NRM (HR = 2.7, $P = .02$) than those with negative findings.[199]

The histologic hallmark of acute liver GVHD is bile duct injury with evidence of nuclear enlargement and pleomorphism, cytoplasmic vacuolization, loss of nuclear polarity, and varying degrees of centrilobular cholestasis.

Table 19–3 Acute GVHD Staging & Grading[a]

Stage	Skin (Active Erythema Only)	Liver (Bilirubin)	Upper Gastrointestinal Tract	Lower Gastrointestinal Tract (Stool Output/Day)
0	No active (erythematous) GVHD rash	<2 mg/dL	No or intermittent nausea, vomiting, or anorexia	Adult: <500 mL/day or <3 episodes/day Child: <10 mL/kg/day or <4 episodes/day
1	Maculopapular rash <25% BSA	2–3 mg/dL	Persistent nausea, vomiting, or anorexia	Adult: 500–999 mL/day or 3–4 episodes/day Child: 10–19.9 mL/kg/day or 4–6 episodes/day
2	Maculopapular rash 25–50% BSA	3.1–6 mg/dL	—	Adult: 1000–1500 mL/day or 5–7 episodes/day Child: 20–30 mL/kg/day or 7–10 episodes/day
3	Maculopapular rash >50% BSA	6.1–15 mg/dL	—	Adult: >1500 mL/day or >7 episodes/day Child: >30 mL/kg/day or >10 episodes/day
4	Generalized erythroderma (>50% BSA) plus bullous formation and desquamation >5% BSA	>15 mg/dL	—	Severe abdominal pain with or without ileus, or grossly bloody stool (regardless of stool volume).

Overall clinical grade (based on most severe target organ involvement):
- **Grade 0:** No stage 1–4 of any organ;
- **Grade I:** Stage 1–2 skin without liver, upper GI, or lower GI involvement;
- **Grade II:** Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI;
- **Grade III:** Stage 2–3 liver and/or stage 2–3 lower GI, with stage 0–3 skin and/or stage 0–1 upper GI; and
- **Grade IV:** Stage 4 skin, liver, or lower GI involvement, with stage 0–1 upper GI.

[a]As per the Mount Sinai Acute GVHD International Consortium (MAGIC), reported by Harris et al.[191]
BSA, body surface area.

Other features such as portal or central vein endotheliitis, centrilobular necrosis, hepatocellular ballooning, and feathery degeneration are less common and may be noticed in advanced cases.[200] There is no universally accepted histologic grading system and we do not ascribe a histologic grade to patients with liver GVHD.

Because this is the most common error made by trainees and non-HCT physicians, it is worth emphasizing yet again that aGVHD staging and grading is based on the clinical presentation, not by histology, as noted in Table 19–3.

Treatment

Limited-stage isolated skin aGVHD (overall grade I, with <50% body surface area involvement) can be treated with topical or systemic corticosteroids or observation alone.[201] Although patients with disease managed by observation have a significantly lower risk of bacterial infections (12% vs 25%; $P = .04$) and less severe fungal infections, they also carry a significantly higher risk of progression to grade II–IV aGVHD than those treated with systemic corticosteroids 1 mg/kg per day (50% vs 33%, $P = .0005$).[201]

Any other aGVHD (grade II–IV) requires systemic treatment. Corticosteroids 2 mg/kg per day is the standard of care, which leads to responses in 40% to 60% of patients.[202,203] A randomized phase 3 trial compared the safety and efficacy of using prednisone 1 mg/kg per day versus 2 mg/kg per day among patients with grades II or higher GVHD.[204] The study found no significant differences in the risk of progression to grade III–IV aGVHD, cGVHD, NRM, relapse, or OS between the arms. However, a significantly higher proportion of patients treated with lower-dose prednisone required secondary systemic immunosuppressive therapy than in the standard-dose arm (41% vs 7%; $P = .001$). Furthermore, the use of lower-dose prednisone was not associated with any meaningful advantage, as suggested by similar risk of invasive infections, hyperglycemia, hypertension, degree of myopathy, and quality-of-life between the arms.[204] The addition of other immunosuppressants to corticosteroids, including MMF,[205,206] pentostatin,[206] denileukin diftitox,[206]

etanercept,[206] daclizumab,[207] anti–IL-2 receptor monoclonal antibody,[208] infliximab,[209] or ATG[210] have not shown additional benefits in multiple randomized trials.

Most recently, sirolimus was tested as a steroid-sparing strategy for patients with standard-risk GVHD (mostly skin ± upper GI GVHD).[211] In the BMT-CTN 1501 clinical trial, patients with standard-risk GVHD (per the Minnesota score[212] plus Ann Arbor biomarker score 1–2[213]) were randomly assigned to receive either sirolimus or prednisone (or prednisone dose equivalent) 2 mg/kg per day. The sirolimus level was kept therapeutic (10–14 ng/mL until aGVHD resolution, and then 5–10 ng/mL after resolution until at least day 56) with concurrent CNI (tacrolimus, 3–7 ng/mL or cyclosporine, 120–200 ng/mL). Overall response rates (ORRs) were comparable for sirolimus and corticosteroids at day 28 (65% vs 73%, respectively), with no differences in the risk of steroid-refractory aGVHD, cGVHD, serious infections, NRM, relapse, or OS. However, there was a higher proportion of nonresponders in the sirolimus arm by day 56 (with an ORR of 64% vs 79%, respectively), and the risk of TMA within 6 months was also significantly higher in the sirolimus than in the steroid arm (10% vs 1.5%, respectively).

Steroid-refractory aGVHD responds poorly to second-line therapies and is associated with increased mortality.[202] Multiple therapies have been tried with varying success, including extracorporeal phototherapy, MMF, methotrexate, basiliximab, daclizumab, inolimomab, denileukin diftitox, alemtuzumab, horse ATG, etanercept, infliximab, sirolimus, or pentostatin, to name a few (reviewed by Martin et al[202]). Other agents being tested include brentuximab vedotin,[214] α-1 antitrypsin,[215] mesenchymal stem cells,[216–218] and vedoluzumab[219] (specifically for lower GI tract GVHD). Among these, ruxolitinib became the first and only drug so far to have received FDA approval (May 2019) for steroid-resistant aGVHD based on the results of an open-label, single-arm, multicenter REACH1 clinical trial (n = 71).[220] The day 28 ORR in this study was 55% (complete response rate of 27%) and the median time to response was 7 (range, 6–49) days.[221]

CHRONIC GRAFT-VERSUS-HOST DISEASE

The pathophysiology of cGVHD is incompletely understood and involves complex interactions between the innate, humoral, and cell-mediated immunity, leading to fibrosis and other syndromes that resemble autoimmune or other immune-mediated disorders. A review by Zeiser and Blazer[222] highlights the key role of B-cell signaling, naïve T-cell differentiation into type 17 helper T (Th17) cells, and type 17 cytotoxic T (Tc17) cells, follicular helper T (Tfh) cells, and follicular regulatory T (Tfr) cells, and fibrosis-promoting factors in the pathophysiology of cGVHD.

Chronic GVHD typically presents insidiously, with a median time to onset of about 4 to 6 months, although about 5% to 10% of cases can present beyond the first year of transplantation. The diagnosis and staging of cGVHD is based on the 2014 NIH Chronic GVHD Diagnosis and Staging Consensus criteria.[223] As elaborated in Table 19–4, the signs and symptoms of cGVHD are consider either "diagnostic" (that establish the presence of cGVHD without need for further testing) or "distinctive" (not sufficient in isolation to establish an unequivocal diagnosis of cGVHD; these are not commonly seen in aGVHD). In certain cases, additional testing such as a biopsy is needed to make a diagnosis.

The common sites of involvement include skin/fascia (~75%–80%), mouth (50%–85%), eyes (20%–33%), liver (10%–50%), GI tract (20%–45%), lung (bronchiolitis obliterans, 5%–20%), muscles/joints, and genitalia.[224–227] At MDACC, patients benefit from comprehensive cGVHD care provided through a multidisciplinary team that includes a dermatologist, oral health specialist, physical therapist, and occupational therapist, who all generally evaluate patients jointly with a HCT physician. In addition, dedicated ophthalmologists and pulmonologists skilled in the diagnosis and management of ocular and lung cGVHD, respectively, are available on site.

It is crucial to recognize that the treatment of cGVHD that requires systemic immunosuppression generally lasts for at least one year, with the median duration of therapy being about 2 to 3 years, and about 15% of patients require treatment for more than 5 to 7 years.[226,228] Treatment generally includes corticosteroids (prednisone 0.5–1 mg/kg/day), which are tapered slowly at a rate that varies considerably from practice to practice. One approach is to taper the dose by approximately 25% every 2 weeks to reach an average dose of about 0.25 mg/kg per day (or 0.4–0.5 mg/kg every other day) within 3 months after starting treatment, followed by much smaller dose reductions toward the end of the taper, until the adrenal replacement dose is reached (roughly 0.10 mg/kg/day).[226] Despite lack of any randomized trial showing benefit, additional therapy is generally added to the corticosteroids with hopes to minimize toxicities from prolonged corticosteroid use.[229] Multiple agents have been tried as adjuncts to corticosteroids, including CNI, sirolimus, extracorporeal phototherapy, ultraviolet light therapy, ruxolitinib, ibrutinib, rituximab, imatinib, pentostatin, MMF, low-dose IL-2, bortezomib, thalidomide, pomalidomide, hydroxychloroquine, infliximab, and etanercept, to name a few.[224,226] Of these, ibrutinib is the first and only drug that received FDA approval (August 2017) for treatment of SR-cGVHD based on a single-arm study

Table 19–4 Signs and Symptoms of Chronic GVHD[a]

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of Chronic GVHD)	Distinctive[b] (Seen in Chronic GVHD, But Insufficient Alone to Establish a Diagnosis)	Other Features or Unclassified Entities[c]	Common[d] (Seen with Both Acute and Chronic GVHD)
Skin	Poikiloderma Lichen planus–like features Sclerotic features Morphea-like features Lichen sclerosus–like features	Depigmentation Papulosquamous lesions	Sweat impairment Ichthyosis Keratosis pilaris Hypopigmentation Hyperpigmentation	Erythema Maculopapular rash Pruritus
Nails		Dystrophy Longitudinal ridging, splitting, or brittle features Onycholysis Pterygium unguis Nail loss (usually symmetric, affects most nails)		
Scalp and body hair		New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) Loss of body hair Scaling	Thinning scalp hair, typically patchy, coarse, or dull (not explained by endocrine or other causes) Premature grey hair	
Mouth	Lichen planus–like changes	Xerostomia Mucoceles Mucosal atrophy Ulcers Pseudomembranes		Gingivitis Mucositis Erythema Pain
Eyes		New-onset dry, gritty, or painful eyes Cicatricial conjunctivitis Keratoconjunctivitis sicca Confluent areas of punctate keratopathy	Photophobia Periorbital hyperpigmentation Blepharitis (erythema of the eyelids with edema)	
Genitalia	Lichen planus–like features Lichen sclerosus–like features	Erosions Fissures Ulcers		
Females	Vaginal scarring or clitoral/labial agglutination			
Males	Phimosis or urethral/meatus scarring or stenosis			

(*Continued*)

Table 19–4 Signs and Symptoms of Chronic GVHD[a] (*Cont.*)

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of Chronic GVHD)	Distinctive[b] (Seen in Chronic GVHD, But Insufficient Alone to Establish a Diagnosis)	Other Features or Unclassified Entities[c]	Common[d] (Seen with Both Acute and Chronic GVHD)
GI tract	Esophageal web Strictures or stenosis in the upper to mid-third of the esophagus		Exocrine pancreatic insufficiency	Anorexia Nausea Vomiting Diarrhea Weight loss Failure to thrive (infants and children)
Liver				Total bilirubin, alkaline phosphatase >2× upper limit of normal ALT >2× upper limit of normal
Lung	Bronchiolitis obliterans diagnosed with lung biopsy Bronchiolitis obliterans syndrome[e]	Air trapping and bronchiectasis on chest CT	Cryptogenic organizing pneumonia Restrictive lung disease[f]	
Muscles, fascia, joints	Fasciitis Joint stiffness or contractures secondary to fasciitis or sclerosis	Myositis or polymyositis[g]	Edema Muscle cramps Arthralgia or arthritis	
Hematopoietic and immune			Thrombocytopenia Eosinophilia Lymphopenia Hypo- or hypergammaglobulinemia Autoantibodies (AIHA, ITP) Raynaud phenomenon	
Other			Pericardial or pleural effusions Ascites Peripheral neuropathy Nephrotic syndrome Myasthenia gravis Cardiac conduction abnormality or cardiomyopathy	

[a]As per the National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease.
[b]In all cases, infection, drug effect, malignancy, or other causes must be excluded.
[c]Can be acknowledged as part of the chronic GVHD manifestations if diagnosis is confirmed.
[d]Commonly refers to shared features by both acute and chronic GVHD.
[e]BOS can be diagnostic for lung chronic GVHD only if distinctive sign or symptom present in another organ (see text).
[f]Pulmonary entities under investigation or unclassified.
[g]Diagnosis of chronic GVHD requires biopsy.
AIHA, autoimmune hemolytic anemia; ALT, alanine aminotransferase; ITP, idiopathic thrombocytopenic purpura.
Reproduced with permission from Jagasia MH, Greinix HT, Arora M, et al: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report, *Biol Blood Marrow Transplant* 2015 Mar;21(3):389-401.e1.

(n = 44) in that population.[225] The trial showed an ORR of 67% (21% complete and 65% partial responses), which was sustained for at least 20 weeks in a majority or patients. However, about one-third of patients had grade 3 or higher infections, about one-third required dose reductions because of toxicities, and about one-third discontinued treatment because of toxicities, most commonly fatigue or pneumonia.[225]

In addition to systemic treatment, skilled ancillary and supportive care are the keys to the management of cGVHD to target specific organs involved, such as oral mucosa (topical steroids, sialogogues), genital (topical steroids and dilators), ocular (artificial lubricant tears, punctal plugs, scleral lenses, or prosthetic replacement of the ocular surface ecosystem [PROSE] lenses), lungs (inhaled corticosteroids, pulmonary rehabilitation), and fascia/joint (physical/occupational therapy, stretching, casting, weight-bearing exercises, compression stockings for peripheral edema).[226]

RELAPSE

Role of Maintenance Therapy Post-Transplantation for Relapse Prevention

Multiple studies suggest a potential benefit of post-HCT maintenance in specific situations, such as in patients with FMS-like tyrosine kinase 3 (FLT3)/internal tandem duplication (ITD; FLT3/ITD), mutated AML, and Philadelphia chromosome–positive (Ph+ve) ALL/CML. The pivotal randomized, double-blind, placebo-controlled phase 2 multicenter (SORMAIN) trial[230] assessed the efficacy of sorafenib maintenance post-HCT but was terminated early because of slow accrual. Nevertheless, it did provide an indication of improved survival in patients who received maintenance. After a median follow-up of almost 42 months post-randomization, 2-year DFS was 53% versus 85% in the placebo versus sorafenib groups, respectively (HR 0.39, 95% CI, 0.18–0.85; P = .0135). Besides sorafenib,[230,231] many other oral FLT3/ITD inhibitors are being evaluated, including quizartinib,[232,233] midostaurin (RADIUS trial),[234] crenolanib,[235] and gilteritinib.[236,237] In patients with Ph+ acute or chronic leukemias, several tyrosine kinase inhibitors (TKIs), including imatinib[238–240] or newer-generation TKIs (dasatinib or ponatinib),[241] have been demonstrated to be safe for post-HCT maintenance.

Besides these targeted agents, there is no established role of maintenance post-HCT, although this has been an area of investigation in multiple trials, most commonly using DNA hypomethylating agents, eg, azacitidine or decitabine for AML/MDS.[242–244] The largest of these was a phase 3 randomized trial conducted at MDACC,[245] which assessed the efficacy of azacytidine (n = 93) versus observation (n = 94) in patients with AML/MDS. Azacytidine dose was 32 mg/m^2 per day given subcutaneously for 5 days, every 28 days for 12 cycles, with the first cycle started between days +42–100. About 93% of patients in the azacytidine arm started the maintenance at a median of about 2 months post-HCT, but about 75% could not complete the planned 12 cycles. The median number of cycles received was four; the most common reason for discontinuation was the relapse/death in about one-half of the patients (47%) followed by toxicity in about one-quarter (26%). The trial was stopped early because of slow accrual and showed no difference in DFS between the arms.[245] Many other clinical trials are underway at MDACC to assess the safety and efficacy of novel higher-potency hypomethylating agents (such as guadecitabine), novel combinations (such as azacytidine plus BCL-2 inhibitor venetoclax) for patients with high-risk myeloid malignancies, and bispecific monoclonal antibodies (such as blinatumomab[246]) for patients with ALL.

Treatment of Relapsed Disease

Although a small minority of "relapsed" disease post-HCT can be donor derived, a majority of relapses are the result of residual host malignant cells that survive the conditioning regimen and escape the GVT effect. This may be caused by loss or reduced expression of tumor-related antigens, loss of mismatched HLA haplotype leading to the development of mutant leukemic cells,[247,248] or development of tolerance in the donor-derived T-cells.[249] The management of relapsed disease post-HCT is complicated and depends on several factors, including time from HCT to relapse, several disease-related factors (impending relapse as assessed by the loss of donor myeloid chimerism, detection of new minimal/measurable residual disease, overt/proliferative relapse), and patient characteristics (performance status, comorbidities, presence or absence of GVHD, etc). Broadly, the options include withdrawal of immunosuppression (with close monitoring because of a high risk of GVHD), immunotherapy (DLI, chimeric antigen receptor cells, use of checkpoint inhibitors or other immunomodulatory drugs), chemotherapy, or subsequent HCT. The prognosis of relapsed leukemia post-HCT is dismal. A study by the CIBMTR in patients with relapsed AML showed that the median time to relapse after HCT was 7 months.[250] Of these, 29% of patients attained CR with subsequent treatment (chemotherapy, DLI, or second HCT), resulting in 1-year OS of 23%. Time to relapse after first HCT was the single most important predictor of survival. Three-year OS was 4% for patients whose disease relapsed within the first 6 months of first HCT, 12% for those whose disease relapsed between 6 and 12 months, 26% for those with disease relapse between 2

and 3 years, and 38% for those whose disease relapsed 3 or more years after first HCT.[250]

LATE COMPLICATIONS

Among long-term survivors of HCT, many patients experience delayed toxicities,[251] which could be a sequela of the conditioning regimen, GVHD, and/or its treatment. These include endocrine abnormalities such as hypothyroidism, hypogonadism, or growth hormone deficiency in younger patients, pulmonary toxicities such as restrictive or obstructive lung disease, cardiac toxicities such as hypertension, dyslipidemia, late infectious complications, impaired bone health (osteopenia, osteoporosis, or avascular necrosis) and secondary malignancies, to name a few.[252–255] The intensive treatment and prolonged recovery from allogeneic transplantation can also have profound psychosocial as well as financial implications for patients and their families. At MDACC, patients are routinely followed by a dedicated survivorship program to screen for and to address these late effects of HCT.

CONCLUSIONS

Allogeneic HCT remains an important therapeutic technique for the management of various malignant and nonmalignant disorders. Over the past decade, better disease risk stratification, identification of high-risk comorbidities, and advances in transplantation techniques, conditioning therapy, GVHD prophylaxis, and supportive care have advanced the field of transplantation immensely. With a wider use of alternative donors, no patient should now be denied transplantation for lack of a donor. Further, with an increasing use of RIC and innovative MAC regimens, older patients and those with high comorbidities can now be transplanted safely. Yet, relapse of the underlying disease, GVHD, and infections remain the Achilles heels that contribute to a vast majority of transplantation failure. Although tremendous strides have been made since that first human BMT performed in the late 1950s to now, we are yet to completely decipher the "Holy Grail" of transplantation—which is to maximize the GVT effect while minimizing the GVHD.

MD ANDERSON PRACTICE TIPS

- Whenever possible, allogeneic HCTs are performed in the context of clinical trials that are assessing novel conditioning regimens and GVHD prophylaxis strategies. Patients who are ineligible for clinical trials because of insurance issues or other reasons are discussed in HCT team meetings to formulate the standard of care plan.
- Most standard of care myeloablative conditioning regimens include busulfan and fludarabine (mostly using the fractionated approach), whereas fludarabine and melphalan are commonly used for reduced-intensity conditioning. Post-transplantation cyclophosphamide is being used more commonly in almost all types of HCT for GVHD prophylaxis, except CBT.
- Older and/or frail patients benefit from referral to the MDACC HCT "Enhanced Recovery program," which entails comprehensive assessment by a multidisciplinary team of HCT physicians, advanced care providers, nutritionists, physical and occupational therapists, pharmacists, rehabilitation physicians, and geriatricians to address frailty issues before HCT, with an aim to improve post-HCT outcomes.
- Allogeneic HCT patients are also assessed in a "survivorship clinic" around 3 months post-HCT for screening and counseling about long-term complications of HCT.
- Patients with GVHD benefit from care at dedicated GVHD multidisciplinary clinics that includes HCT physicians, dermatologists, oral health specialists, physical and occupational therapists, pulmonologists, and ophthalmologists.
- Patients are encouraged to participate in current clinical trials that are evaluating the use of strategies to reduce the relapse risk post-HCT.

REFERENCES

1. D'Souza A, Fretham C. Current Uses and Outcomes of Hematopoietic Cell Transplantation (HCT): CIBMTR Summary Slides, 2019. Accessed April 7, 2021. https://www.cibmtr.org/ReferenceCenter/SlidesReports/SummarySlides/_layouts/15/WopiFrame.aspx?sourcedoc=/ReferenceCenter/SlidesReports/SummarySlides/Documents/2018%20Summary%20Slides%20-%20final%20-%20for%20web%20posting.pptx&action=default
2. Center for International Blood and Marrow Transplant, a contractor for the C.W. Bill Young Cell Transplantation Program operated through the U. S. Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau; Transplant Activity Report; Stem Cell Therapeutic Outcomes Database; last reviewered October 2020. Accessed April 7, 2021. https://bloodstemcell.hrsa.gov/data/donation-and-transplantation-statistics/transplant-activity-report
3. Mehta RS, Weisdorf D. History and current status of hematopoietic cell transplantation. In: Bashir Q, Hamadani M, eds. *Hematopoietic Cell Transplantation for Malignant Conditions, vol. 1*. Dolores Meloni; 2019:1-18.
4. Thomas ED, Lochte HL Jr, Lu WC, Ferrebee JW. Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. *N Engl J Med.* 1957;257(11):491-496.
5. Thomas ED, Lochte HL Jr, Cannon JH, et al. Supralethal whole body irradiation and isologous marrow transplantation in man. *J Clin Invest.* 1959;38:1709-1716.
6. Bortin MM. A compendium of reported human bone marrow transplants. *Transplantation.* 1970;9(6):571-587.
7. Mathe G, Amiel JL, Schwarzenberg L, et al. Successful allogenic bone marrow transplantation in man: chimerism, induced specific tolerance and possible anti-leukemic effects. *Blood.* 1965;25:179-196.
8. Gatti RA, Meuwissen HJ, Allen HD, et al. Immunological reconstitution of sex-linked lymphopenic immunological deficiency. *Lancet.* 1968;2(7583):1366-1369.
9. Bach FH, Albertini RJ, Joo P, et al. Bone-marrow transplantation in a patient with the Wiskott-Aldrich syndrome. *Lancet.* 1968;2(7583):1364-1366.
10. The Westminster Hospitals Bone-Marrow Transplant Team. Bone-marrow transplant from an unrelated donor for chronic granulomatous disease. *Lancet.* 1977;1(8005):210-213.
11. Humble JG, Barrett AJ. Technique of bone marrow transplantation. *Proc R Soc Med.* 1975;68(9):580-582.
12. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood.* 2005;106(8):2912-2919.
13. Sorror ML, Storb RF, Sandmaier BM, et al. Comorbidity-age index: a clinical measure of biologic age before allogeneic hematopoietic cell transplantation. *J Clin Oncol.* 2014;32(29):3249-3256.
14. Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood.* 2017;129(4):424-447.
15. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood.* 2012;120(12):2454-2465.
16. Armand P, Kim HT, Logan BR, et al. Validation and refinement of the Disease Risk Index for allogeneic stem cell transplantation. *Blood.* 2014;123(23):3664-3671.
17. Immuno Polymorphism Database. IPD-IMGT/HLA; Statistics. Accessed April 7, 2021. https://www.ebi.ac.uk/ipd/imgt/hla/stats.html
18. Bertaina A, Andreani M. Major histocompatibility complex and hematopoietic stem cell transplantation: beyond the classical HLA polymorphism. *Int J Mol Sci.* 2018;19(2).
19. Deakin JE, Papenfuss AT, Belov K, et al. Evolution and comparative analysis of the MHC Class III inflammatory region. *BMC Genomics.* 2006;7:281.
20. de Bueger M, Bakker A, Van Rood JJ, et al. Tissue distribution of human minor histocompatibility antigens. Ubiquitous versus restricted tissue distribution indicates heterogeneity among human cytotoxic T lymphocyte-defined non-MHC antigens. *J Immunol.* 1992;149(5):1788-1794.
21. Spierings E, Kim YH, Hendriks M, et al. Multicenter analyses demonstrate significant clinical effects of minor histocompatibility antigens on GvHD and GvL after HLA-matched related and unrelated hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2013;19(8):1244-1253.
22. Alousi AM, Le-Rademacher J, Saliba RM, et al. Who is the better donor for older hematopoietic transplant recipients: an older-aged sibling or a young, matched unrelated volunteer? *Blood.* 2013;121(13):2567-2573.
23. Woolfrey A, Lee SJ, Gooley TA, et al. HLA-allele matched unrelated donors compared to HLA-matched sibling donors: role of cell source and disease risk category. *Biol Blood Marrow Transplant.* 2010;16(10):1382-1387.
24. Ringden O, Pavletic SZ, Anasetti C, et al. The graft-versus-leukemia effect using matched unrelated donors is not superior to HLA-identical siblings for hematopoietic stem cell transplantation. *Blood.* 2009;113(13):3110-3118.
25. Gupta V, Tallman MS, He W, et al. Comparable survival after HLA-well-matched unrelated or matched sibling donor transplantation for acute myeloid leukemia in first remission with unfavorable cytogenetics at diagnosis. *Blood.* 2010;116(11):1839-1848.
26. Walter RB, Pagel JM, Gooley TA, et al. Comparison of matched unrelated and matched related donor myeloablative hematopoietic cell transplantation for adults with acute myeloid leukemia in first remission. *Leukemia.* 2010;24(7):1276-1282.
27. Schetelig J, Bornhauser M, Schmid C, et al. Matched unrelated or matched sibling donors result in comparable survival after allogeneic stem-cell transplantation in elderly patients with acute myeloid leukemia: a report from the cooperative German Transplant Study Group. *J Clin Oncol.* 2008;26(32):5183-5191.
28. Moore J, Nivison-Smith I, Goh K, et al. Equivalent survival for sibling and unrelated donor allogeneic stem cell transplantation for acute myelogenous leukemia. *Biol Blood Marrow Transplant.* 2007;13(5):601-607.
29. Fleischhauer K, Shaw BE, Gooley T, et al. Effect of T-cell-epitope matching at HLA-DPB1 in recipients of unrelated-donor haemopoietic-cell transplantation: a retrospective study. *Lancet Oncol.* 2012;13(4):366-374.
30. Ottinger HD, Muller CR, Goldmann SF, et al. Second German consensus on immunogenetic donor search for allotransplantation of hematopoietic stem cells. *Ann Hematol.* 2001;80(12):706-714.
31. Sanchez-Mazas A, Djoulah S, Busson M, et al. A linkage disequilibrium map of the MHC region based on the analysis of 14 loci haplotypes in 50 French families. *Eur J Hum Genet.* 2000;8(1):33-41.
32. Koskela S, Ritari J, Hyvarinen K, et al. Hidden genomic MHC disparity between HLA-matched sibling pairs in hematopoietic stem cell transplantation. *Sci Rep.* 2018;8(1):5396.
33. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. *Biol Blood Marrow Transplant.* 2009;15(12):1628-1633.
34. Gyurkocza B, Sandmaier BM. Conditioning regimens for hematopoietic cell transplantation: one size does not fit all. *Blood.* 2014;124(3):344-353.

35. Giralt S, Ballen K, Rizzo D, et al. Reduced-intensity conditioning regimen workshop: defining the dose spectrum. Report of a workshop convened by the center for international blood and marrow transplant research. *Biol Blood Marrow Transplant.* 2009;15(3):367-369.
36. Giralt S, Logan B, Rizzo D, et al. Reduced-intensity conditioning for unrelated donor progenitor cell transplantation: long-term follow-up of the first 285 reported to the national marrow donor program. *Biol Blood Marrow Transplant.* 2007;13(7):844-852.
37. Scott BL, Pasquini MC, Logan BR, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. *J Clin Oncol.* 2017;35(11):1154-1161.
38. Gooptu M, Kim HT, Ho VT, et al. A comparison of the myeloablative conditioning regimen fludarabine/busulfan with cyclophosphamide/total body irradiation, for allogeneic stem cell transplantation in the modern era: a cohort analysis. *Biol Blood Marrow Transplant.* 2018;24(8):1733-1740.
39. Arai Y, Kondo T, Shigematsu A, et al. Improved prognosis with additional medium-dose VP16 to CY/TBI in allogeneic transplantation for high risk ALL in adults. *Am J Hematol.* 2018;93(1):47-57.
40. Bredeson C, LeRademacher J, Kato K, et al. Prospective cohort study comparing intravenous busulfan to total body irradiation in hematopoietic cell transplantation. *Blood.* 2013;122(24):3871-3878.
41. Nagler A, Rocha V, Labopin M, et al. Allogeneic hematopoietic stem-cell transplantation for acute myeloid leukemia in remission: comparison of intravenous busulfan plus cyclophosphamide (Cy) versus total-body irradiation plus Cy as conditioning regimen--a report from the acute leukemia working party of the European group for blood and marrow transplantation. *J Clin Oncol.* 2013;31(28):3549-3556.
42. Riddell S, Appelbaum FR, Buckner CD, et al. High-dose cytarabine and total body irradiation with or without cyclophosphamide as a preparative regimen for marrow transplantation for acute leukemia. *J Clin Oncol.* 1988;6(4):576-582.
43. Stephens SJ, Thomas S, Rizzieri DA, et al. Myeloablative conditioning with total body irradiation for AML: Balancing survival and pulmonary toxicity. *Adv Radiat Oncol.* 2016;1(4):272-280.
44. Zohren F, Czibere A, Bruns I, et al. Fludarabine, amsacrine, high-dose cytarabine and 12 Gy total body irradiation followed by allogeneic hematopoietic stem cell transplantation is effective in patients with relapsed or high-risk acute lymphoblastic leukemia. *Bone Marrow Transplant.* 2009;44(12):785-792.
45. Jamy OH, Salzman DE, Stasi AD, et al. A phase II study of myeloablative allogeneic hematopoietic stem cell transplantation (aHSCT) for acute lymphoblastic leukemia (ALL) in older patients using fludarabine and total body irradiation (Flu/TBI). *J Clin Oncol.* 2019;37(suppl 15).
46. Jillella AP, Doria R, Khan K, et al. Cyclophosphamide, cytosine arabinoside and TBI as a conditioning regimen for allogeneic bone marrow transplantation in patients with leukemia. *Bone Marrow Transplant.* 1999;23(11):1095-1100.
47. Clift RA, Buckner CD, Appelbaum FR, et al. Allogeneic marrow transplantation in patients with acute myeloid leukemia in first remission: a randomized trial of two irradiation regimens. *Blood.* 1990;76(9):1867-1871.
48. Gopal R, Ha CS, Tucker SL, et al. Comparison of two total body irradiation fractionation regimens with respect to acute and late pulmonary toxicity. *Cancer.* 2001;92(7):1949-1958.
49. Clift RA, Buckner CD, Appelbaum FR, et al. Long-term follow-Up of a randomized trial of two irradiation regimens for patients receiving allogeneic marrow transplants during first remission of acute myeloid leukemia. *Blood.* 1998;92(4):1455-1456.
50. Zikos P, Van Lint MT, Frassoni F, et al. Low transplant mortality in allogeneic bone marrow transplantation for acute myeloid leukemia: a randomized study of low-dose cyclosporin versus low-dose cyclosporin and low-dose methotrexate. *Blood.* 1998;91(9):3503-3508.
51. Vriesendorp HM, Chu H, Ochran TG, et al. Radiobiology of total body radiation. *Bone Marrow Transplant.* 1994;14(suppl 4):S4-S8.
52. Socie G, Devergie A, Girinsky T, et al. Influence of the fractionation of total body irradiation on complications and relapse rate for chronic myelogenous leukemia. The Groupe d'Etude des greffes de moelle osseuse (GEGMO). *Int J Radiat Oncol Biol Phys.* 1991;20(3):397-404.
53. Brochstein JA, Kernan NA, Groshen S, et al. Allogeneic bone marrow transplantation after hyperfractionated total-body irradiation and cyclophosphamide in children with acute leukemia. *N. Engl. J Med.* 1987;317(26):1618-1624.
54. Tutschka PJ, Copelan EA, Klein JP. Bone marrow transplantation for leukemia following a new busulfan and cyclophosphamide regimen. *Blood.* 1987;70(5):1382-1388.
55. Santos GW, Tutschka PJ, Brookmeyer R, et al. Marrow transplantation for acute nonlymphocytic leukemia after treatment with busulfan and cyclophosphamide. *N. Engl. J Med.* 1983;309(22):1347-1353.
56. Kashyap A, Wingard J, Cagnoni P, et al. Intravenous versus oral busulfan as part of a busulfan/cyclophosphamide preparative regimen for allogeneic hematopoietic stem cell transplantation: decreased incidence of hepatic venoocclusive disease (HVOD), HVOD-related mortality, and overall 100-day mortality. *Biol Blood Marrow Transplant.* 2002;8(9):493-500.
57. McDonald GB, Slattery JT, Bouvier ME, et al. Cyclophosphamide metabolism, liver toxicity, and mortality following hematopoietic stem cell transplantation. *Blood.* 2003;101(5):2043-2048.
58. de Lima M, Couriel D, Thall PF, et al. Once-daily intravenous busulfan and fludarabine: clinical and pharmacokinetic results of a myeloablative, reduced-toxicity conditioning regimen for allogeneic stem cell transplantation in AML and MDS. *Blood.* 2004;104(3):857-864.
59. Bornhauser M, Storer B, Slattery JT, et al. Conditioning with fludarabine and targeted busulfan for transplantation of allogeneic hematopoietic stem cells. *Blood.* 2003;102(3):820-826.
60. Russell JA, Tran HT, Quinlan D, et al. Once-daily intravenous busulfan given with fludarabine as conditioning for allogeneic stem cell transplantation: study of pharmacokinetics and early clinical outcomes. *Biol Blood Marrow Transplant.* 2002;8(9):468-476.
61. Russell JA, Duan Q, Chaudhry MA, et al. Transplantation from matched siblings using once-daily intravenous busulfan/fludarabine with thymoglobulin: a myeloablative regimen with low nonrelapse mortality in all but older patients with high-risk disease. *Biol Blood Marrow Transplant.* 2008;14(8):888-895.
62. Pidala J, Kim J, Anasetti C, et al. Targeted i.v. BU and fludarabine (t-i.v. BU/Flu) provides effective control of AML in adults with reduced toxicity. *Bone Marrow Transplant.* 2011;46(5):641-649.
63. Mehta RS, Bassett R, Olson A, et al. Myeloablative conditioning using timed-sequential busulfan plus fludarabine in older patients with acute myeloid leukemia: long-term results of a prospective phase II clinical trial. *Haematologica.* 2019;104(12):e555-e557.
64. Popat UR, Mehta RS, Bassett R, et al. Fludarabine with a higher versus lower dose of myeloablative timed-sequential busulfan in older patients and patients with comorbidities: an open-label, non-stratified, randomised phase 2 trial. *Lancet Haematol.* 2018;5(11):e532-e542.

65. Weiden PL, Flournoy N, Thomas ED, et al. Antileukemic effect of graft-versus-host disease in human recipients of allogeneic-marrow grafts. *N Engl J Med.* 1979;300(19):1068-1073.
66. Weiden PL, Sullivan KM, Flournoy N, et al, for the Seattle Marrow Transplant Team. Antileukemic effect of chronic graft-versus-host disease: contribution to improved survival after allogeneic marrow transplantation. *N Engl J Med.* 1981;304(25):1529-1533.
67. Sullivan KM, Weiden PL, Storb R, et al. Influence of acute and chronic graft-versus-host disease on relapse and survival after bone marrow transplantation from HLA-identical siblings as treatment of acute and chronic leukemia. *Blood.* 1989;73(6):1720-1728.
68. Sandmaier BM, Mackinnon S, Childs RW. Reduced intensity conditioning for allogeneic hematopoietic cell transplantation: current perspectives. *Biol Blood Marrow Transplant.* 2007;13(suppl 1):87-97.
69. McSweeney PA, Niederwieser D, Shizuru JA, et al. Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects. *Blood.* 2001;97(11):3390-3400.
70. Fefer A, Sullivan KM, Weiden P, et al. Graft versus leukemia effect in man: the relapse rate of acute leukemia is lower after allogeneic than after syngeneic marrow transplantation. *Prog Clin Biol Res.* 1987;244:401-408.
71. Horowitz MM, Gale RP, Sondel PM, et al. Graft-versus-leukemia reactions after bone marrow transplantation. *Blood.* 1990;75(3):555-562.
72. Storb R, Yu C, Wagner JL, et al. Stable mixed hematopoietic chimerism in DLA-identical littermate dogs given sublethal total body irradiation before and pharmacological immunosuppression after marrow transplantation. *Blood.* 1997;89(8):3048-3054.
73. Niederwieser D, Maris M, Shizuru JA, et al. Low-dose total body irradiation (TBI) and fludarabine followed by hematopoietic cell transplantation (HCT) from HLA-matched or mismatched unrelated donors and postgrafting immunosuppression with cyclosporine and mycophenolate mofetil (MMF) can induce durable complete chimerism and sustained remissions in patients with hematological diseases. *Blood.* 2003;101(4):1620-1629.
74. Gyurkocza B, Storb R, Storer BE, et al. Nonmyeloablative allogeneic hematopoietic cell transplantation in patients with acute myeloid leukemia. *J Clin Oncol.* 2010;28(17):2859-2867.
75. Brunstein CG, Barker JN, Weisdorf DJ, et al. Umbilical cord blood transplantation after nonmyeloablative conditioning: impact on transplantation outcomes in 110 adults with hematologic disease. *Blood.* 2007;110(8):3064-3070.
76. Chao NJ, Koh LP, Long GD, et al. Adult recipients of umbilical cord blood transplants after nonmyeloablative preparative regimens. *Biol Blood Marrow Transplant.* 2004;10(8):569-575.
77. Luznik L, O'Donnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, post-transplantation cyclophosphamide. *Biol Blood Marrow Transplant.* 2008;14(6):641-650.
78. Popat U, de Lima MJ, Saliba RM, et al. Long-term outcome of reduced-intensity allogeneic hematopoietic SCT in patients with AML in CR. *Bone Marrow Transplant.* 2012;47(2):212-216.
79. Oran B, Giralt S, Saliba R, et al. Allogeneic hematopoietic stem cell transplantation for the treatment of high-risk acute myelogenous leukemia and myelodysplastic syndrome using reduced-intensity conditioning with fludarabine and melphalan. *Biol Blood Marrow Transplant.* 2007;13(4):454-462.
80. Giralt S, Thall PF, Khouri I, et al. Melphalan and purine analog-containing preparative regimens: reduced-intensity conditioning for patients with hematologic malignancies undergoing allogeneic progenitor cell transplantation. *Blood.* 2001;97(3):631-637.
81. Giralt S, Estey E, Albitar M, et al. Engraftment of allogeneic hematopoietic progenitor cells with purine analog-containing chemotherapy: harnessing graft-versus-leukemia without myeloablative therapy. *Blood.* 1997;89(12):4531-4536.
82. Shimoni A, Hardan I, Shem-Tov N, et al. Allogeneic hematopoietic stem-cell transplantation in AML and MDS using myeloablative versus reduced-intensity conditioning: the role of dose intensity. *Leukemia.* 2006;20(2):322-328.
83. Kharfan-Dabaja MA, Labopin M, Bazarbachi A, et al. Comparing i.v. BU dose intensity between two regimens (FB2 vs FB4) for allogeneic HCT for AML in CR1: a report from the Acute Leukemia Working Party of EBMT. *Bone Marrow Transplant.* 2014;49(9):1170-1175.
84. Alyea EP, Kim HT, Ho V, et al. Comparative outcome of nonmyeloablative and myeloablative allogeneic hematopoietic cell transplantation for patients older than 50 years of age. *Blood.* 2005;105(4):1810-1814.
85. Alatrash G, Kidwell KM, Thall PF, et al. Reduced intensity vs. myeloablative conditioning with fludarabine and PK-guided busulfan in allogeneic stem cell transplantation for patients with AML/MDS. *Bone Marrow Transplant.* 2019;54(8):1245-1253.
86. Bachanova V, Marks DI, Zhang MJ, et al. Ph+ ALL patients in first complete remission have similar survival after reduced intensity and myeloablative allogeneic transplantation: impact of tyrosine kinase inhibitor and minimal residual disease. *Leukemia.* 2014;28(3):658-665.
87. Mohty M, Labopin M, Volin L, et al. Reduced-intensity versus conventional myeloablative conditioning allogeneic stem cell transplantation for patients with acute lymphoblastic leukemia: a retrospective study from the European Group for Blood and Marrow Transplantation. *Blood.* 2010;116(22):4439-4443.
88. Marks DI, Wang T, Perez WS, et al. The outcome of full-intensity and reduced-intensity conditioning matched sibling or unrelated donor transplantation in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia in first and second complete remission. *Blood.* 2010;116(3):366-374.
89. Buckner CD, Clift RA, Sanders JE, et al. Marrow harvesting from normal donors. *Blood.* 1984;64(3):630-634.
90. Styczynski J, Balduzzi A, Gil L, et al. Risk of complications during hematopoietic stem cell collection in pediatric sibling donors: a prospective European Group for Blood and Marrow Transplantation Pediatric Diseases Working Party study. *Blood.* 2012;119(12):2935-2942.
91. Favre G, Beksac M, Bacigalupo A, et al. Differences between graft product and donor side effects following bone marrow or stem cell donation. *Bone Marrow Transplant.* 2003;32(9):873-880.
92. Fabrizio V, Armeson K, Warneke S, et al. Trends in cell dose requests for a NMDP bone marrow collection center. *Biol Blood Marrow Transplant.* 2017;23(3): S408.
93. Prokopishyn NL, Logan BR, Kiefer DM, et al. The Concentration of Total Nucleated Cells in Harvested Bone Marrow for Transplantation Has Decreased over Time. *Biol Blood Marrow Transplant.* 2019;25(7):1325-1330.
94. Dominietto A, Lamparelli T, Raiola AM, et al. Transplant-related mortality and long-term graft function are significantly influenced by cell dose in patients undergoing allogeneic marrow transplantation. *Blood.* 2002;100(12):3930-3934.
95. Schmitz N, Bacigalupo A, Hasenclever D, et al. Allogeneic bone marrow transplantation vs filgrastim-mobilised peripheral blood progenitor cell transplantation in patients with early leukaemia: first results of a randomised multicentre trial of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant.* 1998;21(10):995-1003.
96. Blaise D, Kuentz M, Fortanier C, et al. Randomized trial of bone marrow versus lenograstim-primed blood cell allogeneic

transplantation in patients with early-stage leukemia: a report from the Societe Francaise de Greffe de Moelle. *J Clin Oncol.* 2000;18(3):537-546.
97. Bensinger WI, Martin PJ, Storer B, et al. Transplantation of bone marrow as compared with peripheral-blood cells from HLA-identical relatives in patients with hematologic cancers. *N. Engl. J Med.* 2001;344(3):175-181.
98. Heldal D, Tjonnfjord G, Brinch L, et al. A randomised study of allogeneic transplantation with stem cells from blood or bone marrow. *Bone Marrow Transplant.* 2000;25(11):1129-1136.
99. Pulsipher MA, Chitphakdithai P, Miller JP, et al. Adverse events among 2408 unrelated donors of peripheral blood stem cells: results of a prospective trial from the National Marrow Donor Program. *Blood.* 2009;113(15):3604-3611.
100. Anasetti C, Logan BR, Lee SJ, et al. Peripheral-blood stem cells versus bone marrow from unrelated donors. *N Engl J Med.* 2012;367(16):1487-1496.
101. Friedrichs B, Tichelli A, Bacigalupo A, et al. Long-term outcome and late effects in patients transplanted with mobilised blood or bone marrow: a randomised trial. *Lancet Oncol.* 2010;11(4):331-338.
102. Schmitz N, Eapen M, Horowitz MM, et al. Long-term outcome of patients given transplants of mobilized blood or bone marrow: a report from the International Bone Marrow Transplant Registry and the European Group for Blood and Marrow Transplantation. *Blood.* 2006;108(13):4288-4290.
103. Stem Cell Trialists' Collaborative Group. Allogeneic peripheral blood stem-cell compared with bone marrow transplantation in the management of hematologic malignancies: an individual patient data meta-analysis of nine randomized trials. *J Clin Oncol.* 2005;23(22):5074-5087.
104. Ferrara JL, Levy R, Chao NJ. Pathophysiologic mechanisms of acute graft-vs-host disease. *Biol Blood Marrow Transplant.* 1999;5(6):347-356.
105. Kernan NA, Bordignon C, Heller G, et al. Graft failure after T-cell-depleted human leukocyte antigen identical marrow transplants for leukemia: I. Analysis of risk factors and results of secondary transplants. *Blood.* 1989;74(6):2227-2236.
106. Wagner JE, Zahurak M, Piantadosi S, et al. Bone marrow transplantation of chronic myelogenous leukemia in chronic phase: evaluation of risks and benefits. *J Clin Oncol.* 1992;10(5):779-789.
107. Goldman JM, Gale RP, Horowitz MM, et al. Bone marrow transplantation for chronic myelogenous leukemia in chronic phase. Increased risk for relapse associated with T-cell depletion. *Ann Intern Med.* 1988;108(6):806-814.
108. Devine SM, Carter S, Soiffer RJ, et al. Low risk of chronic graft-versus-host disease and relapse associated with T cell-depleted peripheral blood stem cell transplantation for acute myelogenous leukemia in first remission: results of the blood and marrow transplant clinical trials network protocol 0303. *Biol Blood Marrow Transplant.* 2011;17(9):1343-1351.
109. Tamari R, Chung SS, Papadopoulos EB, et al. CD34-selected hematopoietic stem cell transplants conditioned with myeloablative regimens and antithymocyte globulin for advanced myelodysplastic syndrome: limited graft-versus-host disease without increased relapse. *Biol Blood Marrow Transplant.* 2015;21(12):2106-2114.
110. Li Pira G, Malaspina D, Girolami E, et al. Selective depletion of alphabeta T cells and B cells for human leukocyte antigen-haploidentical hematopoietic stem cell transplantation. A three-year follow-up of procedure efficiency. *Biol Blood Marrow Transplant.* 2016;22(11):2056-2064.
111. Radestad E, Wikell H, Engstrom M, et al. Alpha/beta T-cell depleted grafts as an immunological booster to treat graft failure after hematopoietic stem cell transplantation with HLA-matched related and unrelated donors. *J Immunol Res.* 2014;2014:578741.
112. Bertaina A, Merli P, Rutella S, et al. HLA-haploidentical stem cell transplantation after removal of alphabeta+ T and B cells in children with nonmalignant disorders. *Blood.* 2014;124(5):822-826.
113. Soiffer RJ, Kim HT, McGuirk J, et al. Prospective, randomized, double-blind, phase III clinical trial of anti-T-lymphocyte globulin to assess impact on chronic graft-versus-host disease-free survival in patients undergoing HLA-matched unrelated myeloablative hematopoietic cell transplantation. *J Clin Oncol.* 2017;35(36):4003-4011.
114. Walker I, Panzarella T, Couban S, et al. Pretreatment with anti-thymocyte globulin versus no anti-thymocyte globulin in patients with haematological malignancies undergoing haemopoietic cell transplantation from unrelated donors: a randomised, controlled, open-label, phase 3, multicentre trial. *Lancet Oncol.* 2016;17(2):164-173.
115. Allen CE, Marsh R, Dawson P, et al. Reduced-intensity conditioning for hematopoietic cell transplant for HLH and primary immune deficiencies. *Blood.* 2018;132(13):1438-1451.
116. Marsh RA, Vaughn G, Kim MO, et al. Reduced-intensity conditioning significantly improves survival of patients with hemophagocytic lymphohistiocytosis undergoing allogeneic hematopoietic cell transplantation. *Blood.* 2010;116(26):5824-5831.
117. Oostenbrink LVE, Jol-van der Zijde CM, Kielsen K, et al. Differential elimination of anti-thymocyte globulin of fresenius and genzyme impacts T-cell reconstitution after hematopoietic stem cell transplantation. *Front Immunol.* 2019;10:315.
118. Scheinberg P, Nunez O, Weinstein B, et al. Horse versus rabbit antithymocyte globulin in acquired aplastic anemia. *N. Engl. J Med.* 2011;365(5):430-438.
119. Jones JL, Coles AJ. Mode of action and clinical studies with alemtuzumab. *Exp Neurol.* 2014;262 Pt A:37-43.
120. Juliusson G, Theorin N, Karlsson K, et al. Subcutaneous alemtuzumab vs ATG in adjusted conditioning for allogeneic transplantation: influence of Campath dose on lymphoid recovery, mixed chimerism and survival. *Bone Marrow Transplant.* 2006;37(5):503-510.
121. Uphoff DE. Alteration of homograft reaction by A-methopterin in lethally irradiated mice treated with homologous marrow. *Proc Soc Exp Biol Med (Maywood).* 1958;99(3):651-653.
122. Thomas ED, Buckner CD, Clift RA, et al. Marrow transplantation for acute nonlymphoblastic leukemia in first remission. *N Engl J Med.* 1979;301(11):597-599.
123. Ratanatharathorn V, Nash RA, Przepiorka D, et al. Phase III study comparing methotrexate and tacrolimus (prograf, FK506) with methotrexate and cyclosporine for graft-versus-host disease prophylaxis after HLA-identical sibling bone marrow transplantation. *Blood.* 1998;92(7):2303-2314.
124. Przepiorka D, Ippoliti C, Khouri I, et al. Tacrolimus and mini-dose methotrexate for prevention of acute graft-versus-host disease after matched unrelated donor marrow transplantation. *Blood.* 1996;88(11):4383-4389.
125. Krensky AM, Azzi JR, Hafler DA. Immunosuppressants and tolerogens. In: Brunton LL, Hilal-Dandan R, Knollmann BC, eds. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics.* 13th ed. McGraw-Hill; 2017.
126. Storb R, Deeg HJ, Farewell V, et al. Marrow transplantation for severe aplastic anemia: methotrexate alone compared with a combination of methotrexate and cyclosporine for prevention of acute graft-versus-host disease. *Blood.* 1986;68(1):119-125.
127. Storb R, Deeg HJ, Whitehead J, et al. Methotrexate and cyclosporine compared with cyclosporine alone for prophylaxis of acute graft versus host disease after marrow transplantation for leukemia. *N Engl J Med.* 1986;314(12):729-735.
128. Hiraoka A, Ohashi Y, Okamoto S, et al. Phase III study comparing tacrolimus (FK506) with cyclosporine for graft-versus-host

disease prophylaxis after allogeneic bone marrow transplantation. *Bone Marrow Transplant.* 2001;28(2):181-185.
129. Stallone G, Infante B, Di Lorenzo A, et al. mTOR inhibitors effects on regulatory T cells and on dendritic cells. *J Transl Med.* 2016;14(1):152.
130. Battaglia M, Stabilini A, Migliavacca B, et al. Rapamycin promotes expansion of functional CD4+CD25+FOXP3+ regulatory T cells of both healthy subjects and type 1 diabetic patients. *J Immunol.* 2006;177(12):8338-8347.
131. Gooptu M, Kim HT, Howard A, et al. Effect of sirolimus on immune reconstitution following myeloablative allogeneic stem cell transplantation: an ancillary analysis of a randomized controlled trial comparing tacrolimus/sirolimus and tacrolimus/Methotrexate (Blood and Marrow Transplant Clinical Trials Network/BMT CTN 0402). *Biol Blood Marrow Transplant.* 2019;25(11):2143-2151.
132. Cutler C, Logan B, Nakamura R, et al. Tacrolimus/sirolimus vs tacrolimus/methotrexate as GVHD prophylaxis after matched, related donor allogeneic HCT. *Blood.* 2014;124(8):1372-1377.
133. Cutler C, Stevenson K, Kim HT, et al. Sirolimus is associated with veno-occlusive disease of the liver after myeloablative allogeneic stem cell transplantation. *Blood.* 2008;112(12):4425-4431.
134. Nieto Y, Patton N, Hawkins T, et al. Tacrolimus and mycophenolate mofetil after nonmyeloablative matched-sibling donor allogeneic stem-cell transplantations conditioned with fludarabine and low-dose total body irradiation. *Biol Blood Marrow Transplant.* 2006;12(2):217-225.
135. Yerushalmi R, Shem-Tov N, Danylesko I, et al. The combination of cyclosporine and mycophenolate mofetil is less effective than cyclosporine and methotrexate in the prevention of acute graft-versus host disease after stem-cell transplantation from unrelated donors. *Am J Hematol.* 2017;92(3):259-268.
136. Barker JN, Kurtzberg J, Ballen K, et al. Optimal practices in unrelated donor cord blood transplantation for hematologic malignancies. *Biol Blood Marrow Transplant.* 2017;23(6):882-896.
137. Sandhu KS, Brunstein C, DeFor T, et al. Umbilical cord blood transplantation outcomes in acute myelogenous leukemia/myelodysplastic syndrome patients aged >/=70 tears. *Biol Blood Marrow Transplant.* 2016;22(2):390-393.
138. Owens AH Jr, Santos GW. The effect of cytotoxic drugs on graft-versus-host disease in mice. *Transplantation.* 1971;11(4):378-382.
139. Santos GW, Owens AH. Production of graft-versus-host disease in the rat and its treatment with cytotoxic agents. *Nature.* 1966;210(5032):139-140.
140. Santos GW, Owens AH, Jr., Sensenbrenner LL. Effects of selected cytotoxic agents on antibody production in man; a prelimary report. *Ann N Y Acad Sci.* 1964;114:404-423.
141. Jones RJ, Barber JP, Vala MS, et al. Assessment of aldehyde dehydrogenase in viable cells. *Blood.* 1995;85(10):2742-2746.
142. O'Donnell PV, Luznik L, Jones RJ, et al. Nonmyeloablative bone marrow transplantation from partially HLA-mismatched related donors using posttransplantation cyclophosphamide. *Biol Blood Marrow Transplant.* 2002;8(7):377-386.
143. Nomoto K, Eto M, Yanaga K, et al. Interference with cyclophosphamide-induced skin allograft tolerance by cyclosporin A. *J Immunol.* 1992;149(8):2668-2674.
144. Bolanos-Meade J, Reshef R, Fraser R, et al. Three prophylaxis regimens (tacrolimus, mycophenolate mofetil, and cyclophosphamide; tacrolimus, methotrexate, and bortezomib; or tacrolimus, methotrexate, and maraviroc) versus tacrolimus and methotrexate for prevention of graft-versus-host disease with haemopoietic cell transplantation with reduced-intensity conditioning: a randomised phase 2 trial with a non-randomised contemporaneous control group (BMT CTN 1203). *Lancet Haematol.* 2019;6(3):e132-e143.
145. Bearman SI, Appelbaum FR, Buckner CD, et al. Regimen-related toxicity in patients undergoing bone marrow transplantation. *J Clin Oncol.* 1988;6(10):1562-1568.
146. Keefe DM, Schubert MM, Elting LS, et al. Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer.* 2007;109(5):820-831.
147. Amini S, Hadjibabaie M, Jahangard-Rafsanjani Z, et al. Evaluation of febrile neutropenia in patients undergoing hematopoietic stem cell transplantation. *Acta Med Iran.* 2014;52(1):38-42.
148. Celebi H, Akan H, Akcaglayan E, et al. Febrile neutropenia in allogeneic and autologous peripheral blood stem cell transplantation and conventional chemotherapy for malignancies. *Bone Marrow Transplant.* 2000;26(2):211-214.
149. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer:2010 update by the infectious diseases society of america. *Clin Infect Dis.* 2011;52(4):e56-e93.
150. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant.* 2009;15(10):1143-1238.
151. Arai S, Lee LA, Vogelsang GB. A systematic approach to hepatic complications in hematopoietic stem cell transplantation. *J Hematother Stem Cell Res.* 2002;11(2):215-229.
152. Tichelli A, Bucher C, Rovo A, et al. Premature cardiovascular disease after allogeneic hematopoietic stem-cell transplantation. *Blood.* 2007;110(9):3463-3471.
153. Blaes A, Konety S, Hurley P. Cardiovascular complications of hematopoietic stem cell transplantation. *Curr Treat Options Cardiovasc Med.* 2016;18(4):25.
154. Yen KT, Lee AS, Krowka MJ, Burger CD. Pulmonary complications in bone marrow transplantation: a practical approach to diagnosis and treatment. *Clin Chest Med.* 2004;25(1):189-201.
155. Lunde LE, Dasaraju S, Cao Q, et al. Hemorrhagic cystitis after allogeneic hematopoietic cell transplantation: risk factors, graft source and survival. *Bone Marrow Transplant.* 2015;50(11):1432-1437.
156. Mori Y, Miyamoto T, Kamezaki K, et al. Low incidence of adenovirus hemorrhagic cystitis following autologous hematopoietic stem cell transplantation in the rituximab era. *Am J Hematol.* 2012;87(8):828-830.
157. de Padua Silva L, Patah PA, Saliba RM, et al. Hemorrhagic cystitis after allogeneic hematopoietic stem cell transplants is the complex result of BK virus infection, preparative regimen intensity and donor type. *Haematologica.* 2010;95(7):1183-1190.
158. Ilhan O, Koc H, Akan H, et al. Hemorrhagic cystitis as a complication of bone marrow transplantation. *J Chemother.* 1997;9(1):56-61.
159. Laskin BL, Goebel J, Davies SM, Jodele S. Small vessels, big trouble in the kidneys and beyond: hematopoietic stem cell transplantation-associated thrombotic microangiopathy. *Blood.* 2011;118(6):1452-1462.
160. Ho VT, Cutler C, Carter S, et al. Blood and marrow transplant clinical trials network toxicity committee consensus summary: thrombotic microangiopathy after hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2005;11(8):571-575.
161. Dulamea AO, Lupescu IG. Neurological complications of hematopoietic cell transplantation in children and adults. *Neural Regen Res.* 2018;13(6):945-954.
162. Chaudhary RK, Dhakal P, Aryal A, Bhatt VR. Central nervous system complications after allogeneic hematopoietic stem cell transplantation. *Future Oncol.* 2017;13(25):2297-2312.
163. Maffini E, Festuccia M, Brunello L, et al. Neurologic complications after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2017;23(3):388-397.

164. Marty FM, Ljungman P, Chemaly RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. *N. Engl. J Med.* 2017;377(25):2433-2444.
165. Williams KM, Ahn KW, Chen M, et al. The incidence, mortality and timing of Pneumocystis jiroveci pneumonia after hematopoietic cell transplantation: a CIBMTR analysis. *Bone Marrow Transplant.* 2016;51(4):573-580.
166. Barge AJ. A review of the efficacy and tolerability of recombinant haematopoietic growth factors in bone marrow transplantation. *Bone Marrow Transplant.* 1993;11(suppl 2):1-11.
167. Willmot FC, Robertson G. Senecio disease, or cirrhosis of the liver due to Senecio poisoning. *Lancet.* 1920;196(5069):848-849.
168. Neuman MG, Cohen L, Opris M, et al. Hepatotoxicity of pyrrolizidine alkaloids. *J Pharm Pharm Sci.* 2015;18(4):825-843.
169. Stillman AS, Huxtable R, Consroe P, et al. Hepatic veno-occlusive disease due to pyrrolizidine (Senecio) poisoning in Arizona. *Gastroenterology.* 1977;73(2):349-352.
170. DeLeve LD, Shulman HM, McDonald GB. Toxic injury to hepatic sinusoids: sinusoidal obstruction syndrome (veno-occlusive disease). *Semin Liver Dis.* 2002;22(1):27-42.
171. Coppell JA, Richardson PG, Soiffer R, et al. Hepatic veno-occlusive disease following stem cell transplantation: incidence, clinical course, and outcome. *Biol Blood Marrow Transplant.* 2010;16(2):157-168.
172. Mohty M, Malard F, Abecassis M, et al. Revised diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in adult patients: a new classification from the European Society for Blood and Marrow Transplantation. *Bone Marrow Transplant.* 2016;51(7):906-912.
173. McDonald GB, Hinds MS, Fisher LD, et al. Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study of 355 patients. *Ann Intern Med.* 1993;118(4):255-267.
174. Jones RJ, Lee KS, Beschorner WE, et al. Venoocclusive disease of the liver following bone marrow transplantation. *Transplantation.* 1987;44(6):778-783.
175. McDonald GB, Sharma P, Matthews DE, et al. Venocclusive disease of the liver after bone marrow transplantation: diagnosis, incidence, and predisposing factors. *Hepatology.* 1984;4(1):116-122.
176. Bearman SI. The syndrome of hepatic veno-occlusive disease after marrow transplantation. *Blood.* 1995;85(11):3005-3020.
177. Richardson PG, Corbacioglu S, Ho VT, et al. Drug safety evaluation of defibrotide. *Expert Opin Drug Saf.* 2013;12(1):123-136.
178. Richardson PG, Riches ML, Kernan NA, et al. Phase 3 trial of defibrotide for the treatment of severe veno-occlusive disease and multi-organ failure. *Blood.* 2016;127(13):1656-1665.
179. Imran H, Tleyjeh IM, Zirakzadeh A, et al. Use of prophylactic anticoagulation and the risk of hepatic veno-occlusive disease in patients undergoing hematopoietic stem cell transplantation: a systematic review and meta-analysis. *Bone Marrow Transplant.* 2006;37(7):677-686.
180. Haussmann U, Fischer J, Eber S, et al. Hepatic veno-occlusive disease in pediatric stem cell transplantation: impact of preemptive antithrombin III replacement and combined antithrombin III/defibrotide therapy. *Haematologica.* 2006;91(6):795-800.
181. Bearman SI, Shen DD, Hinds MS, et al. A phase I/II study of prostaglandin E1 for the prevention of hepatic venocclusive disease after bone marrow transplantation. *Br J Haematol.* 1993;84(4):724-730.
182. Song JS, Seo JJ, Moon HN, et al. Prophylactic low-dose heparin or prostaglandin E1 may prevent severe veno-occlusive disease of the liver after allogeneic hematopoietic stem cell transplantation in Korean children. *J Korean Med Sci.* 2006;21(5):897-903.
183. Attal M, Huguet F, Rubie H, et al. Prevention of regimen-related toxicities after bone marrow transplantation by pentoxifylline: a prospective, randomized trial. *Blood.* 1993;82(3):732-736.
184. Clift RA, Bianco JA, Appelbaum FR, et al. A randomized controlled trial of pentoxifylline for the prevention of regimen-related toxicities in patients undergoing allogeneic marrow transplantation. *Blood.* 1993;82(7):2025-2030.
185. Tay J, Tinmouth A, Fergusson D, et al. Systematic review of controlled clinical trials on the use of ursodeoxycholic acid for the prevention of hepatic veno-occlusive disease in hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2007;13(2):206-217.
186. Ruutu T, Juvonen E, Remberger M, et al. Improved survival with ursodeoxycholic acid prophylaxis in allogeneic stem cell transplantation: long-term follow-up of a randomized study. *Biol Blood Marrow Transplant.* 2014;20(1):135-138.
187. Ruutu T, Eriksson B, Remes K, et al. Ursodeoxycholic acid for the prevention of hepatic complications in allogeneic stem cell transplantation. *Blood.* 2002;100(6):1977-1983.
188. Carreras E, Diaz-Ricart M. The role of the endothelium in the short-term complications of hematopoietic SCT. *Bone Marrow Transplant.* 2011;46(12):1495-1502.
189. Cooke KR, Jannin A, Ho V. The contribution of endothelial activation and injury to end-organ toxicity following allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2008;14(suppl 1):23-32.
190. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant.* 1995;15(6):825-828.
191. Harris AC, Young R, Devine S, et al. International, Multicenter Standardization of Acute Graft-versus-Host Disease Clinical Data Collection: A Report from the Mount Sinai Acute GVHD International Consortium. *Biol Blood Marrow Transplant.* 2016;22(1):4-10.
192. Lerner KG, Kao GF, Storb R, et al. Histopathology of graft-vs.-host reaction (GvHR) in human recipients of marrow from HL-A-matched sibling donors. *Transplant Proc.* 1974;6(4):367-371.
193. Weaver J, Bergfeld WF. Quantitative analysis of eosinophils in acute graft-versus-host disease compared with drug hypersensitivity reactions. *Am J Dermatopathol.* 2010;32(1):31-34.
194. Marra DE, McKee PH, Nghiem P. Tissue eosinophils and the perils of using skin biopsy specimens to distinguish between drug hypersensitivity and cutaneous graft-versus-host disease. *J Am Acad Dermatol.* 2004;51(4):543-546.
195. Kohler S, Hendrickson MR, Chao NJ, Smoller BR. Value of skin biopsies in assessing prognosis and progression of acute graft-versus-host disease. *Am J Surg Pathol.* 1997;21(9):988-996.
196. Elliott CJ, Sloane JP, Sanderson KV, et al. The histological diagnosis of cutaneous graft versus host disease: relationship of skin changes to marrow purging and other clinical variables. *Histopathology.* 1987;11(2):145-155.
197. Shulman HM, Cardona DM, Greenson JK, et al. NIH Consensus development project on criteria for clinical trials in chronic graft-versus-host disease: II. The 2014 Pathology Working Group Report. *Biol Blood Marrow Transplant.* 2015;21(4):589-603.
198. Washington K, Jagasia M. Pathology of graft-versus-host disease in the gastrointestinal tract. *Hum Pathol.* 2009;40(7):909-917.
199. Im JS, Abraham SC, Saliba RM, et al. Histologic grade 1 Is associated with increased nonrelapsed mortality in lower gastrointestinal graft versus host disease. *Am J Surg Pathol.* 2017;41(11):1483-1490.
200. Salomao M, Dorritie K, Mapara MY, Sepulveda A. Histopathology of graft-vs-host disease of gastrointestinal tract and liver: an update. *Am J Clin Pathol.* 2016;145(5):591-603.
201. Bacigalupo A, Milone G, Cupri A, et al. Steroid treatment of acute graft-versus-host disease grade I: a randomized trial. *Haematologica.* 2017;102(12):2125-2133.
202. Martin PJ, Rizzo JD, Wingard JR, et al. First- and second-line systemic treatment of acute graft-versus-host disease: recommendations of the American Society of Blood and

Marrow Transplantation. *Biol Blood Marrow Transplant.* 2012;18(8):1150-1163.
203. Ruutu T, Gratwohl A, de Witte T, et al. Prophylaxis and treatment of GVHD: EBMT-ELN working group recommendations for a standardized practice. *Bone Marrow Transplant.* 2014;49(2):168-173.
204. Mielcarek M, Furlong T, Storer BE, et al. Effectiveness and safety of lower dose prednisone for initial treatment of acute graft-versus-host disease: a randomized controlled trial. *Haematologica.* 2015;100(6):842-848.
205. Bolanos-Meade J, Logan BR, Alousi AM, et al. Phase 3 clinical trial of steroids/mycophenolate mofetil vs steroids/placebo as therapy for acute GVHD: BMT CTN 0802. *Blood.* 2014;124(22):3221-3227; quiz 3335.
206. Alousi AM, Weisdorf DJ, Logan BR, et al. Etanercept, mycophenolate, denileukin, or pentostatin plus corticosteroids for acute graft-versus-host disease: a randomized phase 2 trial from the Blood and Marrow Transplant Clinical Trials Network. *Blood.* 2009;114(3):511-517.
207. Lee SJ, Zahrieh D, Agura E, et al. Effect of up-front daclizumab when combined with steroids for the treatment of acute graft-versus-host disease: results of a randomized trial. *Blood.* 2004;104(5):1559-1564.
208. Cahn JY, Bordigoni P, Tiberghien P, et al. Treatment of acute graft-versus-host disease with methylprednisolone and cyclosporine with or without an anti-interleukin-2 receptor monoclonal antibody. A multicenter phase III study. *Transplantation.* 1995;60(9):939-942.
209. Couriel DR, Saliba R, de Lima M, et al. A phase III study of infliximab and corticosteroids for the initial treatment of acute graft-versus-host disease. *Biol Blood Marrow Transplant.* 2009;15(12):1555-1562.
210. Cragg L, Blazar BR, Defor T, et al. A randomized trial comparing prednisone with antithymocyte globulin/prednisone as an initial systemic therapy for moderately severe acute graft-versus-host disease. *Biol Blood Marrow Transplant.* 2000;6(4A):441-447.
211. Pidala J, Hamadani M, Dawson P, et al. Randomized multicenter trial of sirolimus vs prednisone as initial therapy for standard-risk acute GVHD: the BMT CTN 1501 trial. *Blood.* 2020;135(2):97-107.
212. MacMillan ML, Robin M, Harris AC, et al. A refined risk score for acute graft-versus-host disease that predicts response to initial therapy, survival, and transplant-related mortality. *Biol Blood Marrow Transplant.* 2015;21(4):761-767.
213. Hartwell MJ, Ozbek U, Holler E, et al. An early-biomarker algorithm predicts lethal graft-versus-host disease and survival. *JCI Insight.* 2017;2(3): e89798.
214. DeFilipp Z, Li S, Kempner ME, et al. Phase I trial of brentuximab vedotin for steroid-refractory chronic graft-versus-host disease after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant.* 2018;24(9):1836-1840.
215. Magenau JM, Goldstein SC, Peltier D, et al. alpha1-Antitrypsin infusion for treatment of steroid-resistant acute graft-versus-host disease. *Blood.* 2018;131(12):1372-1379.
216. Le Blanc K, Frassoni F, Ball L, et al. Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study. *Lancet.* 2008;371(9624):1579-1586.
217. Ringden O, Uzunel M, Rasmusson I, et al. Mesenchymal stem cells for treatment of therapy-resistant graft-versus-host disease. *Transplantation.* 2006;81(10):1390-1397.
218. Le Blanc K, Rasmusson I, Sundberg B, et al. Treatment of severe acute graft-versus-host disease with third party haploidentical mesenchymal stem cells. *Lancet.* 2004;363(9419):1439-1441.
219. Floisand Y, Lazarevic VL, Maertens J, et al. Safety and effectiveness of vedolizumab in patients with steroid-refractory gastrointestinal acute graft-versus-host disease: a retrospective record review. *Biol Blood Marrow Transplant.* 2019;25(4):720-727.
220. US Food and Drug Administration. FDA approves ruxolitinib for acutegraft-versus-hostdisease;2019.AccessedApril7,2021.https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ruxolitinib-acute-graft-versus-host-disease
221. Jagasia M, Perales M-A, Schroeder MA, et al. Results from REACH1, a single-arm phase 2 study of ruxolitinib in combination with corticosteroids for the treatment of steroid-refractory acute graft-vs-host disease. *Blood.* 2018;132(suppl 1):601.
222. Zeiser R, Blazar BR. Pathophysiology of chronic graft-versus-host disease and therapeutic targets. *N Engl J Med.* 2017;377(26):2565-2579.
223. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant.* 2015;21(3):389-401, e381.
224. Sarantopoulos S, Cardones AR, Sullivan KM. How I treat refractory chronic graft-versus-host disease. *Blood.* 2019;133(11):1191-1200.
225. Miklos D, Cutler CS, Arora M, et al. Ibrutinib for chronic graft-versus-host disease after failure of prior therapy. *Blood.* 2017;130(21):2243-2250.
226. Flowers ME, Martin PJ. How we treat chronic graft-versus-host disease. *Blood.* 2015;125(4):606-615.
227. Stewart BL, Storer B, Storek J, et al. Duration of immunosuppressive treatment for chronic graft-versus-host disease. *Blood.* 2004;104(12):3501-3506.
228. Lee SJ, Flowers ME. Recognizing and managing chronic graft-versus-host disease. *Hematology Am Soc Hematol Educ Program.* 2008:134-141.
229. Koc S, Leisenring W, Flowers ME, et al. Therapy for chronic graft-versus-host disease: a randomized trial comparing cyclosporine plus prednisone versus prednisone alone. *Blood.* 2002;100(1):48-51.
230. Burchert A, Bug G, Finke J, et al. Sorafenib as maintenance therapy post allogeneic stem cell transplantation for FLT3-ITD positive AML: Results from the randomized, double-blind, placebo-controlled multicentre Sormain Trial. *Blood.* 2018;132(suppl 1):631.
231. Brunner AM, Li S, Fathi AT, et al. Haematopoietic cell transplantation with and without sorafenib maintenance for patients with FLT3-ITD acute myeloid leukaemia in first complete remission. *Br J Haematol.* 2016;175(3):496-504.
232. Cortes JE, Khaled S, Martinelli G, et al. Quizartinib versus salvage chemotherapy in relapsed or refractory FLT3-ITD acute myeloid leukaemia (QuANTUM-R): a multicentre, randomised, controlled, open-label, phase 3 trial. *Lancet Oncol.* 2019;20(7):984-997.
233. Sandmaier BM, Khaled S, Oran B, et al. Results of a phase 1 study of quizartinib as maintenance therapy in subjects with acute myeloid leukemia in remission following allogeneic hematopoietic stem cell transplant. *Am J Hematol.* 2018;93(2):222-231.
234. Maziarz RTT, Patnaik MM, Scott BL, et al. Radius: a phase 2 randomized trial investigating standard of care ± midostaurin after allogeneic stem cell transplant in FLT3-ITD-mutated AML. *Blood.* 2018;132(suppl 1):662.
235. Oran B, Ciurea SO, Marin D, et al. Safety analysis of intrapatient dose-study of crenolanib maintenance therapy in patients with FLT3 mutant AML following allogeneic hematopoietic stem cell transplant. *Blood.* 2018;132(suppl 1):3426.
236. Levis MJ, Hamadani M, Logan B, et al. A phase 3, trial of gilteritinib, as maintenance therapy after allogeneic hematopoietic stem cell transplantation in patients with FLT3-ITD+ AML. *J Clin Oncol.* 2018;36(suppl 15).
237. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. *N Engl J Med.* 2019;381(18):1728-1740.

238. Chen H, Liu KY, Xu LP, et al. Administration of imatinib after allogeneic hematopoietic stem cell transplantation may improve disease-free survival for patients with Philadelphia chromosome-positive acute lymphobla stic leukemia. *J Hematol Oncol.* 2012;5:29.
239. Wassmann B, Pfeifer H, Stadler M, et al. Early molecular response to posttransplantation imatinib determines outcome in MRD+ Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL). *Blood.* 2005;106(2):458-463.
240. Anderlini P, Sheth S, Hicks K, et al. Re: imatinib mesylate administration in the first 100 days after stem cell transplantation. *Biol Blood Marrow Transplant.* 2004;10(12):883-884.
241. DeFilipp Z, Langston AA, Chen Z, et al. Does post-transplant maintenance therapy with tyrosine kinase inhibitors improve outcomes of patients with high-risk Philadelphia chromosome-positive leukemia? *Clin Lymphoma Myeloma Leuk.* 2016;16(8):466-471, e461.
242. de Lima M, Oran B, Champlin RE, et al. CC-486 maintenance after stem cell transplantation in patients with acute myeloid leukemia or myelodysplastic syndromes. *Biol Blood Marrow Transplant.* 2018;24(10):2017-2024.
243. Pusic I, Choi J, Fiala MA, et al. Maintenance therapy with decitabine after allogeneic stem cell transplantation for acute myelogenous leukemia and myelodysplastic syndrome. *Biol Blood Marrow Transplant.* 2015;21(10):1761-1769.
244. de Lima M, Giralt S, Thall PF, et al. Maintenance therapy with low-dose azacitidine after allogeneic hematopoietic stem cell transplantation for recurrent acute myelogenous leukemia or myelodysplastic syndrome: a dose and schedule finding study. *Cancer.* 2010;116(23):5420-5431.
245. Oran B, Lima MD, Garcia-Manero G, et al. Maintenance with 5-azacytidine for acute myeloid leukemia and myelodysplastic syndrome patients. *Blood.* 2018;132(suppl 1):971.
246. Kebriaei P, Banerjee PP, Ganesh C, et al. Blinatumomab is well tolerated maintenance therapy following allogeneic hematopoietic cell transplantation for acute lymphoblastic leukemia. *Blood.* 2019;134(suppl 1):1298.
247. Villalobos IB, Takahashi Y, Akatsuka Y, et al. Relapse of leukemia with loss of mismatched HLA resulting from uniparental disomy after haploidentical hematopoietic stem cell transplantation. *Blood.* 2010;115(15):3158-3161.
248. Vago L, Perna SK, Zanussi M, et al. Loss of mismatched HLA in leukemia after stem-cell transplantation. *N Engl J Med.* 2009;361(5):478-488.
249. Barrett AJ, Battiwalla M. Relapse after allogeneic stem cell transplantation. *Expert Rev Hematol.* 2010;3(4):429-441.
250. Bejanyan N, Weisdorf DJ, Logan BR, et al. Survival of patients with acute myeloid leukemia relapsing after allogeneic hematopoietic cell transplantation: a center for international blood and marrow transplant research study. *Biol Blood Marrow Transplant.* 2015;21(3):454-459.
251. Battiwalla M, Tichelli A, Majhail NS. Long-term survivorship after hematopoietic cell transplantation: roadmap for research and care. *Biol Blood Marrow Transplant.* 2017;23(2):184-192.
252. Majhail NS. Long-term complications after hematopoietic cell transplantation. *Hematol Oncol Stem Cell Ther.* 2017;10(4):220-227.
253. Bevans M, El-Jawahri A, Tierney DK, et al. National Institutes of Health Hematopoietic Cell Transplantation Late Effects Initiative: The Patient-Centered Outcomes Working Group Report. *Biol Blood Marrow Transplant.* 2017;23(4):538-551.
254. Mohty B, Mohty M. Long-term complications and side effects after allogeneic hematopoietic stem cell transplantation: an update. *Blood Cancer J* 2011;1(4):e16.
255. Kolb HJ, Socie G, Duell T, et al. Malignant neoplasms in long-term survivors of bone marrow transplantation. Late Effects Working Party of the European Cooperative Group for Blood and Marrow Transplantation and the European Late Effect Project Group. *Ann Intern Med.* 1999;131(10):738-744.

This page intentionally left blank

20 Alternative Donor Transplants: Cord Blood Transplant

Hind Rafei
Amanda Olson
Rohtesh S. Mehta
Betul Oran
Katayoun Rezvani
Elizabeth J. Shpall

KEY CONCEPTS

- Cord blood is a valuable alternative donor source for stem cell transplant, offering a number of advantages: ease of collection, availability for urgent need, less stringent human leukocyte antigen (HLA)-matching requirement, and lower risk of graft-versus-host disease.
- Data are evolving about the difference in outcomes of stem cell transplant using different graft sources, but more recent data suggest that there is no survival advantage of a matched unrelated graft over cord blood.
- To overcome the limitation of low cell doses in single cord blood units, double cord blood transplant has been adopted for many patients.
- High-intensity myeloablative regimens are used in young and fit patients, whereas reduced-intensity regimens are used in older or unfit patients.
- Infections are the leading cause of early nonrelapse mortality after cord blood transplant, and graft-versus-host disease is the leading cause of late mortality.
- Novel strategies to improve cord blood transplant outcomes include improving cell collection, homing and engraftment, ex vivo expansion, and in vivo enhancement.

BACKGROUND

The number of allogeneic stem cell transplants (SCTs) performed in the United States has steadily increased, from more than 8000 per year in 2013 to 8839 in 2017 and an estimated 9028 transplants in 2018.[1] Donor identification has always been a challenge, and only 25% to 30% of patients who need allogeneic SCT have a matched-sibling donor available.[2] The National Marrow Donor Program (NMDP) and its cooperative international registries have more than 19 million volunteer donors, but the majority of them are White; other ethnicities are underrepresented in these large registries, which poses a significant challenge in finding donors for them.[3] Mismatched related (often haploidentical), cord blood (CB), or mismatched unrelated donors (MMUD) with either peripheral blood (PB) or bone marrow (BM) graft sources are potential options for patients in need of SCT but who lack a matched related (MRD) or unrelated donor (MUD).

Cord blood is a valuable alternative donor source for allogeneic SCT, offering many logistic advantages; CB units are easy to collect with little or no risk to the mother or newborn. CB units can be obtained rapidly for 80% to 95% of the patients 20 years or older across all races, and in almost 100% of younger patients.[4] This is particularly advantageous in cases where urgent transplant is needed. Owing to the rapid procurement of CB units, patients can receive CB transplantation (CBT) in 2 to 4 weeks from the initiation of search compared with 3 to 6 months for unrelated donor sources.[5] Further, CBT is associated with a low risk of infection transmission, requires less stringent human leukocyte antigen (HLA) matching criteria, and has a relatively lower risk of graft-versus-host disease (GVHD) with preserved graft-versus-malignancy effects.[6,7] However, it has been historically associated with a greater risk of graft rejection, delayed engraftment, and delayed immune reconstitution, leading to a heightened risk of infection or nonrelapse mortality (NRM).[8–11] Many

of the adverse outcomes noted after CBT are attributed to the naïvety of CB T lymphocytes, and the low numbers of total nucleated cells (TNCs) and CD34+ cells in the graft.

It is important to note, however, that the evolution of transplantation techniques and the optimization of practices of unrelated donor transplants including CBT in the past 2 decades have led to the improvement of outcomes and survival of CBT, as was shown in a recent large study from the European Society for Blood and Marrow Transplantation registry that included 106,188 patients between 2001 and 2015, among them more 3000 CBT recipients, demonstrating an improvement in the 3-year overall survival (OS) from 36% between the years 2006 and 2010 to 44% between the years 2010 and 2015, which owes primarily to a decrease in the incidence of relapse.[12] Comparison of outcomes between CBT, MUD, and MMUD was undertaken by a large, retrospective single-institution study in patients with acute leukemia or myelodysplastic syndrome (MDS) who received a first myeloablative SCT and showed that among patients with pretransplantation minimal residual disease, the probability of OS after receipt of a CBT was at least as favorable as that after receipt of a transplant from a MUD and was significantly higher than that after MMUD. Furthermore, the probability of relapse was lower in the CBT group than in either of the other groups.[13]

A recent prospective study also investigated the outcomes of MUD (91 transplants) and CBT (119 transplants) in adults with acute leukemia and MDS and demonstrated in multivariate analysis that the graft source was not a significant risk factor for OS, cumulative incidences of NRM and relapse, and disease-free survival (DFS). In adjusted analyses, MUD and CBT were shown to lead to similar OS, NRM, and relapse, again proving the importance of CB as an alternative source of transplant.[14] Moreover, the kinetics of immune reconstitution post-CBT might actually yield better outcomes after CBT. In a retrospective analysis of immune reconstitution kinetics after SCT from BM, PB, or CB, mature B cells and differentiated natural killer (NK) cells significantly increased after CBT.[15] A multivariate analysis showed that a higher CD16+ CD57– NK cell count correlates with a lower incidence of relapse, whereas higher CD20+ B-cell and CD8+ CD11b– T-cell counts are associated with lower NRM. This suggests that the collective contribution of graft source–specific and event-related immune reconstitution might yield better outcomes after CBT.[15] Similar results were observed in another recent study of immune recovery in 106 adults undergoing CBT, demonstrating a robust thymus-independent CD4+ T-cell recovery, which in turn is associated with reduced risk of mortality (**Table 20–1**).[16]

CELL DOSE, UNIT QUALITY, AND HLA MATCHING

The outcomes of CBT depend on the impact of cell dose and the degree of HLA match.[17] The TNC dose is a well-established parameter associated with successful engraftment and survival after CBT. However, the adequate TNC dose of a CB unit remains controversial. The randomized phase 3 trial BMT CTN 0501 defined a sufficient cryopreserved TNC dose in a single unit as $>2.5 \times 10^7$/kg.[18] On the other hand, in a large registry study of more than 1500 myeloablative single-unit CBTs, a TNC $<3.0 \times 10^7$/kg was found to be associated with an increased transplant-related mortality (TRM).[19] Moreover, an analysis of more than 1000 recipients of CBT from a single bank, the National Cord Blood Program of the New York Blood Center, suggested that a higher TNC dose is required to offset the effect of increasing HLA mismatch.[17] It is important to note that the CD34+ cell dose is a critical factor to be considered in unit selection along with the TNC dose. Purtill et al demonstrated the essential role that the dominant unit–infused viable CD34+ cell dose plays in determining the speed and success of neutrophil engraftment after double CBT (dCBT).[20] A dominant unit–infused viable CD34+ cell dose $<0.5 \times 10^5$/kg was associated with marked impairment of neutrophil engraftment.[20]

Moreover, the post-thaw CD34+ viability, which defines the unit quality, is another important consideration.[6] A number of studies have shown the importance of post-thaw colony-forming unit dose for successful engraftment.[21,22] CB units with a low proportion of post thaw–viable CD34+ cells have been associated with very poor engraftment potential.[23]

The HLA-matching criteria between the CB units and the recipient have traditionally been less stringent compared with other donor sources. Therefore, although unrelated adult donors are selected to be closely matched to recipients at HLA-A, -B, -C, and -DRB1 by high-resolution testing,[24,25] CB units are selected using lower-resolution HLA typing (antigen-level) for HLA-A and -B and at the allele level for HLA-DRB1.[26] In a study of single CBT, Barker et al showed that recipients of 6/6 matched CB units had the lowest TRM regardless of the dose, followed by 5/6 matched CB units with TNC dose $>2.5 \times 10^7$/kg or 4/6 matched units with TNC dose $>5.0 \times 10^7$/kg, and 5/6 matched units with lower TNC dose ($<2.5 \times 10^7$/kg).[17,27] These findings support the notion that both TNC dose and HLA-matching level should be taken into account for CB unit selection.

Although the standard HLA-matching criteria do not require high-resolution typing at class I antigen in CBT, a study by the Center for International Blood and

Table 20–1 Results of Comparative Studies of Cord Blood Transplant and Other Donor Types in Adults With Hematologic Malignancies

Reference	Donor type	Patients (n)	Engraftment			GVHD		Infection (%)	Relapse (%)	TRM (%)	Survival
			ANC (day)	PLT (day)	Cumulative neutrophil recovery (%)	Acute 2–4 (%)	Chronic (%)				
Eapen et al[8]	UCB	165	24	52	80[a]	30	24	27[b]	26	33	2-year DFS: 59%
	PBPCs	888	14	19	96[a]	49	46	17[b]	31	27	2-year DFS: 48%
	BM	472	19	28	93[a]	41	39	22[b]	33	17	2-year DFS: 57%
Jacobson et al[9]	dUCB	42	21.5	41.5	NS	21	24	69	40[d]	NS	2-year PFS: 49% 2-year OS: 66%
	MUD	102	N/A[c]	N/A[c]	NS	12	54	33	32[d]	NS	2-year PFS: 57% 2-year OS: 68%
Mahjail et al[10]	UCB	43	NS	NS	89[e]	49	17[e]	19[h]	NS	28[g]	3-year PFS: 34% 3-year OS: 34%
	MRD	47	NS	NS	100[e]	42	40[f]	13[h]	NS	23[g]	3-year PFS: 30% 3-year OS: 43%
Brunstein et al[11]	dUCB	128	26	53	~85[i]	60	26[j]	~30[h]	15[k]	NS	5-year DFS: 51%
	MRD	204	16	20	~100[i]	65	47[j]	~10[h]	43[k]	NS	5-year DFS: 33%
	MUD	152	19	21	~100[i]	80	43[j]	~7.5[h]	37[k]	NS	5-year DFS: 48%
	MMUD	52	18.5	21	~100[i]	85	48[j]	~7.5[h]	35[k]	NS	5-year DFS: 38%
Shouval et al[12(l)]	MRD	16,362	NS	NS	NS	22	14	25[h]	37[m]	NS	3-year PFS: 45% 3-year OS: 55%
	MUD	15,556	NS	NS	NS	28	12	27[h]	31[m]	NS	3-year PFS: 44% 3-year OS: 52%
	MMUD	4,089	NS	NS	NS	29	11	30[h]	32[m]	NS	3-year PFS: 34% 3-year OS: 41%
	Haplo	3,009	NS	NS	NS	25	7	34[h]	33[m]	NS	3-year PFS: 40% 3-year OS: 44%
	UCB	1,327	NS	NS	NS	34	8	31[h]	29[m]	NS	3-year PFS: 38% 3-year OS: 44%
Milano et al[13]	UCB	140	NS	NS	NS	18[n]	NS	NS	15[o]	NS	4-year unadjusted rate of survival: 71%
	MUD	344	NS	NS	NS	14[n]	NS	NS	24[o]	NS	4-year unadjusted rate of survival: 63%
	MMUD	98	NS	NS	NS	26[n]	NS	NS	25[o]	NS	4-year unadjusted rate of survival: 49%

(*Continued*)

Table 20–1 Results of Comparative Studies of Cord Blood Transplant and Other Donor Types in Adults With Hematologic Malignancies (*Cont.*)

Reference	Donor type	Patients (n)	Engraftment			GVHD		Infection (%)	Relapse (%)	TRM (%)	Survival
			ANC (day)	PLT (day)	Cumulative neutrophil recovery (%)	Acute 2–4 (%)	Chronic (%)				
Terakura et al[14]	UCB	119	21	38	89	NS	NS	NS	31[p]	NS	Median OS: 66 mo 2-year OS: 62% 2-year DFS: 58%
	UDT	91	15	26	95	NS	NS	NS	25[p]	NS	Median OS: 62 mo 2-year OS: 61% 2-year DFS: 56%
Ando et al[15]	UCB	136	NS	NS	NS	40	28	34[q]	27[p]	NS	2-year OS: 76%
	PBSC	55	NS	NS	NS	45	45	15[q]	40[p]	NS	2-year OS: 67%
	BM	119	NS	NS	NS	54	43	31[q]	33[p]	NS	2-year OS: 62%
Marks et al[47]	UCB	116	NS	NS	57[r]/91[s]	27	39	NS	22[m]	42[t]	3-year OS: 44%
	7/8-HLA matched	140	NS	NS	96[r]/97[s]	41	45	NS	28[m]	39[t]	3-year OS: 43%
	8/8-HLA matched	546	NS	NS	95[r]/97[s]	47	42	NS	25[m]	31[t]	3-year OS: 44%
Rodrigues et al[52]	UCB	104	18	35	81[s]	29	26[u]	NS	28[m]	NS	3-year PFS: 41% 3-year OS: 56%
	MUD	541	14	14	97[s]	32	52[u]	NS	35[m]	NS	3-year PFS: 36% 3-year OS: 49%

[a]Day 42 neutrophil recovery rate.
[b]Infection as early cause of death.
[c]Patients did not experience count nadir.
[d]Two-year relapse rate.
[e]Sustained donor engraftment at 42 days.
[f]Chronic GVHD at 1 year.
[g]180-day TRM.
[h]Infection as primary cause of death.
[i]Day 45 cumulative incidence of neutrophil engraftment.
[j]Chronic GVHD at 2 years.
[k]Relapse at 5 years.
[l]Data taken for Epoch 3 (2011–2015) only.
[m]3-year relapse incidence.
[n]Incidence of severe acute GVHD (grade 3–4).
[o]4-year unadjusted risk of relapse.
[p]2-year cumulative incidence of relapse.
[q]Incidence of infection in the first 100 days post-transplant.
[r]Day 28 cumulative incidence of neutrophil recovery.
[s]Day 60 cumulative incidence of neutrophil recovery.
[t]3-year cumulative incidence of TRM.
[u]Chronic GVHD at 3 years.
ANC, absolute neutrophil count >500; BM, bone marrow; DFS, disease-free survival; dUBC, double umbilical cord blood; GVHD, graft-versus-host disease; Haplo, haploidentical; MMUD, mismatched unrelated donor; MRD, matched related donor; MUD, matched unrelated donor; NS, not stated; OS, overall survival; PBPCs, peripheral blood progenitor cells; PBSCs, peripheral blood stem cells; PFS, progression-free survival; PLT, platelets >20,000; TRM, transplant-related mortality; UCB, umbilical cord blood; UDT, unrelated donor transplant.

Marrow Transplantation Research (CIBMTR) and the Eurocord reported better outcomes in single CBT after myeloablative conditioning (MAC) with improved allele-level matching for 4 HLA loci (-A, -B, -C, and -DRB1).[19] The investigators showed that the frequency of neutrophil recovery was lower for recipients of mismatches at 3–5 but not at 1–2 alleles compared with those of HLA-matched units. NRM was higher with units mismatched at 1–5 alleles compared with matched units. This retrospective study confirmed the clinical importance of selecting better HLA allele–matched units for single CBT, an observation already well described for BM and PB progenitor cell transplantation. Data from our institution have also demonstrated increased TRM with increasing HLA mismatch.[28] In contrast, other studies from the University of Minnesota,[29] Memorial Sloan Kettering Cancer Center,[30] and others[18,31] reported that a high degree of HLA mismatch did not adversely affect transplant outcomes. Further studies to establish the relative contribution of the TNC dose, the CD34+ dose, and the HLA match to the success of engraftment and survival post-CBT are warranted.

SINGLE VERSUS DOUBLE CBT

The relatively low number of progenitor cells in a single CB unit resulting in delayed hematopoietic recovery and engraftment failure limited the use of CBT in adults. Most adults do not have access to a single CB unit containing the recommended nucleated cell dose of 2.5×10^7 TNCs/kg.[32] To overcome the cell-dose limitation, investigators pioneered an approach where two partially HLA-matched CB units are used to augment the progenitor cell dose in circumstances in which a single unit was considered inadequate, and confirmed its feasibility.[32] A CIBMTR analysis investigated the relative risks and benefits of transplanting double CB units compared with an adequately dosed single CB unit. The investigators observed no differences in clinical outcomes after dCBT or adequately dosed single CBT. Both transplant approaches led to comparable outcomes with 78% (95% CI, 72–83) versus 81% (95% CI, 74–88; $P = .83$) probabilities of neutrophil engraftment by day 42, and 68% (95% CI, 62–74) versus 63% (95% CI, 53–72; $P = .34$) probabilities of platelet recovery at 6 months, respectively. There were no differences in grade III–IV acute GVHD ([18% (95% CI, 11%–26%) versus 14% (95% CI, 10–19%); $P = .64$]), 2-year probabilities of chronic GVHD (31% [95% CI, 26–37] versus 24% [95% CI, 15–34]; $P = .27$), TRM (hazard ratio [HR], 0.91; $P = .63$), risk of relapse (HR, 0.90; $P = .64$), and overall mortality (HR, 0.93; $P = .62$).[33] This and other studies[34] demonstrated the role of dCBT in extending the application of CBT to adults with inadequate single units. In addition, some other studies have suggested that dCBT may be associated with a reduced risk of relapse,[35–38] with one analysis proving that dCBT is more cost effective than single CBT.[39]

A unique feature after dCBT is evidence of mixed chimerism from both CB units observed during the initial post-transplant period.[40] In the early post-dCBT period (day +21), both CB units contribute to hematopoiesis in 40% to 50% of patients, but by day +100, one unit predominates in a vast majority.[41,42] Although the nonengrafting unit does not contribute to hematopoiesis, it may have a facilitatory effect on engraftment. In fact, an analysis of 129 dCBT recipients has shown that in patients receiving a low-dose dominant unit (defined as an infused viable CD34+ cell dose $<1.2 \times 10^5$/kg), a higher TNC dose in the nondominant unit is associated with improved neutrophil recovery.[43] The factors leading to unit dominance are not well-defined. It is however recognized that there is no association with the TNC or CD34+ cell doses, HLA match, gender match, ABO typing, or the order in which CB units are infused.[32,41,42,44,45] Moreover, there are no sufficient data to support interunit HLA matching when selecting double-unit grafts.[46] This current lack of evidence is a major limitation to dCBT, and identifying predictive factors for unit dominance would optimize CB-unit selection algorithms by allowing for the selection of two CB units with a high probability of long-term engraftment.

CONDITIONING REGIMENS

Myeloablative Conditioning Regimens

High-intensity MAC regimens are reserved for young and otherwise fit patients who can tolerate the associated regimen morbidity. Such regimens are associated with a low risk of relapse at the expense of a high TRM compared with reduced-intensity conditioning (RIC) regimens. One of the largest registry studies comparing single-unit CB (n = 165) with PB (n = 888) or BM (n = 472) transplants in adults with acute leukemia using MAC regimens from 2002 through 2006 showed promising outcomes with CBT. Total body irradiation (TBI) constituted part of the preparative regimen in about half of patients in the CB group and about two-thirds in the comparative groups. Despite a significantly higher number of patients with fully HLA-matched PB or BM grafts (70%) compared with CB grafts (6%), the rates of DFS and relapse were similar among the groups, whereas the risks of acute or chronic GVHD were significantly lower with CBT.

Also, TRM was similar with CBT compared with mismatched PB or BM grafts, but higher in contrast to fully matched PB (HR, 1.62 [95% CI, 1.18–2.23]; P = .0030) or BM transplants (HR, 1.69 [95% CI, 1.19–2.39]; P = .003). This was offset by a significantly lower incidence of chronic GVHD compared with fully matched PB (HR, 0.38 [95% CI, 0.27–0.53]; P = .001) or BM transplants (HR, 0.63 [95% CI, 0.44–0.90]; P = .01].[8] Therefore, in the absence of matched PB or BM donors, CBT potentially offers better outcomes compared with mismatched alternative donor transplants.

Similar encouraging results were noted in a study that compared 4–6/6 matched dCBT exclusively (using the MAC regimen including fludarabine 75 mg/m^2, cyclophosphamide 120 mg/kg, and TBI 1200–1320 cGy Flu/Cy/TBI) to 8/8 MRD or MUD, or 1 allele–MMUD donors.[11] This study also noted lower risk of relapse, higher NRM, lower GVHD, and comparable DFS after CBT compared with other groups. The risk of relapse was significantly lower after dCBT (15%, 95% CI, 9–22%) compared with MRD (43%, 95% CI, 35%–52%) or MUD (37%, 95% CI, 29%–46%) transplants. Higher NRM was noted after dCBT (34%, 95% CI, 25%–42%) compared with MRD (24%, 95% CI, 17%–39%) or MUD (14%, 95% CI, 9%–20%) transplants, which resulted in comparable 5-year DFS between CB (51%, 95% CI, 41%–59%), MRD (33%, 95% CI, 26%–41%), and MUD (48%, 95% CI, 40%–56%) transplants. The cumulative incidence of grade II–IV GVHD at day 100 after dCBT, MRD, and MUD was 60% (95% CI, 50%–70%), 65% (95% CI, 57%–73%), and 80% (95% CI, 70%–90%). The rate of chronic GVHD at 2 years was 26% (95% CI, 15%–35%), 47% (95% CI, 39%–55%), and 43% (95% CI, 34%–52%), respectively.[11]

In adults with high-risk acute lymphoblastic leukemia (ALL), CBT leads to similar OS, TRM, and relapse risk, with significantly lower risk of acute or chronic GVHD, compared with PB or BM transplants. This was demonstrated in a registry study that compared outcomes after single or double 4–6/6 matched CB (n = 116) and 7–8/8 matched PB (n = 546) or BM (n = 140) transplants after MAC regimens.[47] More than half of the patients in the CBT group received Flu/Cy/TBI as the conditioning regimen, and about 75% of the patients in the PB or BM groups received TBI/Cy-based regimens. There were no differences in the 3-year OS rates (44%, 44%, and 43%), relapse risk (22%, 25%, and 28%), or TRM (42%, 31%, and 39%) among the groups. However, the risk of acute grade II–IV GVHD (27%, 47%, and 41%) or grade III–IV acute GVHD (9%, 16%, 24%) was appreciably lower after CBT compared with 8/8-matched and 7/8-matched PB or BM transplants, respectively.[47]

The major concern with MAC regimens remains their associated toxicity, which was shown in more recent studies. A prospective multicenter study of high-dose myeloablative dCBT in adults with high-risk acute leukemia and MDS between 2007 and 2011 demonstrated 89% neutrophil engraftment at day 100, grade II–IV acute GVHD incidence at day 180 of 64%, and a 3-year incidence of chronic GVHD of 36%. At 3 years post-transplant, the TRM was 39% (95% CI, 26%–52%), and the 3-year relapse incidence was 11% (95% CI, 4%–21%). With a median follow-up of 37 months, the 3-year DFS was 50% (95% CI, 37%–63%). This study again shows the importance of CBT as an alternative therapy for high-risk acute leukemia/MDS in patients lacking a MUD with a low incidence of relapse. Yet the TRM risk remains high and strategies to ameliorate toxicities are warranted.[48]

Reduced-Intensity Conditioning Regimens

The advent of RIC regimens extended the utility of CBT to older patients and those with comorbid conditions that otherwise restrict the use of the MAC regimens. A majority of trials of MRD or MUD transplants used an arbitrary age definition of older than 55 to 60 years (to define "older patients") as a threshold of using a RIC regimen. However, age more than 40 to 45 years is generally chosen as a threshold for RIC in the CBT setting.

Barker et al reported that the RIC with fludarabine 200 mg/m^2, cyclophosphamide 50 mg/kg, and 2 Gy TBI (Flu/Cy/2 Gy TBI) was well tolerated, with rapid neutrophil recovery, a sustained donor engraftment rate of 94%, and a low incidence of TRM.[49] This regimen is associated with significantly better DFS compared with other RIC regimens (51% vs 28%, HR, 0.53; P = .0002).[50] Multiple studies supporting the use of RIC CBT in patients who would not be able to tolerate more intensive preparative regimens have subsequently been reported.[10,41,42,51–53]

A retrospective single-center study compared the outcomes in patients older than 55 years who underwent CB and MRD SCT with RIC (primarily of Flu/Cy/2 Gy TBI). There were no differences in TRM at 180 days (28%, 95% CI, 14%–41% vs 23%, 95% CI, 11%–36%), 3-year DFS (34%, 95% CI, 19%–48% vs 30%, 95% CI, 16%–44%), or 3-year OS (34%, 95% CI, 17%–50% vs 43%, 95% CI, 29%–58%) between the groups.[10] These findings were confirmed by a registry analysis of patients with acute leukemia comparing the outcomes after CB (n = 161), 8/8-matched (n = 313), and 7/8-matched PB (n = 111) transplant with

RIC regimens. Patients who underwent CBT after the Flu/Cy/2 Gy TBI regimen had comparable results with 8/8 HLA-matched PB donors. However, higher TRM and lower OS and DFS were observed in recipients of CBT if they were treated with alternative RIC regimens including busulfan plus melphalan, or cyclophosphamide with fludarabine and in vivo T-cell depletion with antithymocyte globulin (ATG).[53] Similar findings were reported by Eurocord and the EMBT in patients with lymphoid malignancies. When patients with CB units (n = 104) were compared with 8/8-matched PB MUD (n = 541) transplants, no difference was noted in NRM (29% vs 28%), PFS (41% vs 36%), or OS (56% vs 49%) at 3 years. Further, the risk of chronic GVHD was significantly lower in the CBT group (26% vs 52% at 3 years; $P = .0005$).[52]

More recently, intensification of the standard RIC regimen was investigated in a retrospective analysis of adult recipients of first dCBT comparing standard RIC regimen with an intensified regimen of fludarabine 150 mg/m^2, cyclophosphamide 50 mg/kg, thiotepa 10 mg/kg, and 400 cGy TBI (intensified RIC). The cumulative incidence of relapse was significantly lower with intensified RIC compared with standard RIC ($P = .0013$). TRM was comparable between the two groups ($P = .99$), whereas OS was significantly better after intensified RIC compared with standard RIC ($P = .03$); median OS was 17 months after standard RIC but was not reached after intensified RIC. Grade II–IV acute GVHD was significantly higher in the intensified RIC cohort compared with the standard RIC cohort ($P = .007$), whereas the incidence of grade III–IV acute GVHD, any chronic GVHD, and moderate-to-severe chronic GVHD was comparable between the two cohorts ($P = .20$, $P = .21$, and $P = .61$, respectively).[54] These studies support the use of CBT with RIC as a suitable alternative for patients who may benefit from RIC SCT and who do not have a suitable related or unrelated volunteer donor in the period in which transplantation is needed, with the possibility of intensifying the RIC regimen when appropriate in higher-risk patients (Table 20–2).

POST-TRANSPLANT COMPLICATIONS

Disease relapse is the most common cause of mortality after allogeneic SCT, whereas GVHD and infections are the two leading causes of NRM. Treatment options post-SCT relapse include withdrawal of immunosuppression, chemotherapy, or donor lymphocyte infusion (DLI). Although DLI is currently unavailable for CBT patients outside clinical trials, a study showed that in adults who have AML relapse after CB or MRD transplants, DLI in the latter group did not affect OS (19% CB vs 28% MRD at 1 year; $P = .36$), and patients with disease relapse had a poor prognosis independent of the donor source.[55]

In the CBT setting, infections are the leading cause of early 100-day NRM (27%), whereas GVHD contributes to most (20%) of the delayed NRM (beyond 100 days).[8] The reported probabilities of acute grade III–IV GVHD at day 100 (10%–40%), and chronic GVHD (25%–35%), TRM (20%–50%), risk of relapse (10%–50%), DFS (15%–60%), and OS (20%–70%) at 2 to 5 years vary, depending on conditioning regimens, study population, HLA matching, and other factors.[11–14,33,42,47,48,50,53,54] The rates of post-transplant complications are comparable after the use of dCBT and single CBT.[56]

Early infections (within 100 days) are primarily caused by neutropenia and mucosal damage caused by conditioning regimens. Delayed infections are related to the speed of cell-mediated immune reconstitution and use of immunosuppressants. Most early infections are bacterial; more than half of the invasive fungal infections and 45% of cytomegalovirus (CMV) occur beyond day +100.[57]

The heightened risk of infections in CBT is partly explained by the naïvety of CB T-cells, and delayed T-lymphocyte immune reconstitution and neutrophil engraftment in contrast to other donor sources.[8,11,53,58,59] Although significant B-cell recovery starts within 3 to 4 months and may approach normal numbers by 6 months after transplant, T-cell reconstitution is substantially prolonged.[59] The CD4+ and CD8+ T-cell counts are strikingly reduced after CBT, remain low for up to 6 months, and approach normal values by one year. The PB T-cells after CBT are more dysfunctional as compared with other types of allogeneic SCTs. Patients also do not recover thymic function after CBT in contrast to other allogeneic SCT recipients.[60]

A retrospective registry analysis from the CIBMTR comparing CB (n = 150) with matched (n = 367) or antigen-mismatched (n = 83) BM transplants reported higher risk of early (within 100 days) infection-related deaths after CBT compared with other groups (45%, 21%, and 24%, respectively; $P = .01$).[56] In another study, the risk of severe infection, especially bacterial infections in the first 100 days, was significantly higher after CBT in contrast to BM or PB graft (85% vs 69%; $P < .01$). The risk of infection-related mortality did not differ at day 100 or at 3 years. In a multivariate analysis of a CMV-seropositive recipient who received CBT, prolonged neutropenia beyond day 30 and low cell dose ($<2 \times 10^7$/kg) were the predictors for infection-related mortality.[57]

Table 20–2 Outcomes of Cord Blood Transplant After Myeloablative Conditioning and Reduced-Intensity Conditioning in Adult Patients With Hematologic Malignancies

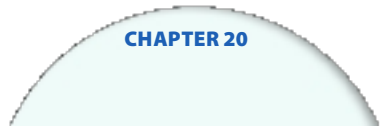
Reference	Conditioning regimen	Patients (n)	Engraftment			GVHD		Infection (%)	Relapse (%)	TRM (%)	Survival
			ANC (day)	PLT (day)	Cumulative neutrophil recovery (%)	Acute 2-4 (%)	Chronic (%)				
Eapen et al[8]	MAC	165	24	52	80[a]	30	24	27[b]	26	33	2-year DFS: 59%
Mahjail et al[10]	RIC	43	NS	NS	89[j]	49	17[k]	19[c]	NS	28[t]	3-year PFS: 34% 3-year OS: 34%
Brunstein et al[11]	MAC	128	26	53	~85[d]	60	26[e]	~30[c]	15[f]	NS	5-year DFS: 51%
Ballen et al[41]	RIC	21	20	41	NS	40	31	NS	NS	14[n]	1-year DFS: 67% 1-year OS: 71% 2-year DFS: 55% 2-year OS: 71%
Brunstein et al[42]	RIC	110	12	49	92	59	23[o]	27[c]	31[l]	26[i]	3-year EFS: 38% 3-year OS: 45%
Marks et al[47]	MAC	116	NS	NS	57[g]/91[h]	27	39	NS	22[l]	42[i]	3-year OS: 44%
Barker et al[48]	MAC	56	22	49	89[j]	64	36[k]	5[c]	11[l]	39[i]	1-year OS: 57% 3-year OS: 52% 1-year DFS: 55% 3-year DFS: 50%
Barker et al[49]	RIC Bu/Flu/TBI	18	26	NS	76[m]	44% for the entire group	21% for the entire group at 1 year	NS	NS	48[n]	100-day DFS: 38% 1-year DFS: 24%
	RIC Cy/Flu/TBI	21	9.5	NS	94[m]			NS	NS	28[n]	100-day DFS: 68% 1-year DFS: 41%
Miyakoshi et al[51]	RIC	30	17.5	39	87	27	23	40	NS	27[n]	1-year OS: 33% 1-year EFS: 22%
Rodrigues et al[52]	RIC	104	18	35	81[h]	29	26[p]	NS	28[l]	NS	3-year PFS: 41% 3-year OS: 56%

(*Continued*)

Table 20–2 Outcomes of Cord Blood Transplant After Myeloablative Conditioning and Reduced-Intensity Conditioning in Adult Patients With Hematologic Malignancies *(Cont.)*

Reference	Conditioning regimen	Patients (n)	Engraftment			GVHD		Infection (%)	Relapse (%)	TRM (%)	Survival
			ANC (day)	PLT (day)	Cumulative neutrophil recovery (%)	Acute 2-4 (%)	Chronic (%)				
Brunstein et al[53]	RIC Cy/Flu/TBI	121	9	NS	93[a]	50	34[e]	16[c]	49[q]	19[p]	2-year DFS: 31% 2-year OS: 37%
	RIC other	40	20	NS	90[a]	33	36[e]	29[c]	35[q]	52[p]	2-year DFS: 15% 2-year OS: 19%
Sharma et al[54]	Intensified RIC	47	21	38	~90[a]	55	22[o]	85 infections	8[r]	22[s]	Median OS: not reached
	Standard RIC	52	13	37	~90[a]	29	13[o]	60 infections	36[r]	18[s]	Median OS: 17 mo

[a]Day 42 neutrophil recovery rate.
[b]Infection as early cause of death.
[c]Infection as primary cause of death.
[d]Day 45 cumulative incidence of neutrophil engraftment.
[e]Chronic GVHD at 2 years.
[f]Relapse at 5 years.
[g]Day 28 cumulative incidence of neutrophil recovery.
[h]Day 60 cumulative incidence of neutrophil recovery.
[i]3-year cumulative incidence of TRM.
[j]Sustained donor neutrophil engraftment at 100 days.
[k]Chronic GVHD at 3 years.
[l]3-year relapse incidence.
[m]Sustained donor neutrophil engraftment at 42 days.
[n]TRM at day 100.
[o]Chronic GVHD at 1 year.
[p]2-year cumulative incidence of TRM.
[q]2-year relapse rate,
[r]1-year relapse rate.
[s]1-year cumulative incidence of TRM.
[t]180-day TRM
ANC, absolute neutrophil count >500; Bu, busulfan; Cy, cyclophosphamide; DFS, disease-free survival; EFS, event-free survival; Flu, fludarabine; GVHD, graft-versus-host disease; NS, not stated; OS, overall survival; PFS, progression-free survival; PLT, platelets >20,000; TBI, total body irradiation; TRM, transplant-related mortality.



MD ANDERSON APPROACH TO CBT

At MDACC, patients with various hematologic malignancies who do not have a MRD or MUD but require SCT are considered for CBT, and a search for a CB unit is initiated (Fig. 20–1).

Unit Selection

Within the first days to weeks of the initial donor search, coordinators determine the likelihood of obtaining a suitably matched donor based on the patient's ancestry, the preliminary search results, and review of the HLA typing. If the likelihood of finding a matched donor is deemed to be low, we proceed with confirmatory HLA typing of CB units. Alternatively, we may delay typing of CB units if multiple 10/10 HLA-A, -B, -C, -DRB1, or -DQ allele–MUD are probable, or if the transplantation is not urgent. If an unrelated donor collection is delayed because of problems with donor health or availability, a prompt decision is made about whether to abandon the unrelated donor search in favor of CB.

To maximize the chance of identifying optimal CB unit(s), we conduct a global search while being aware that there is no global regulatory oversight of CB banking standards. It is important to know which banks are included in the NMDP consortium of banks, in the Netcord, and in the NMDP Cooperative Registries. We give equal consideration to domestic and international units as the primary units of the graft, whereas we prefer domestic units for backup.

Our current institutional policy is to use a double-unit graft in an effort to augment engraftment and reduce TRM. Given that either unit may engraft after a dCBT, each unit of a double-unit graft is equally important. We give a strong priority to HLA match over a pre-cryopreservation TNC threshold of ~2.0 × 10^7/kg for each unit of a double-unit graft. This approach gives strong priority to HLA match but augments the

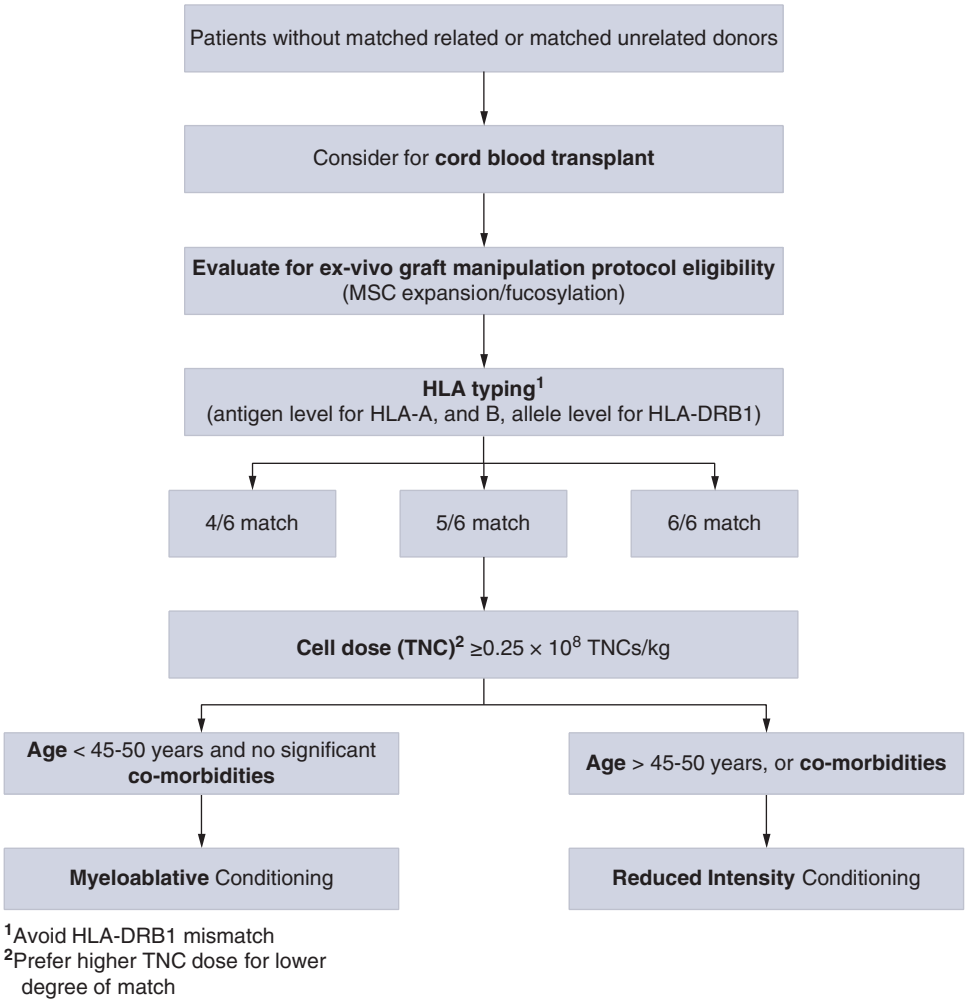


FIGURE 20–1 Approach to a patient for cord blood transplant.

chance of engraftment by infusing two units with at least an adequate dose in each.

We use novel ex vivo graft manipulation techniques pioneered at MDACC, such as ex vivo CB expansion with mesenchymal stromal cells (MSCs)[61] and ex vivo CB fucosylation.[62] With these techniques, remarkable improvement in engraftment is noted compared with historical controls. The median time to neutrophil engraftment is 15 days (range, 9–42) with MSC expansion[61] and 14 days (range, 12–28) with fucosylation, which is significantly faster than the 24 days (range, 12–52) noted in the CIBMTR controls, ($P \leq .001$).[62] Similarly, platelet engraftment is 42 days (range, 15–62) with MSC expansion and 33 days (range, 18–100) with fucosylation, compared with 49 days (range, 18–264) in the CIBMTR controls ($P = .03$).[61,62] We are investigating the impact of CB-unit killer cell immunotype receptor (KIR) genotype on transplant outcomes with an aim to integrate KIR information into a CB-unit selection algorithm.

Conditioning Regimens

We have investigated various MAC regimens for CBT, which include combinations of (1) melphalan, fludarabine, and thiotepa; (2) busulfan and fludarabine; (3) busulfan, clofarabine, fludarabine, and low-dose TBI given 9 days after chemotherapy; and (4) busulfan, clofarabine, fludarabine, and low-dose TBI given immediately after the chemotherapy.[63] The most favorable outcomes appear to be associated with the latest regimen, which is well tolerated and associated with prompt engraftment and effective disease control. This regimen consists of fludarabine 10 mg/m^2 per day (days –7 through –4), clofarabine 30 mg/m^2 per day (days –7 through –4), busulfan at a dose calculated to deliver a daily area under the curve of 4000 µmol/min for 4 days (days –7 through –4) based on an outpatient test dose of 32 mg/m^2, and 2 Gy TBI on day –3. Our preferred RIC regimen consists of fludarabine 40 mg/m^2 per day (days –5 through –2) and melphalan 140 mg/m^2 (day –2) in addition to the Flu/Cy/2 Gy TBI for patients older than 50 years and/or those who are not medically fit to tolerate the MAC regimen.

Prophylaxis

Prophylaxis against GVHD is provided with mycophenolate mofetil (MMF) and tacrolimus. We start MMF from day –3 at a dose of 15 mg/kg (maximum of 1 g orally twice daily) and continue it through day +100. Tacrolimus is started from day –2 and taper is started at day 180 in the absence of GVHD. We use rabbit ATG, 3 mg/kg infused over 2 days on days –4 and –3 in all patients. Patients taking azole antifungals require appropriate dose adjustments for adding tacrolimus. Other drug interactions and creatinine clearance need to be considered while calculating the dosage.

Filgrastrim is administered from day 0 until neutrophil engraftment and blood products are transfused as indicated. Standard infectious disease prophylaxis with antibacterial (levofloxacin), antiviral (valacyclovir), and antifungal (voriconazole, posaconazole, or caspofungin—the choice depending on risk factors) and against *Pneumocystis jiroveci* pneumonia (PCP) are also provided for all CBT patients. The surveillance for cytomegalovirus using quantitative polymerase chain reaction (or antigenemia assay if absolute neutrophil count is >1 × 10^9/L) is performed routinely, twice weekly for the first 100 days after CBT or longer if any complications are present. We routinely perform Epstein-Barr virus testing using quantitative polymerase chain reaction every 2 weeks from day +30 until day +100. Testing for other viruses including adenovirus, BK virus, respiratory syncytial virus, influenza, human herpesvirus 6, and parainfluenza is done as clinically indicated.

NOVEL STRATEGIES TO IMPROVE CBT OUTCOMES

Improving Cell Collection

Despite the availability of automated methods to increase the recovery of hematopoietic progenitor cells from banked CB units,[64] optimization of the number of cells collected remains a necessity. The BM environment where hematopoietic stem cells expand is very hypoxic, with oxygen levels as low as 1%–5%, and hypoxia is involved in stem cell regulation pathways.[65] The immediate exposure of collected CB cells to the high oxygen content of the ambient air grossly alters the numbers and function of stem and progenitor cells, a phenomenon referred to as "extra physiologic oxygen shock/stress (EPHOSS)."[66,67] Strategies to mitigate the oxygen shock have been investigated, such as the immediate collection and procession of the CB cells in the presence of cyclosporine A, which was shown to lead to an increase in the yield of hematopoietic stem cells.[66,67] However, this strategy necessitates more optimization and standardization. More recent in vivo studies showed that combinations of antioxidants and/or of epigenetic enzyme inhibitors allow for enhanced collection of mouse BM hematopoietic stem cells in ambient air,[68] although these procedures remain to be validated for human CB-unit collections. Research in this field is ongoing and aims to enhance the procedures used to collect CB for the best stem cell yield.

Improving Homing and Engraftment

To enhance the engraftment of hematopoietic stem cells after their administration, researchers have attempted to improve their capability to home to the BM. Different

methods have been tested, such as fucosylation of the CB progenitor cells[62,69,70]; the use of prostaglandin E2 derivatives[71] or dipeptidyl peptidase-4 (DPP4) inhibitors[72]; short-term treatment of cells with hyperthermia[73]; short-pulse glucocorticoid hormone stimulation[74]; inhibition of the negative epigenetic regulation by histone deacetylase 5 (HDAC5)[75]; the pharmacologic activation of nitric oxide signaling[76]; or a combination of strategies.[77] Many of these techniques have demonstrated significantly improved time to neutrophil engraftment (13–17 days) comparable with other donor types.

Ex Vivo Expansion

To increase CB cell dose, a variety of ex vivo expansion techniques have been developed, which yield significantly higher final numbers of TNC. These include coculturing the CB cells with cytokine support and or MSCs to simulate the BM "hematopoietic niche" ex vivo[61] or using nicotinamide analogs,[78–80] copper chelators (such as tetraethylenepentamine),[81,82] and targeting the *Notch* signaling pathway,[83] all of which block the differentiation of early progenitor cells leading to expansion of hematopoietic stem cells.

Other approaches include the use of small molecules such as StemRegenin 1 (SR1) in combination with cytokines, which was investigated in a phase 1/2 study, leading to a 330-fold increase in CD34+ cells and engraftment in all 17 patients who underwent dCBT at a median of 15 days for neutrophils and 49 days for platelets, significantly faster than in patients treated with unmanipulated CB.[84] A more recent study investigated the use of UM171, a hematopoietic stem cell self-renewal agonist,[85] in a phase 1/2 study of 27 patients undergoing single CBT, which showed promising results. UM171 led to the successful expansion of 26 (96%) of 27 CB units. Among the 22 patients who received single UM171-expanded CBT, the median time to engraftment was 18 days, median time to platelet recovery was 42 days, and no graft failure occurred. At one year, the incidence of TRM was 5% and the incidence of relapse was 21%. Overall survival, progression-free survival, GVHD-free and relapse-free survival, and chronic GVHD-free relapse-free survival at 12 months were 90%, 74%, 64%, and 74%, respectively.[86]

Other small molecules such as antagonists of peroxisome proliferation-activated receptor (PPAR)-gamma,[87] structural analogs of SB20358 (p38-map kinase inhibitor),[88] and OAC1 that activates the pluripotent transcription factor Oct4[89] have been used to enhance cytokine-mediated ex vivo expansion of CB hematopoietic stem cells. DEK is a secreted nuclear protein that was demonstrated to enhance the ex vivo expansion of hematopoietic stem and progenitor cells when used as a purified recombinant protein and hence was shown to act as a hematopoietic cytokine with potential clinical applicability.[90] N6-methyladenosine (m6A) is the most abundant epigenetic modification on eukaryocytic messenger RNAs, has been implicated in the regulation of a wide range of biological processes, and is recognized by its reader YTH domain family members. A recent work showed that the knockdown of YTHDF2 results in increased numbers of hematopoietic stem cells from CD34+ CB cells and could be a promising strategy for clinical application in the ex vivo expansion of CB.[91,92]

Apart from augmenting the cell dose, ex vivo graft manipulation techniques are being increasingly explored, which has permitted the generation and clinical use of antiviral and antitumor adoptive immunotherapies, as well as cellular therapies for GVHD prevention.[93,94] A variety of "designer" CB lymphocytes can now be engineered and expanded ex vivo—for instance, T-cells with specific cytotoxicity against tumors and or viruses,[95–98] chimeric antigen receptor (CAR) T-cells,[99] NK cells,[100] CAR-NK cells,[101] and regulatory T-cells,[102] which are being tested in clinical trials.

In Vivo Enhancement

The means to enhance the efficacy of CBT by accelerating the renewal and differentiation of already transplanted CB cells have also been investigated. Such methods include the administration of growth factors and the use of DPP4 inhibitors such as sitagliptin before and after the engraftment process has started.[72,103,104] Other groups have investigated the use of hyperbaric oxygen for the recipient to enhance engraftment.[105,106]

Research to enhance the yield of collected CB, its ex vivo expansion, and engraftment is very active and continues to evolve to eventually help elucidate the optimal means for ex vivo CB expansion. However, guidelines such as those published by an international group of clinical investigators associated with the Cord Blood Association have now been published to standardize CB banking and procedures and provide guidance on means to enhance the efficiency of CBT (**Table 20–3**, **Fig. 20–2**).[107]

CONCLUSION

CB transplantation is an attractive option for patients who lack a matched PB or BM donor. We and other researchers and investigators continue to work on improving our understanding of the biology and regulation of the CB progenitor and stem cells. The outcomes of alternative donor transplantation with CBT

Table 20–3 Clinical Advances in Cord Blood Transplant in Adult Patients With Hematologic Malignancies

Reference	Clinical advance	Patients (n)	Engraftment			GVHD		Infection (%)	Relapse (%)	TRM (%)	Survival
			ANC (day)	PLT (day)	Cumulative neutrophil recovery (%)	Acute 2–4 (%)	Chronic (%)				
de Lima et al[61]	Expansion ex vivo in cocultures with allogeneic mesenchymal stromal cells	31	15	42	96[b]	42	45	35[c]	13	55	1-year OS: 32%
Popat et al[62]	Fucosylation of CB progenitor cells	22	17	35	86[a]	41	5	NS	14	41	8-month OS: 45%
Cutler et al[71]	Use of PGE2 derivatives	12 (cohort 2)	18	43	100[b]	17	8	NS	25	33	1-year PFS: 62% 2-year PFS: 31% 1-year OS: 75% 2-year OS: 39%
Farag et al[72]	High dose of DPP4 inhibitor	15	19	NS	100[b]	0	NS	53[c]	NS	47[d]	NS
Horwitz et al[79]	Expansion with nicotinamide	11	13	33	NS	42	17	NS	17	8	1-year OS: 82% 1-year PFS: 73%
Stiff et al[81]	Expansion with copper chelator[e]	101	21	54	~90[b]	32	18	NS	NS	NS	100-day OS: 84%
Wagner et al[84]	Expansion with SR-1	17	15	49	86[f]	29 (grade 3–4)	NS	NS	NS	45	45%

(*Continued*)

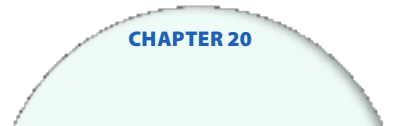
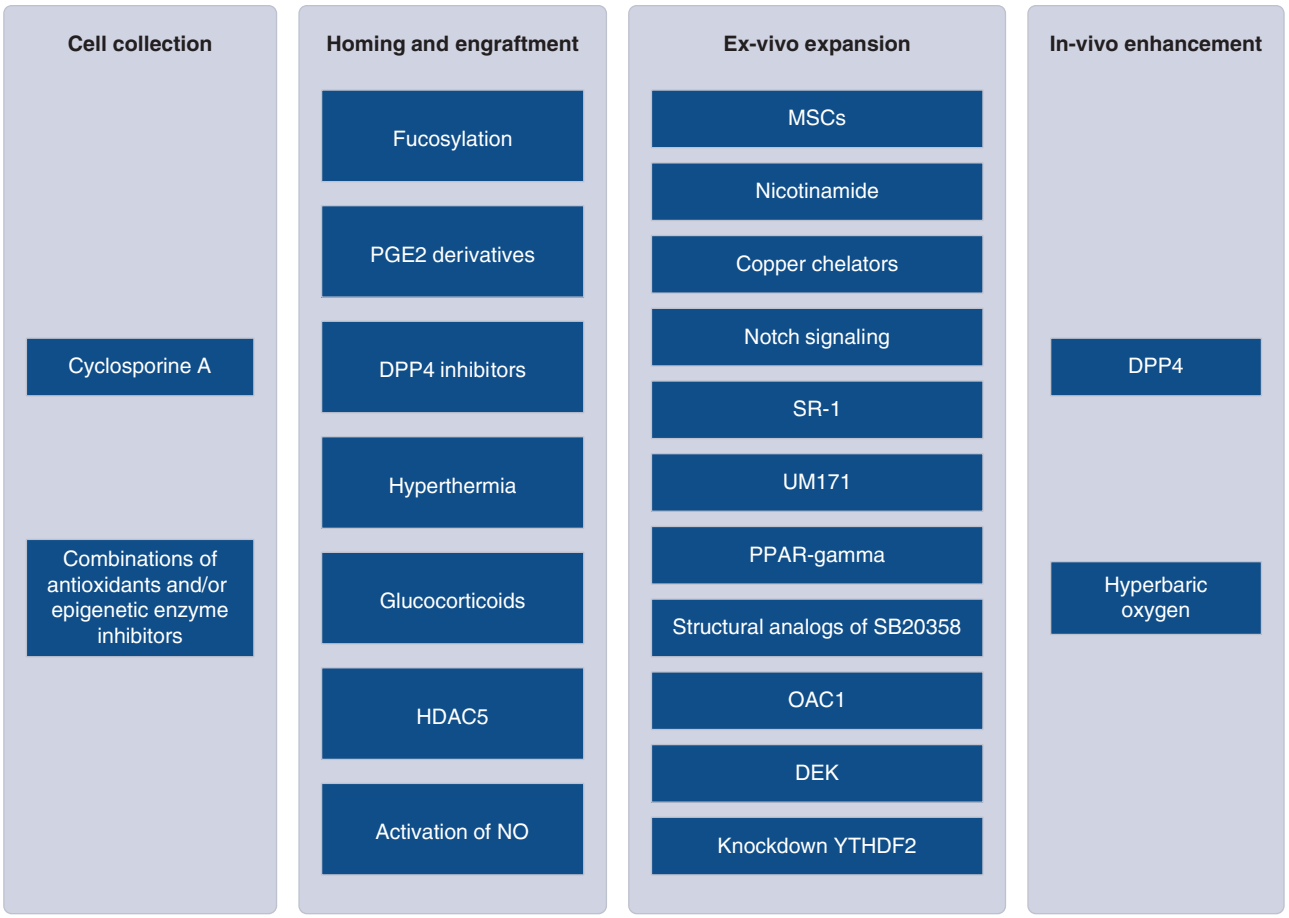


Table 20–3 Clinical Advances in Cord Blood Transplant in Adult Patients With Hematologic Malignancies (*Cont.*)

Reference	Clinical advance	Patients (n)	Engraftment			GVHD		Infection (%)	Relapse (%)	TRM (%)	Survival
			ANC (day)	PLT (day)	Cumulative neutrophil recovery (%)	Acute 2–4 (%)	Chronic (%)				
Cohen et al[86]	Expansion with UM171	27 (part 1) 23 (part 2)	18	42	100	64 (1-year)	17	ADV: 9% Asp: 9% Bacteremia: 41% BK: 9% C. diff: 5% CMV: 23% Device-related: 9% EBV: 14% HHV-6: 5% PCP: 9% UTI: 5%	21[h]	5[g]	1-year OS: 90% 1-year PFS: 74%

[a]Day 65 cumulative incidence of neutrophil engraftment.
[b]Day 42 cumulative incidence of neutrophil engraftment.
[c]Infection as primary cause of death.
[d]At 6 months.
[e]Tetraethylenepentamine (carlecortemcel-L).
[f]Day 24 cumulative incidence of neutrophil engraftment.
[g]1-year cumulative incidence of TRM.
[h]1-year relapse rate.
ADV, adenovirus cystitis (with adenovirus viremia); ANC, absolute neutrophil count >500; Asp, Aspergillus pneumonia; BK, BK virus–associated cystitis; C. diff, *Clostridium difficile* colitis; CB, cord blood; DPP4, dipeptidyl peptidase 4; EBV, Epstein-virus viremia; GVHD, graft-versus-host disease; HHV-6, human herpesvirus-6 reactivation; OS, overall survival; PCP, *Pneumocystis jiroveci* pneumonia; PGE2, prostaglandin E2; PLT, platelets >20,000; SR-1, StemRegenin-1; TRM, transplant-related mortality; UTI, urinary tract infection.
* Avoid HLA-DRB1 mismatch
** Prefer higher TNC dose for lower degree of match



PGE2: Prostaglandin E2; DPP4: Dipeptidyl peptidase-4; HDAC5: Histone deacetylase 5; NO: Nitric oxide; MSCs: Mesenchymal stromal cells; SR-1: StemRegenin 1; PPAR: Peroxisome proliferation-activated receptor.

FIGURE 20–2 Strategies to improve cord blood transplant.

have significantly improved over the past decade, leading to survival and relapse rates comparable with those with other donor sources while offering the advantage of being logistically more practical and faster. To overcome the limitation of low cell doses in single CB units, dCBT has been adopted for many patients, and promising strategies to improve engraftment with ex vivo expansion or homing and to enhance immune reconstitution with the infusion of CB-derived NK cells and cytotoxic T lymphocytes with antiviral and antileukemic specificities have been investigated. The unmet need as of this writing remains instituting more prospective multicenter clinical trials to determine the efficacy of these promising technologies.

MD ANDERSON PRACTICE TIPS

- Within the first days to weeks after donor search is initiated, the likelihood of finding a matched donor is determined. If this likelihood is deemed to be low, we proceed with confirmatory HLA typing of CB units.
- Our current institutional policy is to use a double-unit graft in an effort to augment engraftment and reduce TRM. We give a strong priority to HLA match over a pre-cryopreservation TNC threshold of ~2.0 × 10^7/kg for each unit of a double-unit graft.
- We use novel ex vivo graft manipulation techniques pioneered at MDACC, such as ex vivo CB expansion with MSCs and ex vivo CB fucosylation.
- Our preferred MAC regimen consists of fludarabine 10 mg/m^2 per day (days –7 through –4), clofarabine 30 mg/m^2 per day (days –7 through –4), busulfan at a dose calculated to deliver a daily area under the curve of 4000 µmol/min for 4 days (days –7 through –4) based on an outpatient test dose of 32 mg/m^2, and 2 Gy TBI on day –3.
- Our preferred RIC regimen consists of fludarabine 40 mg/m^2/day (days –5 through –2) and melphalan 140 mg/m^2 (day –2) in addition to the Flu/Cy/2 Gy TBI for patients older than 50 years and/or those not medically fit to tolerate the MAC regimen.
- Prophylaxis against GVHD is provided with MMF and tacrolimus. We use rabbit ATG 3 mg/kg infused over 2 days on days –4 and –3 in all patients.
- Filgrastrim is administered from day 0 until neutrophil engraftment and blood products are transfused as indicated.
- Standard infectious disease prophylaxis with antibacterial (levofloxacin), antiviral (valacyclovir), and antifungal (voriconazole, posaconazole, or caspofungin—the choice depending on risk factors) and against PCP are also provided for all CBT patients.

REFERENCES

1. D'Souza A, Fretham C. Current Uses and Outcomes of Hematopoietic Cell Transplantation (HCT): CIBMTR Summary Slides, 2019. Accessed April 7, 2021. https://www.cibmtr.org/ReferenceCenter/SlidesReports/SummarySlides/_layouts/15/WopiFrame.aspx?sourcedoc=/ReferenceCenter/SlidesReports/SummarySlides/Documents/2018%20Summary%20Slides%20-%20final%20-%20for%20web%20posting.pptx&action=default
2. Rosenmayr A, Pointner-Prager M, Mitterschiffthaler A, et al. What are a patient's current chances of finding a matched unrelated donor? Twenty years' central search experience in a small country. *Bone Marrow Transplant*. 2012;47(2):172-180.
3. Aljurf M, Weisdorf D, Alfraih F, et al. Worldwide Network for Blood & Marrow Transplantation (WBMT) special article, challenges facing emerging alternate donor registries. *Bone Marrow Transplant*. 2019;54(8):1179-1188.
4. Gragert L, Eapen N, Williams E, et al. HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry. *N Engl J Med*. 2014;371(4):339-348.
5. Cheuk DK. Optimal stem cell source for allogeneic stem cell transplantation for hematological malignancies. *World J Transplant*. 2013;3(4):99-112.
6. Barker JN, Kurtzberg J, Ballen K, et al. Optimal practices in unrelated donor cord blood transplantation for hematologic malignancies. *Biol Blood Marrow Transplant*. 2017;23(6):882-896.
7. Kanda J, Umeda K, Kato K, et al. Effect of graft-versus-host disease on outcomes after pediatric single cord blood transplantation. *Bone Marrow Transplant*. 2020;55(7):1430-1437.
8. Eapen M, Rocha V, Sanz G, et al. Effect of graft source on unrelated donor haemopoietic stem-cell transplantation in adults with acute leukaemia: a retrospective analysis. *Lancet Oncol*. 2010;11(7):653-660.
9. Jacobson CA, Turki AT, McDonough SM, et al. Immune reconstitution after double umbilical cord blood stem cell transplantation: comparison with unrelated peripheral blood stem cell transplantation. *Biol Blood Marrow Transplant*. 2012;18(4):565-574.
10. Majhail NS, Brunstein CG, Tomblyn M, et al. Reduced-intensity allogeneic transplant in patients older than 55 years: unrelated umbilical cord blood is safe and effective for patients without a matched related donor. *Biol Blood Marrow Transplant*. 2008;14(3):282-289.
11. Brunstein CG, Gutman JA, Weisdorf DJ, et al. Allogeneic hematopoietic cell transplantation for hematologic malignancy: relative risks and benefits of double umbilical cord blood. *Blood*. 2010;116(22):4693-4699.
12. Shouval R, Fein JA, Labopin M, et al. Outcomes of allogeneic haematopoietic stem cell transplantation from HLA-matched and alternative donors: a European Society for Blood and Marrow Transplantation registry retrospective analysis. *Lancet Haematol*. 2019;6(11):e573-e584.
13. Milano F, Applebaum FR, Delaney C. Cord-blood transplantation in patients with minimal residual disease. *N Engl J Med*. 2016;375(10):944-953.
14. Terakura S, Nishida T, Sawa M, et al. Prospective evaluation of alternative donor from unrelated donor and cord blood in adult acute leukemia and myelodysplastic syndrome. *Bone Marrow Transplant*. 2020;55(7):1399-1409.
15. Ando T, Tachibana T, Tanaka M, et al. Impact of graft sources on immune reconstitution and survival outcomes following allogeneic stem cell transplantation. *Blood Adv*. 2020;4(2):408-419.
16. Politikos I, Lavery JA, Hilden P, et al. Robust CD4+ T-cell recovery in adults transplanted with cord blood and no antithymocyte globulin. *Blood Adv*. 2020;4(1):191-202.
17. Barker JN, Scaradavou A, Stevens CE. Combined effect of total nucleated cell dose and HLA match on transplantation outcome in 1061 cord blood recipients with hematologic malignancies. *Blood*. 2010;115(9):1843-1849.
18. Wagner JE Jr, Eapen M, Carter S, et al. One-unit versus two-unit cord-blood transplantation for hematologic cancers. *N Engl J Med*. 2014;371(18):1685-1694.
19. Eapen M, Klein JP, Ruggeri A, et al. Impact of allele-level HLA matching on outcomes after myeloablative single unit umbilical cord blood transplantation for hematologic malignancy. *Blood*. 2014;123(1):133-140.
20. Purtill D, Smith K, Devlin S, et al. Dominant unit CD34+ cell dose predicts engraftment after double-unit cord blood transplantation and is influenced by bank practice. *Blood*. 2014;124(19):2905-2912.
21. Migliaccio AR, Adamson JW, Stevens CE, et al. Cell dose and speed of engraftment in placental/umbilical cord blood transplantation: graft progenitor cell content is a better predictor than nucleated cell quantity. *Blood*. 2000;96(8):2717-2722.
22. Page KM, Zhang L, Mendizabal A, et al. Total colony-forming units are a strong, independent predictor of neutrophil and platelet engraftment after unrelated umbilical cord blood transplantation: a single-center analysis of 435 cord blood transplants. *Biol Blood Marrow Transplant*. 2011;17(9):1362-1374.
23. Scaradavou A, Smith KM, Hawke R, et al. Cord blood units with low CD34+ cell viability have a low probability of engraftment after double unit transplantation. *Biol Blood Marrow Transplant*. 2010;16(4):500-508.
24. Lee SJ, Klein J, Haagenson M, et al. High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. *Blood*. 2007;110(13):4576-4583.
25. Petersdorf EW. Optimal HLA matching in hematopoietic cell transplantation. *Curr Opin Immunol*. 2008;20(5):588-593.
26. Gluckman E, Rocha V, Arcese W, et al. Factors associated with outcomes of unrelated cord blood transplant: guidelines for donor choice. *Exp Hematol*. 2004;32(4):397-407.
27. Tucunduva L, Ruggeri A, Sanz G, et al. Impact of myeloablative and reduced intensity conditioning on outcomes after unrelated cord blood transplantation for adults with acute lymphoblastic leukemia. *Biol Blood Marrow Transplant.* 2013;19(2):S127.
28. Oran B, Cao K, Saliba RM, et al. Better allele-level matching improves transplant-related mortality after double cord blood transplantation. *Haematologica*. 2015;100(10):1361-1370.
29. Brunstein CG, Petersdorf EW, DeFor TE, et al. Impact of allele-level HLA mismatch on outcomes in recipients of double umbilical cord blood transplantation. *Biol Blood Marrow Transplant*. 2016;22(3):487-492.
30. Kosuri S, Hilden P, Devlin SM, et al. High progression-free survival (PFS) in adult double unit cord blood (dCB) transplant recipients with high risk disease after a novel intermediate intensity conditioning regimen. *Biol Blood Marrow Transplant*. 2016;22(3):S76-S77.
31. Sanz J, Jaramillo FJ, Planelles D, et al. Impact on outcomes of human leukocyte antigen matching by allele-level typing in adults with acute myeloid leukemia undergoing umbilical cord blood transplantation. *Biol Blood Marrow Transplant.* 2014;20(1):106-110.
32. Barker JN, Weisdorf DJ, DeFor TE, et al. Transplantation of 2 partially HLA-matched umbilical cord blood units to enhance engraftment in adults with hematologic malignancy. *Blood*. 2005;105(3):1343-1347.
33. Scaradavou A, Brunstein CG, Eapen M, et al. Double unit grafts successfully extend the application of umbilical cord blood transplantation in adults with acute leukemia. *Blood*. 2013;121(5):752-758.
34. Ruggeri A, Sanz G, Bittencourt H, et al. Comparison of outcomes after single or double cord blood transplantation in

adults with acute leukemia using different types of myeloablative conditioning regimen, a retrospective study on behalf of Eurocord and the Acute Leukemia Working Party of EBMT. *Leukemia*. 2014;28(4):779-786.
35. Kindwall-Keller TL, Hegerfeldt Y, Meyerson HJ, et al. Prospective study of one- vs two-unit umbilical cord blood transplantation following reduced intensity conditioning in adults with hematological malignancies. *Bone Marrow Transplant*. 2012;47(7):924-933.
36. Rodrigues CA, Sanz G, Brunstein CG, et al. Analysis of risk factors for outcomes after unrelated cord blood transplantation in adults with lymphoid malignancies: a study by the Eurocord-Netcord and lymphoma working party of the European group for blood and marrow transplantation. *J Clin Oncol*. 2009;27(2):256-263.
37. Michel G, Galambrun C, Sirvent A, et al. Single- vs double-unit cord blood transplantation for children and young adults with acute leukemia or myelodysplastic syndrome. *Blood*. 2016;127(26):3450-3457.
38. Verneris MR, Brunstein CG, Barker J, et al. Relapse risk after umbilical cord blood transplantation: enhanced graft-versus-leukemia effect in recipients of 2 units. *Blood*. 2009;114(19):4293-4299.
39. Labopin M, Ruggeri A, Gorin NC, et al. Cost-effectiveness and clinical outcomes of double versus single cord blood transplantation in adults with acute leukemia in France. *Haematologica*. 2014;99(3):535-540.
40. Hashem H, Lazarus HM. Double umbilical cord blood transplantation: relevance of persistent mixed-unit chimerism. *Biol Blood Marrow Transplant*. 2015;21(4):612-619.
41. Ballen KK, Spitzer TR, Yeap BY, et al. Double unrelated reduced-intensity umbilical cord blood transplantation in adults. *Biol Blood Marrow Transplant*. 2007;13(1):82-89.
42. Brunstein CG, Barker JN, Weisdorf DJ, et al. Umbilical cord blood transplantation after nonmyeloablative conditioning: impact on transplantation outcomes in 110 adults with hematologic disease. *Blood*. 2007;110(8):3064-3070.
43. Purtill D, Stevens CE, Lubin M, et al. Association between nondominant unit total nucleated cell dose and engraftment in myeloablative double-unit cord blood transplantation. *Biol Blood Marrow Transplant*. 2015;21(11):1981-1984.
44. Arachchillage DR, Dalley CD, Reilly JT, et al. Long-term dual donor derived haematopoietic reconstitution following double unrelated cord blood transplantation--single unit dominance is not always the case. *Br J Haematol*. 2010;149(2):298-299.
45. Gluckman E. Ten years of cord blood transplantation: from bench to bedside. *Br J Haematol*. 2009;147(2):192-199.
46. Brunstein C, Zhang M-J, Barker J, et al. The effect of inter-unit HLA matching in double umbilical cord blood transplantation for acute leukemia. *Haematologica*. 2017;102(5):941-947.
47. Marks DI, Woo KA, Zhong X, et al. Unrelated umbilical cord blood transplant for adult acute lymphoblastic leukemia in first and second complete remission: a comparison with allografts from adult unrelated donors. *Haematologica*. 2014;99(2):322-328.
48. Barker JN, Fei M, Karanes C, et al. Results of a prospective multicentre myeloablative double-unit cord blood transplantation trial in adult patients with acute leukaemia and myelodysplasia. *Br J Haematol*. 2015;168(3):405-412.
49. Barker JN, Weisdorf DJ, DeFor TE, et al. Rapid and complete donor chimerism in adult recipients of unrelated donor umbilical cord blood transplantation after reduced-intensity conditioning. *Blood*. 2003;102(5):1915-1919.
50. Arcese W. Myeloablative versus reduced intensity conditioning regimen cord blood transplants. 37th Annual Meeting of the European Group for Blood and Marrow Transplantation. Paris, France; 2011.
51. Miyakoshi S, Yuji K, Kami M, et al. Successful engraftment after reduced-intensity umbilical cord blood transplantation for adult patients with advanced hematological diseases. *Clin Cancer Res*. 2004;10(11):3586-3592.
52. Rodrigues CA, Rocha V, Dreger P, et al. Alternative donor hematopoietic stem cell transplantation for mature lymphoid malignancies after reduced-intensity conditioning regimen: similar outcomes with umbilical cord blood and unrelated donor peripheral blood. *Haematologica*. 2014;99(2):370-377.
53. Brunstein CG, Eapen M, Ahn KW, et al. Reduced-intensity conditioning transplantation in acute leukemia: the effect of source of unrelated donor stem cells on outcomes. *Blood*. 2012;119(23):5591-5598.
54. Sharma P, Pollyea DA, Smith CA, et al. Thiotepa-based intensified reduced-intensity conditioning adult double-unit cord blood hematopoietic stem cell transplantation results in decreased relapse rate and improved survival compared with transplantation following standard reduced-intensity conditioning: a retrospective cohort comparison. *Biol Blood Marrow Transplant*. 2018;24(8):1671-1677.
55. Bejanyan N, Oran B, Shanley R, et al. Clinical outcomes of AML patients relapsing after matched-related donor and umbilical cord blood transplantation. *Bone Marrow Transplant*. 2014;49(8):1029-1035.
56. Laughlin MJ, Eapen M, Rubinstein P, et al. Outcomes after transplantation of cord blood or bone marrow from unrelated donors in adults with leukemia. *N Engl J Med*. 2004;351(22):2265-2275.
57. Parody R, Martino R, Rovira M, et al. Severe infections after unrelated donor allogeneic hematopoietic stem cell transplantation in adults: comparison of cord blood transplantation with peripheral blood and bone marrow transplantation. *Biol Blood Marrow Transplant*. 2006;12(7):734-748.
58. Weisdorf D, Eapen M, Ruggeri A, et al. Alternative donor transplantation for older patients with acute myeloid leukemia in first complete remission: a center for international blood and marrow transplant research-eurocord analysis. *Biol Blood Marrow Transplant*. 2014;20(6):816-822.
59. Szabolcs P, Cairo MS. Unrelated umbilical cord blood transplantation and immune reconstitution. *Semin Hematol*. 2010;47(1):22-36.
60. Komanduri KV, St John LS, de Lima M, et al. Delayed immune reconstitution after cord blood transplantation is characterized by impaired thymopoiesis and late memory T-cell skewing. *Blood*. 2007;110(13):4543-4551.
61. de Lima M, McNiece I, Robinson SN, et al. Cord-blood engraftment with ex vivo mesenchymal-cell coculture. *N Engl J Med*. 2012;367(24):2305-2315.
62. Popat U, Mehta RS, Rezvani K, et al. Enforced fucosylation of cord blood hematopoietic cells accelerates neutrophil and platelet engraftment after transplantation. *Blood*. 2015;125(19):2885-2892.
63. Mehta RS, Di Stasi A, Andersson BS, et al. The development of a myeloablative, reduced-toxicity, conditioning regimen for cord blood transplantation. *Clin Lymphoma Myeloma Leuk*. 2014;14(1):e1-e5.
64. Muñiz Alers SM, Page K, Simmons R, et al. Automated thawing increases recovery of colony-forming units from banked cord blood unit grafts. *Transfusion*. 2018;58(12):2911-2917.
65. Huang X, Trinh T, Aljoufi A, Broxmeyer HE. Hypoxia signaling pathway in stem cell regulation: good and evil. *Curr Stem Cell Rep*. 2018;4(2):149-157.
66. Mantel CR, O'Leary HA, Chitteti BR, et al. Enhancing hematopoietic stem cell transplantation efficacy by mitigating oxygen shock. *Cell*. 2015;161(7):1553-1565.
67. Broxmeyer HE, O'Leary HA, Huang X, Mantel C. The importance of hypoxia and extra physiologic oxygen shock/stress

for collection and processing of stem and progenitor cells to understand true physiology/pathology of these cells ex vivo. *Curr Opin Hematol*. 2015;22(4):273-278.
68. Cai Q, Capitano M, Huang X, et al. Combinations of antioxidants and/or of epigenetic enzyme inhibitors allow for enhanced collection of mouse bone marrow hematopoietic stem cells in ambient air. *Blood Cells Mol Dis*. 2018;71:23-28.
69. Robinson SN, Thomas MW, Simmons PJ, et al. Fucosylation with fucosyltransferase VI or fucosyltransferase VII improves cord blood engraftment. *Cytotherapy*. 2014;16(1):84-89.
70. Xia L, McDaniel JM, Yago T, et al. Surface fucosylation of human cord blood cells augments binding to P-selectin and E-selectin and enhances engraftment in bone marrow. *Blood*. 2004;104(10):3091-3096.
71. Cutler C, Multani P, Robbins D, et al. Prostaglandin-modulated umbilical cord blood hematopoietic stem cell transplantation. *Blood*. 2013;122(17):3074-3081.
72. Farag SS, Nelson R, Cairo MS, et al. High-dose sitagliptin for systemic inhibition of dipeptidylpeptidase-4 to enhance engraftment of single cord umbilical cord blood transplantation. *Oncotarget*. 2017;8(66):110350-110357.
73. Capitano ML, Hangoc G, Cooper S, Broxmeyer HE, et al. Mild heat treatment primes human CD34(+) cord blood cells for migration toward SDF-1α and enhances engraftment in an NSG mouse model. *Stem Cells*. 2015;33(6):1975-1984.
74. Guo B, Huang X, Cooper C, Broxmeyer HE. Glucocorticoid hormone-induced chromatin remodeling enhances human hematopoietic stem cell homing and engraftment. *Nat Med*. 2017;23(4):424-428.
75. Huang X, Guo B, Liu S, et al. Neutralizing negative epigenetic regulation by HDAC5 enhances human haematopoietic stem cell homing and engraftment. *Nat Commun*. 2018;9(1): p. 2741.
76. Xu D, Yang M, Capitano M, et al. Pharmacological activation of nitric oxide signaling promotes human hematopoietic stem cell homing and engraftment. *Leukemia*. 2020;35(1):229-234.
77. Broxmeyer HE, Pelus LM. Inhibition of DPP4/CD26 and $dmPGE_2$ treatment enhances engraftment of mouse bone marrow hematopoietic stem cells. *Blood Cells Mol Dis*. 2014;53(1-2):34-38.
78. Saber W, Cutler CS, Nakamura R, et al. Impact of donor source on hematopoietic cell transplantation outcomes for patients with myelodysplastic syndromes (MDS). *Blood*. 2013;122(11):1974-1982.
79. Horwitz ME, Chao NJ, Rizzieri DA, et al. Umbilical cord blood expansion with nicotinamide provides long-term multilineage engraftment. *J Clin Invest*. 2014;124(7):3121-3128.
80. Islam P, Horwitz ME. Small-molecule nicotinamide for ex vivo expansion of umbilical cord blood. *Exp Hematol*. 2019;80:11-15.
81. Stiff PJ, Montesinos P, Peled T, et al. Cohort-controlled comparison of umbilical cord blood transplantation using carlecortemcel-L, a single progenitor-enriched cord blood, to double cord blood unit transplantation. *Biol Blood Marrow Transplant*. 2018;24(7):1463-1470.
82. de Lima M, McMannis J, Gee A, et al. Transplantation of ex vivo expanded cord blood cells using the copper chelator tetraethylenepentamine: a phase I/II clinical trial. *Bone Marrow Transplant*. 2008;41(9):771-778.
83. Delaney C, Heimfeld S, Brashem-Stein C, et al. Notch-mediated expansion of human cord blood progenitor cells capable of rapid myeloid reconstitution. *Nat Med*. 2010;16(2):232-236.
84. Wagner JE Jr, Brunstein CG, Boitano AE, et al. Phase I/II trial of StemRegenin-1 expanded umbilical cord blood hematopoietic stem cells supports testing as a stand-alone graft. *Cell Stem Cell*. 2016;18(1):144-155.
85. Fares I, Chagraoui J, Gareau Y, et al. Pyrimidoindole derivatives are agonists of human hematopoietic stem cell self-renewal. *Science*. 2014;345(6203):1509-1512.
86. Cohen S, Roy J, Lachance S, et al. Hematopoietic stem cell transplantation using single UM171-expanded cord blood: a single-arm, phase 1-2 safety and feasibility study. *Lancet Haematol*. 2020;7(2):e134-e145.
87. Guo B, Huang X, Lee MR, et al. Antagonism of PPAR-γ signaling expands human hematopoietic stem and progenitor cells by enhancing glycolysis. *Nat Med*. 2018;24(3):360-367.
88. Bari S, Zhong Q, Fan X, et al. Ex vivo expansion of CD34(+) CD90(+) CD49f(+) hematopoietic stem and progenitor cells from non-enriched umbilical cord blood with azole compounds. *Stem Cells Transl Med*. 2018;7(5):376-393.
89. Huang X, Lee M-R, Cooper S, et al. Activation of OCT4 enhances ex vivo expansion of human cord blood hematopoietic stem and progenitor cells by regulating HOXB4 expression. *Leukemia*. 2016;30(1):144-153.
90. Capitano ML, Mor-Vaknin N, Saha AK, et al. Secreted nuclear protein DEK regulates hematopoiesis through CXCR2 signaling. *J Clin Invest*. 2019;129(6):2555-2570.
91. Li Z, Qian P, Shao W, et al. Suppression of m(6)A reader Ythdf2 promotes hematopoietic stem cell expansion. *Cell Res*. 2018;28(9):904-917.
92. Huang X, and Broxmeyer HE. m6A reader suppression bolsters HSC expansion. *Cell Res*. 2018;28(9):875-876.
93. Thompson PA, Rezvani K, Hosing CM, et al. Umbilical cord blood graft engineering: challenges and opportunities. *Bone Marrow Transplant*. 2015;50(suppl 2):S55-S62.
94. Mehta RS, Dave H, Bollard CM, et al. Engineering cord blood to improve engraftment after cord blood transplant. *Stem Cell Investig*. 2017;4:41.
95. Hanley P, Leen A, Gee AP, et al. Multi-virus-specific T-cell therapy for patients after hematopoietic stem cell and cord blood transplantation. *Blood*. 2013;122(21):140.
96. Weber G, Gerdemann U, Caruana I, et al. Generation of multileukemia antigen-specific T cells to enhance the graft-versus-leukemia effect after allogeneic stem cell transplant. *Leukemia*. 2013;27(7):1538-1547.
97. Micklethwaite KP, Savoldo B, Hanley PJ, et al. Derivation of human T lymphocytes from cord blood and peripheral blood with antiviral and antileukemic specificity from a single culture as protection against infection and relapse after stem cell transplantation. *Blood*. 2010;115(13):2695-2703.
98. Hanley PJ, Melenhorst JJ, Nikiforow S, et al. CMV-specific T cells generated from naïve T cells recognize atypical epitopes and may be protective in vivo. *Sci Transl Med*. 2015;7(285):285ra63.
99. Kebriaei P, Huls H, Singh H, et al. First clinical trials employing *Sleeping Beauty* gene transfer system and artificial antigen presenting cells to generate and infuse T cells expressing CD19-specific chimeric antigen receptor. *Blood*. 2013;122(21):166.
100. Shah N, Martin-Antonio B, Yang H, et al. Antigen presenting cell-mediated expansion of human umbilical cord blood yields log-scale expansion of natural killer cells with anti-myeloma activity. *PLoS One*. 2013;8(10):e76781.
101. Liu E, Marin D, Banerjee P, et al. Use of CAR-transduced natural killer cells in CD19-positive lymphoid tumors. *N Engl J Med*. 2020;382(6):545-553.
102. Brunstein CG, Miller JS, Cao Q, et al. Infusion of ex vivo expanded T regulatory cells in adults transplanted with umbilical cord blood: safety profile and detection kinetics. *Blood*. 2011;117(3):1061-1070.
103. Farag SS, Srivastava S, Messina-Graham S, et al. In vivo DPP-4 inhibition to enhance engraftment of single-unit cord blood transplants in adults with hematological malignancies. *Stem Cells Dev*. 2013;22(7):1007-1015.

104. Vélez de Mendizábal N, Strother RM, Farag SS, et al. Modelling the sitagliptin effect on dipeptidyl peptidase-4 activity in adults with haematological malignancies after umbilical cord blood haematopoietic cell transplantation. *Clin Pharmacokinet*. 2014;53(3):247-259.
105. Aljitawi OS, Paul S, Ganguly A, et al. Erythropoietin modulation is associated with improved homing and engraftment after umbilical cord blood transplantation. *Blood*. 2016;128(25):3000-3010.
106. Mina A, Shune L, Abdelhakim H, et al. Long-term results of a pilot study evaluating hyperbaric oxygen therapy to improve umbilical cord blood engraftment. *Ann Hematol*. 2019;98(2):481-489.
107. Broxmeyer HE. Long-overdue guidelines for the cord blood banking community. *Stem Cells Transl Med*. 2019;8(4):320-322.

21

Alternative Donor Transplants: Haploidentical Hematopoietic Stem Cell Transplantation

Samer A. Srour
Richard E. Champlin
Stefan O. Ciurea

KEY CONCEPTS

- Allogeneic stem cell transplantation (allo-SCT) remains the only curative intervention for a variety of high-risk hematologic malignancies. Haploidentical grafts from a first-degree related mismatched donor extends the applicability of this lifesaving treatment to a large proportion of patients who otherwise do not have a suitable human leukocyte antigen–matched donor.
- Breakthrough advances achieved over past decade in controlling the bidirectional alloreactivity and in graft engineering have led to a decreased incidence of complications, including graft-versus-host disease and nonrelapse mortality (NRM), without compromising the graft-versus-tumor effect.
- The use of haploidentical transplantation continues to increase with growing evidence for its effectiveness in several myeloid and lymphoid neoplasms. Haploidentical use has taken precedence compared with some other alternative donor sources given its immediate availability and cost-effectiveness.
- Fully matched related donors remain the preferred graft source for allo-SCT. However, several transplant registry studies in United States and Europe have confirmed comparable survival outcomes between matched unrelated and haploidentical transplants.
- The results of the large phase 3 randomized Bone and Marrow Transplant Clinical Trials Network multicenter clinical trials were reported recently confirming superiority of haploidentical transplant over double cord transplant in terms of improved overall survival and decreased NRM.
- Several factors are considered when choosing the best haploidentical donor. The donor-specific antibodies remain one of the most important factors to consider because the presence of antibodies is associated with a high risk of graft failure. Younger donors, male donors, fathers rather than mothers, and first-degree to second-degree donors are preferred graft sources for recipients of haploidentical transplants.

Haploidentical stem cell transplantation (HaploSCT) from a first-degree related mismatched haplotype donor (siblings, children, parents) extends the application of this lifesaving treatment to a large proportion of patients with high-risk hematologic malignancies who otherwise do not have a suitable human leukocyte antigen (HLA)–matched donor.[1] As the average family size continues to shrink, the likelihood of finding an HLA-matched related sibling donors continues to decrease.[2] Moreover, with aging of the United States population, finding a young healthy sibling donor becomes increasingly less likely. The use of matched unrelated donors (MUDs) is limited by a longer time to transplantation (median, 3–4 months), which makes it difficult to treat patients with more advanced disease in rapid need for a transplant. The ethnicity or race of the recipient can have great impact as well in identifying a suitable MUD because approximately 30%, 70%, and 90% of the white, Hispanic, and African American population do not have a MUD in the worldwide registries.[3] In contrast to unrelated donor grafts, haploidentical (or "half-matched") donors can be immediately available, and there are no costs associated with an unrelated donor search, graft acquisition, maintaining a registry, or coordinating logistics with distant donor centers. This is an especially valuable option for

nonwhite and mixed-race individuals who frequently have no available matched donors to proceed with transplantation.[3] This approach might also be particularly useful in developing countries that may not have the resources to procure unrelated donor transplants or maintain complex unrelated donor registries. Moreover, haploidentical donors offer the advantage of ad hoc availability to quickly collect donor cells for cellular therapy interventions after transplant. Over the recent decade, significant breakthrough advances in controlling alloreactivity have been made, and important steps have been taken toward graft engineering and posttransplant cellular therapy, approaches that may further change landscape of HaploSCT in the future. Improved haploidentical transplant outcomes represent a major advancement in transplantation, which has practically eliminated the limitation of donor availability for allogeneic stem cell transplantation (allo-SCT).

COMPLETE T-CELL DEPLETION: CONTROL OF GRAFT-VERSUS-HOST DISEASE BUT WITH A HIGH TREATMENT-RELATED MORTALITY RATE

Historically, the use of unmanipulated T-cell-replete HaploSCT grafts with conventional graft-versus-host disease (GVHD) prophylaxis in the late 1970s was associated with intense bidirectional alloreactivity and unacceptably high morbidity and mortality rates because of hyperacute GVHD and graft rejection.[4–6] This led in the 1980s to the development of complete ex vivo depletion of T-cells using CD34+-selected grafts. Complete T-cell depletion has been associated with much lower incidence of acute GVHD (aGVHD). However, this came at the expense of markedly delayed immune recovery after transplant and was associated with high nonrelapse mortality (NRM) from infections, higher disease relapse rates, given the decreased graft-versus-leukemia effect, and high rates of graft rejection.[7–9] Although graft rejection was partially overcome with "mega" doses of CD34+ cells (typically >10^7 CD34+ cells/kg) and a myeloablative conditioning regimen (including total body irradiation, cyclophosphamide, thiotepa), severe T-cell depletion of the graft delayed immune recovery led to an unacceptably high incidence of infectious complications and increased NRM in excess of 40%.[10] We have used this approach with our conditioning regimen (fludarabine, melphalan, and thiotepa) and showed that most patients died of NRM related to infectious complications.[11] Improved outcomes with selected α-β T-cell depletion has been subsequently adopted mostly in children with better results.[12] During the past decade, several advances have enabled investigators to selectively deplete alloreactive T-cells and successfully control GVHD rates while maintaining memory T-cells in the graft to accelerate immune recovery and prevent significant infectious complications post transplant. Table 21–1 summarizes the major contemporaneous approaches to HaploSCT. These advances have significantly improved the treatment outcomes of patients receiving haploidentical donor transplants, which are now comparable to matched transplants. In the following sections, we aim to summarize the recent developments with this type of transplant focusing on advances made at MD Anderson Cancer Center (MDACC).

TABLE 21–1 Current Approaches to Haploidentical Stem Cell Transplantation

Approach	Rationale	Stage of Clinical Development
High-dose posttransplantation cyclophosphamide	Eliminating the only the alloreactive T-cells. Rapid immune recovery with low infectious complications Acceptable rates of GVHD Lower cost	Phase II/III
Selective αβ T-cell depletion	Removing αβ T-cells that are most responsive for aGVHD Remaining γδ T-cells are thought to have an innate immune-like response capability without inducing GVHD	Phase I/II
Photodepletion	Ex vivo depletion of alloreactive T-cells with TH9402 that accumulates in activated T-cells	Phase I/II
Selective CD45RA+ T-cell depletion	Elimination of CD45RA+ naïve T-cells thought to play a major role in GVHD Preserves memory T-cells that are active against infections	Phase I

aGVHD, acute graft-versus-host disease; GVHD, graft-versus-host disease.

BALANCING GRAFT-VERSUS-HOST DISEASE, IMMUNE RECOVERY, AND THE CONCEPT OF SELECTIVE ALLODEPLETION: POSTTRANSPLANT CYCLOPHOSPHAMIDE

The introduction of high-dose posttransplant cyclophosphamide (PTCy) for GVHD prevention represented a major turning point for HaploSCT. The concept of inducing immune tolerance with PTCy was introduced by Berenbaum and Brown in 1963, who showed that the life of a skin allograft can be prolonged with the use of PTCy administered 1 to 3 days after the allograft.[13] Moreover, Mayumi et al demonstrated that microchimerism and robust tolerance to minor histocompatibility antigens can be achieved in mice receiving allogeneic splenic cells by intraperitoneal high-dose cyclophosphamide administered on days 2 or 3 posttransplant.[14] This concept found its best applicability in allogeneic transplantation, particularly in haploidentical transplantation, in which PTCy induces bidirectional immune tolerance by selectively eliminating the highly dividing alloreactive donor and recipient T-cells generated early after transplant in the setting of an HLA-mismatched transplant, which has led to decreased rates of GVHD and graft rejection.[15] Interestingly, preclinical and clinical studies have shown that stem cells are resistant to high-dose PTCy (because of high levels of aldehyde dehydrogenase present in these cells) and likewise the memory T-cells are spared, leading to excellent hematopoietic engraftment and a better immune reconstitution with relatively lower rates of infections.[16–18] Our group has demonstrated that this approach was superior to complete T-cell depletion approaches because of a significantly lower NRM and risk of infectious complications after transplant.[19]

We first used PTCy-based GVHD prophylaxis for HaploSCT in 2009 in a phase 2 clinical trial shortly after the first clinical trials in humans showed the safety of this approach.[17] Initial studies used a nonmyeloablative conditioning regimen with fludarabine, cyclophosphamide, and 2-Gy TBI, which was associated with a low incidence of grades 2 to 4 aGVHD and NRM at 1 year (35% and 15%, respectively); however, a remarkably high relapse rate of 51% at 1 year was observed particularly for patients with acute leukemia.[17] We hypothesized that a more intense but tolerable conditioning is needed, particularly for these patients; hence, we used our melphalan-based conditioning platform, previously used in T-cell-depleted HaploSCT,[11,19] which includes fludarabine 160 mg/m^2, melphalan 100 to 140 mg/m^2, and thiotepa 5 to 10 mg/kg (subsequently changed to 2-Gy TBI). Dose of thiotepa was decreased because of higher gastrointestinal toxicity in combination with melphalan, and melphalan dose was subsequently decreased for older patients and patients with lymphoma. Initial results were very promising and proved to be very effective in inducing remission in the great majority of patients with leukemia, including those with advanced disease.[11,19] The results of our phase 2 clinical trial in 60 patients, the majority with myeloid leukemias, showed 2-year progression-free survival (PFS) and overall survival (OS) rates of 53% and 55%, respectively, with 2-year NRM and relapse rates of 23% and 24%, respectively.[20] More recently, outcomes of 25 patients with lymphoma who underwent HaploSCT at our institution were reported with 3-year NRM, PFS, and OS of 31%, 49%, and 52%, respectively.[21] Patients with acute myeloid leukemia (AML) and lymphoma receiving haploidentical transplants had similar outcomes with other donor types, but older patients and those with lymphoma appeared to benefit from a reduced-intensity melphalan-based conditioning with lower doses of melphalan (100 mg/m^2),[21–23] with one exception— patients with Hodgkin lymphoma not in remission at transplant, who had better survival with the more intense regimen (140 mg/m^2).[24]

With HaploSCT outcomes significantly improved, we and others have subsequently compared transplant outcomes of patients treated with a haploidentical versus MUD, mismatched MUD, matched related donors, or cord transplants (Table 21–2).[20,25–27] All these single-institution studies uniformly showed at least comparable outcomes between patients treated with a haploidentical transplant with PTCy and those received HLA-matched donors or cord transplants with conventional GVHD prophylaxis and for mismatched MUD received PTCy-based GVHD prophylaxis.[20,25–27] In addition, the final results of the Bone and Marrow Transplant Clinical Trials Network (BMTCTN) phase 3 randomized trial comparing double cord transplant with HaploSCT were recently reported.[28] A total of 368 patients were enrolled, and with a an approximate median follow-up of 24 months, there were significantly better outcomes for HaploSCT in regards to OS (57% vs 46% for cord transplant; $P = .037$) and NRM (11% vs 18% for cord transplant; $P = .039$), albeit comparable PFS rates (41% for HaploSCT vs 35% for cord transplant; $P = .409$) and with no difference in relapse rates.[28] Several retrospective registry studies have been reported since confirming that haploidentical transplants have similar survival with MUD transplants (see Table 21–2).[29–34] Among the first and largest reports, that of Ciurea et al compared outcomes of patients with AML receiving HaploSCT with MUD transplants using the Center for International Blood and Marrow

TABLE 21–2 Selected Transplant Registry Studies Comparing Haploidentical Stem Cell Transplantation with Matched Unrelated Donor Stem Cell Transplantation

Disease Subtype	Patients (n)	aGVHD (%)	cGVHD (%)	TRM (%)	Relapse (%)	3-Year PFS (%)	GRFS
AML[29]							
MAC							—
Haplo							—
MUD	104	16	30	14	44	45	
RIC	1245	33	53	20	39	50	
Haplo							
MUD	88	19	34	9	58	46	
Lymphomas[30]							
Haplo	737	28	52	23	42	44	
MUD with ATG	185	27	13	11	36	47	—
MUD without ATG	241	40	33	13	36	38	—
	491	49	51	20	28	49	—
Hodgkin lymphoma[31]							
Haplo	98	33	26	17	39	43[a]	-
MUD	273	30	41	21	32	45[a]	
DLBCL[32]							
Haplo	132	34	18	22	41	38	36
MUD TCD+	403	32	27	17	38	36	33
MUD TCD-	378	42	57	26	34	37	19
ALL[33]							
Haplo	136	28	44	23	28	49	44
MUD	809	32	39	19	28	53	39
ALL[34b]							
Haplo	487	33	30	24	37	39	31
MUD	974	32	28	24	34	41	32

[a]Two-year survival is reported.
[b]Haploidentical recipients were matched (1:2) with matched unrelated donor (MUD) control participants.
aGVHD, acute graft-versus-host disease; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ATG, antithymocyte globulin; DLBCL, diffuse large B-cell lymphoma; GRFS, GVHD-free relapse-free survival; GVHD, graft-versus-host disease, Haplo, haploidentical stem cell transplantation; MAC, myeloablative conditioning; PFS, progression-free survival; RIC, reduced-intensity conditioning; TCD, T-cell depletion; TRM, transplant-related mortality.

Transplant Registry (CIBMTR) database.[29] Results of this retrospective analysis of 2174 patients showed similar 3-year OS between these two donor sources (45% for HaploSCT vs 50% for MUD with myeloablative conditioning; *P*= .38 and 46% vs 44% with reduced-intensity conditioning [RIC] for HaploSCT and MUD, respectively; *P* = .71). The incidence of grade 2 to 4 aGVHD was lower for haploidentical compared with MUD transplants (16% vs 33% for myeloablative and 19% vs 28% for RIC transplants), likely related to the use of PTCy and the predominant receipt of bone marrow graft in the haploidentical group.[29] Table 21–2 summarizes key findings from selected large transplant registry studies comparing HaploSCT versus MUD transplants in myeloid and lymphoid neoplasms. Based on these findings, we have proposed a prospective multicenter observational study comparing the two donor sources (BMTCTN 1702), which will help answer some of the questions not addressed to date in the retrospective studies.

GRAFT ENGINEERING

Several research strategies are being investigated to optimize the haploidentical graft, maximize the immune recovery, and minimize GVHD after transplant. A very promising approach is selective depletion of αβ T-cells that capable of eliciting GVHD while preserving in the graft the memory T-cells and γδ T

TABLE 21–3 Post transplant Cellular Therapies Aimed at Decreasing Disease Relapse in Haploidentical Hematopoietic Stem Cell Transplantation

Approach	Rationale	Pitfalls
Unmodified DLI	To fight disease relapse via harnessing graft-versus-malignancy effect	Limited experience in HaploSCT Potential for GVHD precipitation Not targeted to specific antigen(s)
Engineered donor lymphocytes with a safety suicide switch	To fight disease relapse via harnessing graft-versus-malignancy effect Safety switch allows T-cell suicide in case of GVHD development	Not targeted to specific antigen(s) Clinical efficacy not yet demonstrated
γ-δ DLI	Infusion of selected γ-δ T-cells No GVHD potential	Graft-versus-malignancy effect not yet demonstrated
CAR T-cells	T-cells engineered to recognize specific antigens (eg, CD19) that provide graft-versus-malignancy effect without GVHD	Clinical efficacy after HaploSCT not yet demonstrated
Infusion of ex vivo expanded NK cells	Potential graft-versus-malignancy effect without GVHD	Clinical efficacy demonstrated in a phase II study

CAR, chimeric antigen receptor; DLA, donor lymphocyte infusion; GVHD, graft-versus-host disease; HaploSCT, haploidentical hematopoietic stem cell transplantation; NK, natural killer.

cells.[12] γδ T-cells possess innate and adaptive immune responses, and similar to natural killer (NK) cells, can function without requiring antigen presentation by the HLA system, which makes them unlikely to generate GVHD.[35] Accordingly, methods to deplete αβ T-cells, leaving the γδ subsets intact, are being investigated with encouraging results especially in children.[36] Another approach involves depletion of naïve T-cells (CD45RA+) thought to play a major role in the development of GVHD in mouse models.[37–39] A phase 1 safety study testing safety of this approach in haploidentical donor transplants at MDACC has been completed, and preliminary results demonstrated excellent control of GVHD. Another approach to mitigate risks of complete T-cell depletion is administration of T-regulatory cells along with conventional T-cells to prevent GVHD; in a preliminary report, this approach was shown to reduce the risk of GVHD and leukemia relapse.[40] Future clinical trials will explore these approaches at MDACC because they may control GVHD and facilitate a rapid immune recovery without the need for posttransplant immunosuppression.

POSTTRANSPLANT CELLULAR THERAPY TO PREVENT DISEASE RELAPSE

With significant improvements in NRM, relapse remains the major cause of treatment failure, not only in HaploSCT patients but also in HLA-matched transplants. Several approaches are currently under investigation at our institution to prevent and treat disease relapse after transplant (Table 21–3).

Unmodified Donor Lymphocyte Infusion

The readily available haploidentical donors can be useful sources of lymphocytes for posttransplant donor lymphocyte infusion (DLI), which could be infused to prevent or treat early relapse. Although there is a theoretical higher risk of inducing severe aGVHD with the use of haploidentical DLI, the incidence of GVHD was not shown to be higher than in HLA-matched transplants,[41–43] possibly in part because of the tolerizing effect of PTCy. In one of the earliest reports, 40 patients with various hematologic malignancies received unmodified haploidentical DLI for relapsed disease after HaploSCT with PTCy-based GVHD prophylaxis.[41] Most patients received a dose of 1 ° 10^6/kg CD3+ T-cells. Acute GVHD developed in 25% of patients, and 15% of patients had grade III to IV aGVHD. Interestingly, most of these patients received cytoreductive therapy before the DLI infusion, and one third of patients achieved a complete response with a median duration of response of 12 months. Two more recent studies reported similar outcomes.[42,43] Because DLIs are expected to be more effective in patients with low tumor burden, such as patients with minimal residual disease,[44] preemptive DLI has been explored in the HaploSCT setting with encouraging results.[45,46] Prophylactic DLIs from haploidentical donors are also being explored for patients with high-risk of relapse after transplant.[47] These reports suggest that cellular

therapy with haploidentical DLI and other therapeutic cells can be applied safely after transplant, and future approaches should focus on improving the safety and efficacy of this therapeutic strategy.[48]

Modified Donor Lymphocyte Infusion Using T-Cells with a Safety Switch (Suicide Gene)

Improved control of GVHD posttransplant can be achieved by inserting a suicide gene in the haploidentical donor T-cells. If significant aGVHD develops, a "safety off switch" can be used to "turn off" these T-cells and avoid excessive aGVHD. This approach has so far been investigated to boost posttransplant immune recovery after T-cell-depleted haploidentical grafts. Ciceri et al infused DLI engineered T-cells to express *herpes simplex virus–thymidine kinase suicide gene* that can be triggered by ganciclovir to induce apoptosis.[49] This was used to boost posttransplant immune reconstitution by adding back T-cells after a complete or partial T-cell-depleted HaploSCT. Grade 1 to 4 aGVHD developed in 20% of the patients, and GVHD was successfully controlled by inducing the suicide gene with ganciclovir. However, ganciclovir may not be the ideal drug in this setting because it is commonly used after transplantation to control cytomegalovirus reactivation. Another approach developed by the Baylor group used modified DLIs engineered to express an inducible *caspase-9 transgene*.[50] This gene can be induced by a synthetic dimerizing drug leading to rapid cell death. GVHD, which occurred in four of the five HaploSCT patients after infusing the safety switch-modified T-cells, was rapidly reversed by administering the dimerizing drug.[50] Long-term outcomes were reported for 10 HaploSCT pediatric patients infused with same product, showing persistence of these modified cells for over 2 years and potentially contributing to opportunistic infection control and promoting endogenous T-cell recovery.[51] This approach could be explored in the future using preemptive DLI in patients who have advanced disease before transplant.

Chimeric Antigen Receptor T-Cells

Although DLI offers nonspecific antitumor activity, its effect is nontargeted. Recently, the introduction of chimeric antigen receptor (CAR) T-cells that can recognize a specific antigen on cancer cell surface has demonstrated excellent activity in CD19-expressing lymphoid malignancies. The Food and Drug Administration granted accelerated approval for treatment of relapsed or refractory B-cell acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL). In the initial pilot studies, Maude et al used autologous CARs against CD19 (CTL019) in 30 patients with relapsed refractory ALL and achieved complete remission in 90% of patients.[52] Subsequently, 75 patients were enrolled in a phase 2 clinical trial that confirmed an overall remission rate of 81% at 3 years, with 1-year PFS and OS rates of 50% and 76%, respectively.[53] Likewise, CD19 CAR T-cell therapy showed impressive results in patients with relapsed or refractoryDLBCL.[54,55] Our group has been exploring the use of CAR T-cells in the peritransplant setting to improve outcomes after autologous and allogeneic transplantation.[56,57] Results from the phase 1 clinical trial showed very encouraging outcomes, including in HaploSCT recipients ($n = 8$), with 1-year PFS and OS rates of 75% and 100%, respectively, and with no increased risk of GVHD.[56] These preliminary results suggested that allogeneic CAR T-cells can be safely given peritransplant without significant GVHD to decrease relapse posttransplant. Future studies should explore the use of CAR T-cells after allo-SCT for different diseases.

Natural Killer Cells and Killer Immunoglobulin-like Receptor Mismatch

NK cells are part of the innate immune system and normally are involved in identifying and killing tumor cells or virally infected cells. NK cells recognize and target "foreign" cells that lack one or more HLA class I alleles specific to the inhibitory receptors (killer immunoglobulin-like receptors [KIRs]).[58] NK cells, which target malignantly transformed or virally infected cells, do not contribute to the development of GVHD, making them ideal to use to decrease relapse in the posttransplant setting. Prior studies in T-cell-depleted haploidentical transplants showed a lower incidence of relapse when patients had a KIR-ligand mismatched (KIR-LM) donor.[59] Several studies suggest a lower risk of relapse with donors who possess specific activating *KIR* genes such as *KIR2DS1, KIR2DS2,* or the KIR "B" haplotype.[60–62] Although no definitive role for a KIR-LM donor has been confirmed to date, our group explored the use of high doses of ex vivo expanded and activated NK cells before and after transplant with very encouraging results. In a phase 1 dose-escalation stud,[63] using the mb-IL21 method as developed at MDACC,[64] 13 patients with high-risk myeloid malignancies were infused with mb-IL21–expanded donor NK cells on days -2, +7, and +28 of HaploSCT. The study demonstrated feasibility of infusing high doses of ex vivo expanded NK cells without significant toxicities or increased risk of GVHD and with notable low posttransplant relapse rates and incidence of viral infections.[63] Preliminary results from a subsequent phase 2 study confirmed the findings, and in a matched-pair analysis independently performed with a CIBMTR cohort, NK cell–treated patients showed a significantly lower relapse and improved PFS than patients who did not receive NK

cells.[65] Based on these data, a multicenter phase 2 study was initiated by the BMTCTN (BMTCTN 1803).

DONOR SELECTION FOR HAPLOIDENTICAL STEM CELL TRANSPLANTATION AND RISKS FROM DONOR-SPECIFIC ANTI–HUMAN LEUKOCYTE ANTIGEN ANTIBODIES

Unlike matched related donor transplants, in whom the number of matched donors is usually small, multiple donors are usually available to choose from in the HaploSCT. Several factors are considered when choosing the best donor.[66] One of the first and most important factors is to evaluate is the presence of donor-specific anti-HLA antibodies (DSAs).[67,68] Patients may develop antibodies against foreign HLA antigens, particularly parous women and multiply transfused patients. We have shown for the first time that patients with high levels of complement-fixing anti-HLA antibodies against donor HLA antigens are at high risk of engraftment failure.[68] Routine evaluation of all donors with HLA mismatches has now been incorporated into standard practice worldwide. Criteria to optimize donor selection to improve outcomes have been developed.[62,66,69] Patients with high DSAs should be avoided as donors but if not possible should be treated to decrease risk before transplant.[66] Younger donors, male donors, fathers rather than mothers, and first-degree to second-degree haploidentical donors are preferred for recipients of haploidentical transplants with PTCy.[66,67] In addition, ABO-matched or minor mismatched grafts are preferred to major ABO-mismatched grafts.[66] There is controversy whether patients should be selected based on NK cell alloreactivity; more studies are needed to clarify this aspect.[68]

CONCLUSIONS AND FUTURE DIRECTIONS

The field of HaploSCT has significantly grown over the past decade with the introduction of PTCy and novel methods of partial T-cell depletion. These newer techniques effectively control strong alloreactive reactions in HaploSCT and are associated with robust immune recovery, translating into fewer infectious complications and lower NRM. Data from several studies suggest that haploidentical transplants have similar outcomes to MUD transplants, but when faster transplantation is needed, haploidentical grafts may be preferred.[70] Because of these, the use of this type of transplant continues to expand worldwide. Prospective controlled clinical trials are needed to address important questions in different clinical settings and impact of donor choice and time to transplant on outcomes because approximately half of patients do not get to transplant in time. In addition, exploration of various cellular therapy interventions in the peritransplant setting, particularly NK cell therapy, represents a great opportunity to improve the graft-versus-malignancy effect and decrease relapse posttransplant, which is the next most important next step in improving transplant outcomes.

MD ANDERSON PRACTICE TIPS

- Haploidentical transplantation use at MDACC has increased significantly over past decade, and it is a preferred alternative donor source in the absence of a fully matched donor.
- There are no prospective randomized clinical trials comparing haploidentical with matched unrelated transplants. Haploidentical transplant is preferred over double cord transplant. MDACC is a lead in the ongoing multicenter BMTCTN prospective observational clinical trial comparing the outcomes of alternative donors in the absence of a fully matched sibling donor.
- The introduction of PTCy for GVHD prevention represented a major turning point for improving outcomes of haploidentical transplants. The concept was first adopted at MDACC in 2009, incorporated into our fludarabine–melphalan conditioning platform, and since has become our standard of care option.
- Incorporation of donor NK cell into haploidentical transplant for patients with high-risk myeloid malignancies has led to significantly deceased relapse and viral infections and improved survival outcome in our experience. A multicenter phase 2 study is initiated by the BMTCTN based on our data.
- The DSAs remain one of the most important factors to consider for best haploidentical donor because the presence of antibodies is associated with high risk of graft failure. Patients with high DSAs should be avoided as donors but if not possible should be treated to decrease risk before transplant.
- Prospective controlled clinical trials are a priority to address important questions in different clinical settings, impact of donor choice, and time to transplant on outcomes because approximately half of patients do not get to transplant in time.

REFERENCES

1. Ciurea SO, Bayraktar UD. "No donor"? Consider a haploidentical transplant. *Blood reviews.* 2015;29(2):63-70.
2. Allan DS, Takach S, Smith S, Goldman M. Impact of declining fertility rates in Canada on donor options in blood and marrow transplantation. *Biol Blood Marrow Transplant.* 2009;15(12):1634-1637.
3. Gragert L, Eapen M, Williams E, et al. HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry. *N Engl J Med.* 2014;371(4):339-348.
4. Beatty PG, Clift RA, Mickelson EM, et al. Marrow transplantation from related donors other than HLA-identical siblings. *N Engl J Med.* 1985;313(13):765-771.
5. Clift RA, Hansen JA, Thomas ED, et al. Marrow transplantation from donors other than HLA-identical siblings. *Transplantation.* 1979;28(3):235-242.
6. Powles RL, Morgenstern GR, Kay HE, et al. Mismatched family donors for bone-marrow transplantation as treatment for acute leukaemia. *Lancet.* 1983;1(8325):612-615.
7. Ball LM, Lankester AC, Bredius RG, et al. Graft dysfunction and delayed immune reconstitution following haploidentical peripheral blood hematopoietic stem cell transplantation. *Bone Marrow Transplant.* 2005;35(suppl 1):S35-S38.
8. Rizzieri DA, Koh LP, Long GD, et al. Partially matched, nonmyeloablative allogeneic transplantation: clinical outcomes and immune reconstitution. *J Clin Oncol.* 2007;25(6):690-697.
9. Mehta J, Singhal S, Gee AP, et al. Bone marrow transplantation from partially HLA-mismatched family donors for acute leukemia: single-center experience of 201 patients. *Bone Marrow Transplant.* 2004;33(4):389-396.
10. Aversa F, Tabilio A, Velardi A, et al. Treatment of high-risk acute leukemia with T-cell-depleted stem cells from related donors with one fully mismatched HLA haplotype. *N Engl J Med.* 1998;339(17):1186-1193.
11. Ciurea SO, Saliba R, Rondon G, et al. Reduced-intensity conditioning using fludarabine, melphalan and thiotepa for adult patients undergoing haploidentical SCT. *Bone Marrow Transplant.* 2010;45(3):429-436.
12. Bertaina A, Merli P, Rutella S, et al. HLA-haploidentical stem cell transplantation after removal of alphabeta+ T and B cells in children with nonmalignant disorders. *Blood.* 2014;124(5):822-826.
13. Berenbaum MC, Brown IN. Prolongation of homograft survival in mice with single doses of cyclophosphamide. *Nature.* 1963;200:84.
14. Mayumi H, Himeno K, Shin T, Nomoto K. Drug-induced tolerance to allografts in mice. VI. Tolerance induction in H-2-haplotype-identical strain combinations in mice. *Transplantation.* 1985;40(2):188-194.
15. Luznik L, Jalla S, Engstrom LW, et al. Durable engraftment of major histocompatibility complex-incompatible cells after nonmyeloablative conditioning with fludarabine, low-dose total body irradiation, and posttransplantation cyclophosphamide. *Blood.* 2001;98(12):3456-3464.
16. Jones RJ, Barber JP, Vala MS, et al. Assessment of aldehyde dehydrogenase in viable cells. *Blood.* 1995;85(10):2742-2746.
17. Luznik L, O'Donnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. *Biol Blood Marrow Transplant.* 2008;14(6):641-650.
18. Kanakry CG, Ganguly S, Zahurak M, et al. Aldehyde dehydrogenase expression drives human regulatory T cell resistance to posttransplantation cyclophosphamide. *Sci Transl Med.* 2013;5(211):211ra157.
19. Ciurea SO, Mulanovich V, Saliba RM, et al. Improved early outcomes using a T cell replete graft compared with T cell depleted haploidentical hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2012;18(12):1835-1844.
20. Gaballa S, Ge I, El Fakih R, et al. Results of a 2-arm, phase 2 clinical trial using post-transplantation cyclophosphamide for the prevention of graft-versus-host disease in haploidentical donor and mismatched unrelated donor hematopoietic stem cell transplantation. *Cancer.* 2016;122(21):3316-3326.
21. Saini NY, Saliba RM, Rondon G, et al. Impact of donor type and melphalan dose on allogeneic transplantation outcomes for patients with lymphoma. *Biol Blood Marrow Transplant.* 2019;25(7):1340-1346.
22. Ciurea SO, Kongtim P, Varma A, et al. Is there an optimal conditioning for older patients with AML receiving allogeneic hematopoietic cell transplantation? *Blood.* 2020;135(6):449-452.
23. Brammer JE, Khouri I, Gaballa S, et al. Outcomes of haploidentical stem cell transplantation for lymphoma with melphalan-based conditioning. *Biol Blood Marrow Transplant.* 2016;22(3):493-498.
24. Ciurea SO, Kongtim P, Srour S, et al. Can we cure refractory Hodgkin's lymphoma with transplantation? *Bone Marrow Transplant.* 2021;56(1):278-281.
25. Di Stasi A, Milton DR, Poon LM, et al. Similar transplantation outcomes for acute myeloid leukemia and myelodysplastic syndrome patients with haploidentical versus 10/10 human leukocyte antigen-matched unrelated and related donors. *Biol Blood Marrow Transplant.* 2014 ;20(12):1975-1981
26. Bashey A, Zhang X, Sizemore CA, et al. T-cell-replete HLA-haploidentical hematopoietic transplantation for hematologic malignancies using post-transplantation cyclophosphamide results in outcomes equivalent to those of contemporaneous HLA-matched related and unrelated donor transplantation. *J Clin Oncol.* 2013;31(10):1310-1316.
27. Raiola AM, Dominietto A, di Grazia C, et al. Unmanipulated haploidentical transplants compared with other alternative donors and matched sibling grafts. *Biol Blood Marrow Transplant.* 2014;20(10):1573-1579.
28. Brunstein CG, O'Donnell P, Eapen M, et al. Results of Blood and Marrow Transplant Clinical Trials Network Protocol 1101 a multicenter phase III randomized trial of transplantation of double umbilical cord blood vs. HLA-haploidentical-related bone marrow for hematologic malignancy. Paper presented at: Transplantation & Cellular Therapy Meetings of ASTCT and CIBMTR2020; Orlando, Florida, 2020.
29. Ciurea SO, Zhang MJ, Bacigalupo AA, et al. Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia. *Blood.* 2015;126(8):1033-1040.
30. Kanate AS, Mussetti A, Kharfan-Dabaja MA, et al. Reduced-intensity transplantation for lymphomas using haploidentical related donors vs HLA-matched unrelated donors. *Blood.* 2016;127(7):938-947.
31. Martinez C, Gayoso J, Canals C, et al. Post-transplantation cyclophosphamide-based haploidentical transplantation as alternative to matched sibling or unrelated donor transplantation for Hodgkin lymphoma: a registry study of the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation. *J Clin Oncol.* 2017;35(30):3425-3432.
32. Dreger P, Sureda A, Ahn KW, et al. PTCy-based haploidentical vs matched related or unrelated donor reduced-intensity conditioning transplant for DLBCL. *Blood Adv.* 2019;3(3):360-369.
33. Shem-Tov N, Peczynski C, Labopin M, et al. Haploidentical vs. unrelated allogeneic stem cell transplantation for acute lymphoblastic leukemia in first complete remission: on behalf of the ALWP of the EBMT. *Leukemia.* 2020;34(1):283-292.
34. Al Malki MM, Yang D, Labopin M, et al. Comparing transplant outcomes in ALL patients after haploidentical with PTCy or matched unrelated donor transplantation. *Blood Adv.* 2020;4(9):2073-2083.

35. Bonneville M, O'Brien RL, Born WK. Gammadelta T cell effector functions: a blend of innate programming and acquired plasticity. *Nat Rev Immunol.* 2010;10(7):467-478.
36. Locatelli F, Bauquet A, Palumbo G, et al. Negative depletion of alpha/beta+ T cells and of CD19+ B lymphocytes: a novel frontier to optimize the effect of innate immunity in HLA-mismatched hematopoietic stem cell transplantation. *Immunol Lett.* 2013;155(1-2):21-23.
37. Anderson BE, McNiff J, Yan J, et al. Memory CD4+ T cells do not induce graft-versus-host disease. *J Clin Invest.* 2003;112(1):101-108.
38. Chen BJ, Cui X, Sempowski GD, et al. Transfer of allogeneic CD62L- memory T cells without graft-versus-host disease. *Blood.* 2004;103(4):1534-1541.
39. Zheng H, Matte-Martone C, Li H, et al. Effector memory CD4+ T cells mediate graft-versus-leukemia without inducing graft-versus-host disease. *Blood.* 2008;111(4):2476-2484.
40. Martelli MF, Di Ianni M, Ruggeri L, et al. HLA-haploidentical transplantation with regulatory and conventional T-cell adoptive immunotherapy prevents acute leukemia relapse. *Blood.* 2014;124(4):638-644.
41. Zeidan AM, Forde PM, Symons H, et al. HLA-haploidentical donor lymphocyte infusions for patients with relapsed hematologic malignancies after related HLA-haploidentical bone marrow transplantation. *Biol Blood Marrow Transplant.* 2014;20(3):314-318.
42. Ghiso A, Raiola AM, Gualandi F, et al. DLI after haploidentical BMT with post-transplant CY. *Bone Marrow Transplant.* 2015;50(1):56-61.
43. Goldsmith SR, Slade M, DiPersio JF, et al. Donor-lymphocyte infusion following haploidentical hematopoietic cell transplantation with peripheral blood stem cell grafts and PTCy. *Bone Marrow Transplant.* 2017;52(12):1623-1628.
44. Tan Y, Du K, Luo Y, et al. Superiority of preemptive donor lymphocyte infusion based on minimal residual disease in acute leukemia patients after allogeneic hematopoietic stem cell transplantation. *Transfusion.* 2014;54(6):1493-1500.
45. Yan CH, Liu DH, Liu KY, et al. Risk stratification-directed donor lymphocyte infusion could reduce relapse of standard-risk acute leukemia patients after allogeneic hematopoietic stem cell transplantation. *Blood.* 2012;119(14):3256-3262.
46. Mo XD, Zhang XH, Xu LP, et al. Salvage chemotherapy followed by granulocyte colony-stimulating factor-primed donor leukocyte infusion with graft-vs.-host disease control for minimal residual disease in acute leukemia/myelodysplastic syndrome after allogeneic hematopoietic stem cell transplantation: prognostic factors and clinical outcomes. *Eur J Haematol.* 2016;96(3):297-308.
47. Dholaria B, Savani BN, Labopin M, et al. Clinical applications of donor lymphocyte infusion from an HLA-haploidentical donor: consensus recommendations from the Acute Leukemia Working Party of the EBMT. *Haematologica.* 2020;105(1):47-58.
48. Kongtim P, Lee DA, Cooper LJ, et al. Haploidentical hematopoietic stem cell transplantation as a platform for post-transplantation cellular therapy. *Biol Blood Marrow Transplant.* 2015;21(10):1714-1720.
49. Ciceri F, Bonini C, Stanghellini MT, et al. Infusion of suicide-gene-engineered donor lymphocytes after family haploidentical haemopoietic stem-cell transplantation for leukaemia (the TK007 trial): a non-randomised phase I-II study. *Lancet Oncol.* 2009;10(5):489-500.
50. Di Stasi A, Tey SK, Dotti G, et al. Inducible apoptosis as a safety switch for adoptive cell therapy. *N Engl J Med.* 2011;365(18):1673-1683.
51. Zhou X, Di Stasi A, Tey SK, et al. Long-term outcome after haploidentical stem cell transplant and infusion of T cells expressing the inducible caspase 9 safety transgene. *Blood.* 2014;123(25):3895-3905.
52. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med.* 2014;371(16):1507-1517.
53. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med.* 2018;378(5):439-448.
54. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med.* 2017;377(26):2531-2544.
55. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med.* 2019;380(1):45-56.
56. Kebriaei P, Singh H, Huls MH, et al. Phase I trials using Sleeping Beauty to generate CD19-specific CAR T cells. *J Clin Invest.* 2016;126(9):3363-3376.
57. Srour SA, Singh H, McCarty J, et al. Long-term outcomes of Sleeping Beauty-generated CD19-specific CAR T-cell therapy for relapsed-refractory B-cell lymphomas. *Blood.* 2020;135(11):862-865.
58. Ruggeri L, Capanni M, Casucci M, et al. Role of natural killer cell alloreactivity in HLA-mismatched hematopoietic stem cell transplantation. *Blood.* 1999;94(1):333-339.
59. Ruggeri L, Capanni M, Urbani E, et al. Effectiveness of donor natural killer cell alloreactivity in mismatched hematopoietic transplants. *Science.* 2002;295(5562):2097-2100.
60. Cooley S, Trachtenberg E, Bergemann TL, et al. Donors with group B KIR haplotypes improve relapse-free survival after unrelated hematopoietic cell transplantation for acute myelogenous leukemia. *Blood.* 2009;113(3):726-732.
61. Sivori S, Carlomagno S, Falco M, et al. Natural killer cells expressing the KIR2DS1-activating receptor efficiently kill T-cell blasts and dendritic cells: implications in haploidentical HSCT. *Blood.* 2011;117(16):4284-4292.
62. Chen DF, Prasad VK, Broadwater G, et al. Differential impact of inhibitory and activating killer Ig-like receptors (KIR) on high-risk patients with myeloid and lymphoid malignancies undergoing reduced intensity transplantation from haploidentical related donors. *Bone Marrow Transplant.* 2012;47(6):817-823.
63. Ciurea SO, Schafer JR, Bassett R, et al. Phase 1 clinical trial using mbIL21 ex vivo-expanded donor-derived NK cells after haploidentical transplantation. *Blood.* 2017;130(16):1857-1868.
64. Denman CJ, Senyukov VV, Somanchi SS, et al. Membrane-bound IL-21 promotes sustained ex vivo proliferation of human natural killer cells. *PLoS One.* 2012;7(1):e30264.
65. Stefan O, Ciurea RS, Soebbing D, et al. Enhanced antitumor effect and lower viral reactivation with high doses of ex vivo expanded NK cells administered after haploidentical transplantation. Paper presented at: American Society of Clinical Oncology; 2019.
66. Ciurea SO, Champlin RE. Donor selection in T cell-replete haploidentical hematopoietic stem cell transplantation: knowns, unknowns, and controversies. *Biol Blood Marrow Transplant.* 2013;19(2):180-184.
67. Yoshihara S, Maruya E, Taniguchi K, et al. Risk and prevention of graft failure in patients with preexisting donor-specific HLA antibodies undergoing unmanipulated haploidentical SCT. *Bone Marrow Transplant.* 2012;47(4):508-515.
68. Ciurea SO, de Lima M, Cano P, et al. High risk of graft failure in patients with anti-HLA antibodies undergoing haploidentical stem-cell transplantation. *Transplantation.* 2009;88(8):1019-1024.
69. Wang Y, Chang YJ, Xu LP, et al. Who is the best donor for a related HLA haplotype-mismatched transplant? *Blood.* 2014;124(6):843-850.
70. Ciurea SO, Bittencourt MCB, Milton DR, et al. Is a matched unrelated donor search needed for all allogeneic transplant candidates? *Blood Adv.* 2018;2(17):2254-2261.

This page intentionally left blank

22 Cellular Therapy in Allogeneic Hematopoietic Cell Transplantation

Amanda Olson
Jeremy Ramdial
Uri Greenbaum
Paul Lin
Katayoun Rezvani
Partow Kebriaei

KEY CONCEPTS

- The efficacy of allogeneic hematopoietic cell transplantation (HCT) is based on the graft-versus-tumor effect, by which the donor immune system achieves immunologic control of the tumor via the human leukocyte antigen (HLA) system.
- Three key barriers to successful HCT are relapse caused by failure of immunologic control of the underlying disease, graft-versus-host disease (GVHD), and infectious complications, and studies are underway to improve on these complications.
- Strategies to mitigate relapse include using prophylactic donor lymphocyte infusions, chimeric antigen receptor modified T-cells derived typically from the patient, and natural killer (NK) T-cells.
- In contrast to B and T lymphocytes, NK T-cells do not express rearranged, antigen-specific receptors and as a consequence have a low risk for GVHD, allowing the use of allogeneic NK cells. An allogeneic product is advantageous because it is readily available and furthermore uses healthy immune cells for product production.
- The pathogenesis of GVHD is complex and includes the differentiation of naïve donor T-cells into effector cells that attack host tissues. Increasing numbers of HLA mismatches are associated with higher incidence of GVHD and transplant-related mortality. Grades II to IV acute GVHD occur in 25% to 60% of cases with matched related donors and 45% to 70% of cases with matched unrelated donors. Recent improvements in GVHD include the approval of ruxolitinib for steroid-refractory acute GVHD and the use of posttransplant cyclophosphamide to decrease the incidence of GVHD.
- Viral infection is a major cause of death after HCT, resulting from cellular and humoral immune deficiency. Viral infections of particular relevance after HCT are cytomegalovirus, Epstein-Barr virus, the polyoma viruses BK and JC, adenovirus, and human herpesvirus 6. Pharmacotherapy for these infections has limited efficacy. Viral-specific T-cells directed against these infections is feasible to generate and effective.

The efficacy of allogeneic hematopoietic cell transplantation (HCT) in hematologic malignancies can in large part be attributed to a graft-versus-tumor (GVT) effect, by which the donor immune system achieves immunologic control of the tumor. As such, it is the prototype of cellular therapy. The human leukocyte antigen (HLA) system is fundamental to transplant biology. The HLAs are highly polymorphic proteins that have a key role in antigen presentation and immune regulation. Class I HLAs are expressed on the surfaces of all nucleated cells; class II are expressed on specialized antigen-presenting cells (APCs), such as macrophages, dendritic cells, and B cells.

Peptides derived from microbes are presented on class I HLAs to CD8+ T-cells and result in immunologic destruction of infected cells; class II HLAs are recognized by CD4+ T-cells. T-cell activation requires costimulatory signals from the APC, specifically CD80/86 binding to CD28 or LFA-3 binding to CD2.[1] Absence of a costimulatory signal results in T-cell anergy, which is a key mechanism of peripheral immune tolerance to self-antigen in normal immune

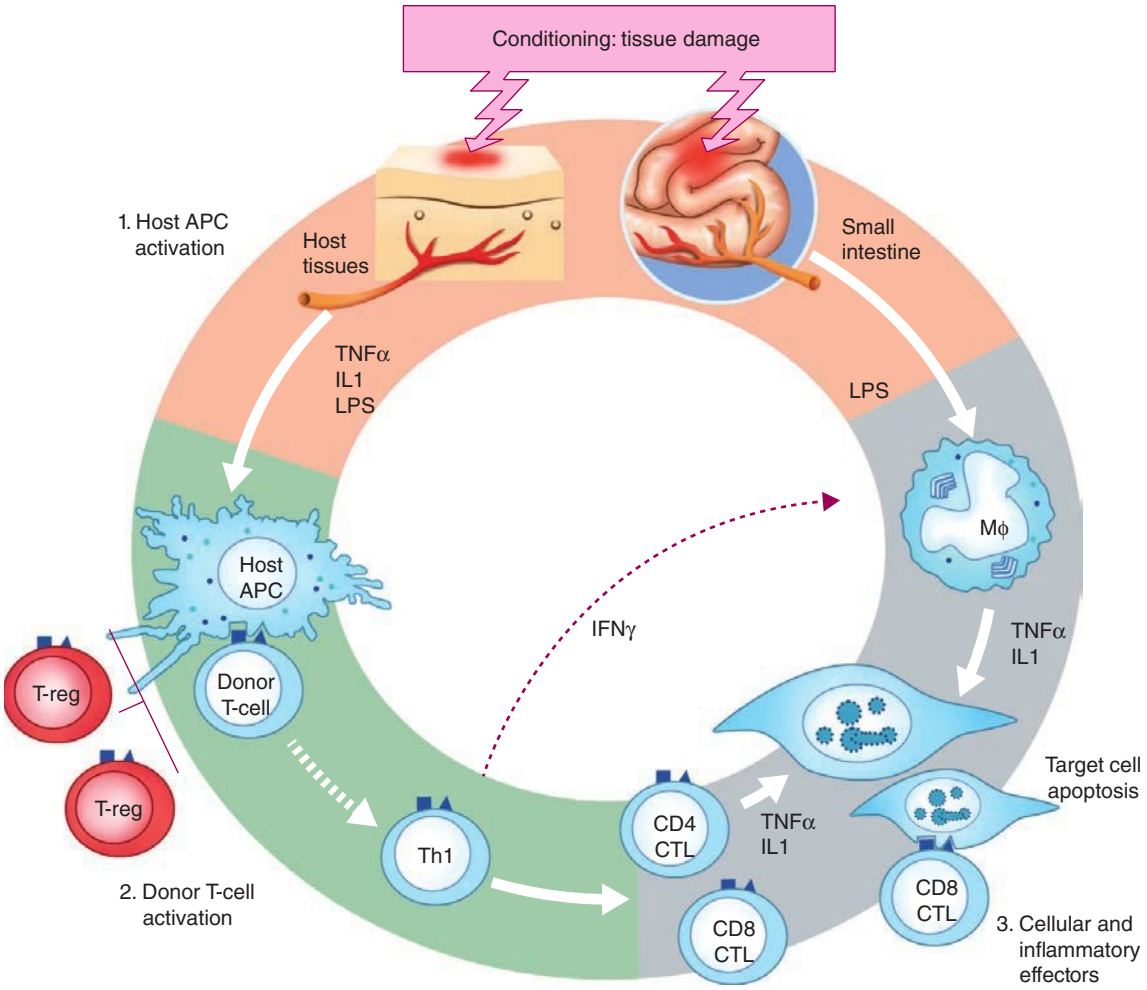


FIGURE 22–1 **Pathogenesis of graft-versus-host disease (GVHD). In phase I, chemotherapy or radiotherapy as part of transplant conditioning causes host tissue damage and release of inflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin (IL)-1, and IL-6, with resulting priming of host antigen-presenting cells (APCs). In phase II, host APCs activate mature donor cells, which subsequently proliferate and differentiate; release of additional effector molecules, such as TNF-α and IL-1, mediates further tissue damage. Lipopolysaccharide (LPS) that has leaked through damaged intestinal mucosa triggers additional TNF-α production. The TNF-α can damage tissue directly by inducing necrosis and apoptosis in the skin and gastrointestinal tract through either TNF receptors or the Fas pathway. TNF-α plays a direct role in intestinal GVHD damage, which further amplifies damage in the skin, liver, and lung in a "cytokine storm." The process culminates in death of host cells through CD8-positive cytotoxic T-cell-mediated apoptosis. (Reproduced with permission from Ferrara JL, Levine JE, Reddy P, et al: Graft-versushost disease, *Lancet* 2009 May 2;373(9674):1550-1561)**

regulation. Early after transplantation, there is a "cytokine storm"; release of proinflammatory cytokines, such as tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6), is induced by tissue damage from the conditioning regimen, activating the host innate immune system (Fig. 22–1). Donor T-cells interact with host APCs and recognize foreign peptides; helper T-cells produce further cytokines, especially IL-2, and prime host APCs via CD40–CD40L interaction. Differentiation of naïve donor T-cells into effector cells subsequently occurs, resulting in immunologic attack on host tissues and the potential development of graft-versus-host disease (GVHD).[2] Increasing numbers of HLA mismatches are associated with higher incidence of GVHD and transplant-related mortality (TRM) rate.[3] However, even in a fully HLA matched HCT, GVHD still occurs because of donor T-cells directed against minor histocompatibility antigens (MiHAs), polymorphic peptides displayed on host HLA molecules.

There are three key barriers to successful HCT: relapse caused by failure of immunologic control of the underlying disease, GVHD, and infectious complications. Herein, we review these issues in greater detail with an emphasis on recent cellular therapeutic approaches to address these complications.

ENHANCING GRAFT-VERSUS-TUMOR EFFECT TO OVERCOME RELAPSE

Pathophysiology of the Graft-versus-Tumor Effect

The GVT effect occurs because of a predominantly T-cell-mediated immunologic attack on tumor cells. In HLA-identical transplants, GVT effect is mediated by naïve T-cells; for development of effector function, these must first be primed by host APCs. This requires the following: presentation of MiHAs or tumor-specific antigens on HLA; appropriate costimulatory molecules, including CD28, OX40, CD40L, and 41BB; and an appropriate "third signal," provided by IL-12, interferon g (IFN-g) or adjuvant.[4] Restraining influences limiting the degree of immune activation are present to protect the host from an excessive immune response and include expression of CTLA4 (which competes with CD28 for binding to CD80/86) and programmed cell death protein 1 (PD-1) and its interactions with its ligand PDL1, which limit T-cell activation and expansion during normal, pathogen-directed immune responses.

Soon after transplant, there are activation and expansion of MiHA-reactive T-cells followed by a decline, similar to that seen in pathogen-directed immune reactions. This may in part relate to the development of peripheral tolerance or anergy and to replacement of host hematopoiesis, with resulting loss of host APCs. For tumor-associated antigen presentation to continue, there must be cross presentation on donor APCs. In addition, the initial allogeneic response to MiHAs results in recruitment of T-cells targeting either tumor-associated antigens or nonpolymorphic genes, which are either overexpressed or aberrantly expressed by the tumor.[4]

Tumor Escape From Immunologic Destruction

Tumors use numerous mechanisms to escape immunologic destruction, including the following:

- Induction of regulatory T-cells
- Production of inhibitory cytokines
- Downregulation of costimulatory molecules and HLA class I
- Induction of co-inhibitory molecules
- Induction of myeloid-derived suppressor cells in the microenvironment that inhibit immune responses through multiple mechanisms.
- Invasion of immunologically privileged sites

Cellular therapeutic approaches are designed with the intent to abrogate these escape mechanisms.

Cellular Therapy to Induce Graft-Versus-Tumor Effect

Donor Lymphocyte Infusions

Donor lymphocyte infusion (DLI) may induce remissions in patients with molecular or overt low volume relapse of their malignancy and can reverse CD8+ T-cell exhaustion.[5] However, the likelihood of success varies significantly according to the underlying disease. Chronic myelogenous leukemia is most sensitive; follicular lymphoma (FL) and Hodgkin lymphoma (HL) are also highly responsive.[6,7] Responses to DLI in AML or myelodysplastic syndrome (MDS) are less frequent, and durability is often poor. Acute lymphoblastic leukemia (ALL) is the least responsive to DLI. Reported response rates are 60% to 73% in CML, 15% to 29% in AML, and 0% to 18% in ALL.[8] Limitations to DLI therapy include most notably, development of GVHD, which occurs in 40% to 60% of patients.[8] The GVHD rates may be reduced by reducing the T-cell dose; a dose–response relationship exists for both GVT and GVHD effects. Additionally, if there is insufficient residual donor hematopoiesis before DLI, eradication of host hematopoiesis by the infused lymphocytes can result in marrow aplasia; chimerism studies should therefore be performed before DLI to ensure adequate donor hematopoiesis.[9] Finally, responses to DLI may not be seen for up to 2 months.[8]

In efforts to enhance the response to DLI in AML, combination therapy with hypomethylating agents (HMAs) has been studied. Based on preclinical studies that azacitidine increases T-regulatory (T-reg) cells, suppressing GVHD while sparing GVT, Ghobadi and colleagues reported on a phase I trial testing three escalating doses of azacitidine (30 mg/m^2,45 mg/m^2, 75 mg/m^2) administered after DLI.[10] With a median follow-up period of 5.2 months, 6 of 8 treated patients responded, with no grades III or IV GVHD noted.[10] Schroeder and colleagues reviewed the outcomes of 36 patients with relapsed AML ($n = 29$) or MDS ($n = 7$) after HCT and treated with DLI and median two cycles of decitabine.[11] The median duration of complete remission (CR) was 10 months for the group, with acute and chronic GVHD rates of 19% and 5%, respectively; the 2-year survival rate was only 11%,[11] underscoring the limited impact of DLI, even with the addition of other agents.

Prophylactic Donor Lymphocyte Infusion in High-Risk Patients

The limited benefit of DLI in overt relapse after transplant has led investigators to study the potential of DLI for the prevention of relapse. In a study by Kothari and colleagues, 75 patients with high-risk hematologic malignancies underwent an alemtuzumab-based, T-cell-deplete transplant with matched related donors (MRDs $n = 46$) or matched unrelated donors (MUDs; $n = 29$) with planned early withdrawal of immune suppression (WOI) and DLI in efforts to decrease relapse.[12] Twenty-eight patients with MRDs were able to undergo early WOI, and 93% received at least one DLI; only seven patients with MUDs were able to undergo WOI and 57% received at least one DLI. The estimated 2-year progression-free survival (PFS) and overall survival (OS) rates for all patients were 41% and 51%, respectively; for patients who received at least one prophylactic DLI, 2-year PFS and OS were 57% and 67%. In addition, patients who received DLI had faster immune reconstitution and improved donor chimerism. This novel approach may be an effective strategy in patients undergoing MRD transplants.

In another study, low-dose azacitidine and DLI was tested in a prophylactic fashion in patients with AML ($n = 20$) or MDS ($n = 10$) deemed at high risk for relapse after allogeneic HCT.[13] The median number of azacitidine cycles was 5 (range, 1–12) with 33% completing the 12 intended cycles; 17 patients received 1-3 infusions of DLI. At a median follow-up period of 49 months (range, 27–63 months), the OS and disease-free survival (DFS) rates were 65.5% at 2 years; the rates for 2-year grades I to III acute GVHD and chronic GVHD were 31.5% and 53%, respectively, suggesting that this may be a reasonable strategy in high-risk patients.[13]

Cellular Therapy to Prevent Relapse: Chimeric Antigen Receptor T-Cells

Chimeric antigen receptor (CAR) T-cells have become one of the new and promising treatment modalities for hematologic malignancies. They are genetically modified T-cells, transfected with a viral vector or a plasmid coding for a chimeric receptor (Fig. 22–2). The extracellular portion of the receptor is a single-chain variable fragment (scFv) of an antibody, acting as the antigen recognition domain. First-generation constructs contained only the extracellular scFv domain coupled with an activating intracellular CD3 ζ component. because of limited in vivo proliferation and persistence of CAR T-cells, second-generation CAR includes an additional costimulatory domain (eg, CD28 or 4-1BB), resulting in improved CAR T proliferation and persistence in vivo, and third-generation CAR constructs have two costimulatory domains (eg, both CD28 and 4-1BB), with potential for even better expansion and longer persistence. This advantage for third-generation CAR was shown in a study in which both second- and third-generation CARs were infused simultaneously in the same patient.[14] Since second-generation CAR T-cells were approved by the Food and Drug Administration (FDA) in 2017, they are becoming more widely available and used as standard of care therapy for patients with relapsed or refractory B-cell non-Hodgkin lymphoma (NHL) or ALL. CAR T therapy induce high rates of responses, up to 74% in NHL and 90% in ALL, but are also associated

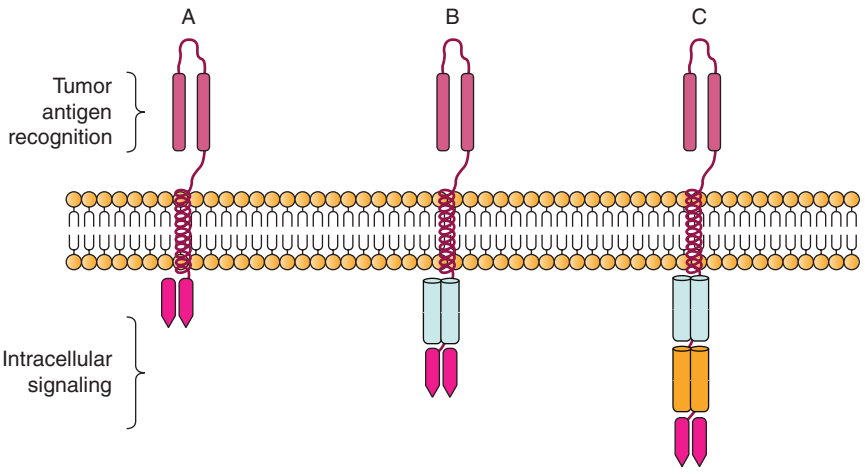


FIGURE 22–2 Schematic of chimeric antigen receptor (CAR) constructs. A. The first-generation CAR consists of an antigen recognition domain (usually a single-chain monoclonal antibody [scFv]) targeting a tumor-associated antigen), coupled via an extracellular hinge domain and transmembrane domain to an intracytoplasmic signaling domain, typically the CD3ζ chain. B. C. In second- and third-generation CAR constructs, the intracellular component includes costimulatory domains, typically 4-1BB, CD28, or both, that enhance persistence and proliferation.

with rates of serious toxicity in the form of cytokine release syndrome (CRS) of up to 44% and severe neurotoxicity of up to 42%.[15] With a longer follow-up period, up to 50% of ALL patients and 60% of NHL patients relapse, sometimes with an antigen-negative relapse.[16,17] In many ALL studies, despite a CR rate of 70% to 90% after CAR T therapy, more than half relapse within 1 year without consolidative allogeneic HCT.[18–25] Thus, studies are underway to investigate the ideal sequence for these therapies and if there is any benefit to combining with transplant.

Chimeric Antigen Receptor T-Cell Therapy Combined with Autologous Transplant

Several studies have looked at CAR T administration combined with autologous HCT for NHL. Sauter and colleagues reported on 15 patients with relapsed or refractory NHL who had positron emission tomography–positive disease before HCT and showed a 2-year PFS of 30% when CAR T-cells were administered on days 2 and 3 of the transplant.[26] Furthermore, 10 of 15 patients experienced high-grade neurotoxicity, perhaps because of the intense chemotherapy during the transplant. A study conducted at MD Anderson Cancer Center (MDACC) used the Sleeping Beauty transposon–transposase system (as opposed to a viral platform) to produce CD19 CAR T-cells, which were infused 2 days after autologous HCT in seven patients with relapsed or refractory B-cell NHL.[27] In this trial, the 5-year PFS and OS rates were 71% and 86%, respectively. Interestingly, 4 of 6 evaluable patients had persistence of the CAR T-cells at last follow-up, at a median of 4.5 years.

Current CAR T trials in multiple myeloma (MM) are mainly using the B-cell maturation antigen (BCMA) as the target and are usually enrolling relapsed or refractory patients who have had prior autologous transplant. However, one of the first trials used a CD19-directed CAR as an adjunct to a second transplant and compared each patient's PFS after the CAR T + HCT strategy to the previous PFS attained with transplant only.[28] The use of CD19, not usually present on mature plasma cells, was thought to target the myeloma-propagating cells. In this study, among 10 patients treated, only two had longer PFS after the CAR T + HCT versus transplant alone. Interestingly, these two patients eventually progressed with isolated extramedullary plasmacytomas, and the authors suggested this may hint at continuing bone marrow immune surveillance. Another trial reported on infusion of both CD19- and BCMA-directed CAR T-cells 14 to 20 days after HCT in nine patients.[29] The overall response (OR) rate was 100% with all patients achieving CR or very good partial response after CAR T-cell therapy, although response duration was not reported.

Chimeric Antigen Receptor T-Cell Therapy Combined with Allogeneic Transplant

Combining CAR T therapy with allogeneic HCT is also under investigation. The transplant preparative regimen may have a deleterious effect on any remaining circulating CAR T-cells and impair their immune surveillance. Furthermore, CAR T-cell therapy and its associated toxicity may impact transplant-related toxicities, such as increasing GVHD. Currently, the available data regarding the safety and possible benefit for allogeneic HCT after CAR T therapy comes from retrospective series, largely without preplanned consolidation with transplant (Table 22–1). The data in aggregate indicate that transplant consolidation may confers protection against relapse at the expense of greater TRM, thus not providing a survival benefit for all patients. Zhang et al reported on the outcomes of 52 adult patients with ALL who received treatment with either CD19 or CD22 autologous CAR T followed by planned allogeneic HCT with reduced-intensity conditioning therapy.[22] At 1 year, the relapse rate was 24.7%, TRM was very low at 2.2% without excess GVHD, and there was an excellent 1-year OS of 87.7%. More studies will need to be conducted with planned consolidation of allogeneic HCT after CAR T to confirm these highly encouraging results. Similarly, in children, data for consolidation with HCT after CAR T-cell therapy is mainly reported from retrospective studies without planned transplant consolidation.[30] A retrospective study of 15 pediatric or adolescent and young adult patients with relapsed or refractory B-cell ALL who went on to an allogeneic HCT after achieving an MRD-negative remission with CAR T-cells, reported OS of 80% at 24 months and relapse and TRM rates at 16% and 20%, respectively.[31] In this study, patients were treated with myeloablative conditioning regimens followed by either a CD34-selected T-cell-depleted allogeneic graft ($n = 9$) or unmanipulated graft ($n = 6$); TRM and OS were 0 and 100% versus 50% and 50% for the manipulated versus unmanipulated groups, respectively. This very small study hints at the possibility that a T-cell-replete graft may not be necessary if transplant is used as consolidation in this setting, sparing patients some degree of toxicity, such as GVHD. As we continue to investigate the role of CAR T therapy and its sequence in the treatment of different diseases and patient populations, we will be able to refine the role of transplant consolidation. The patient's disease characteristics, the CAR T construct, and the patient's response to therapy will help to delineate who may benefit from this approach. One such example of this approach was investigated by Summers and colleagues, in which patients with B-cell aplasia of less than 63 days after CAR T treatment were offered a transplant. Among 50 evaluable

TABLE 22–1 Outcomes in Studies with Patients with B-Cell Acute Lymphoblastic Leukemia Who Received Allogeneic Hematopoietic Cell Transplantation After Chimeric Antigen Receptor T-Cell Therapy

Reference	Structure of CAR T	Allogeneic HCT After CAR T Infusion	
		Yes	No
Park et al[25] ($n = 43$)	CD19–28z	($n = 17$) Relapse, 6 of 17 (35%); TRM, 6 of 17 (35%)	($n = 26$) Relapse, 17 of 26 (65%)
Lee et al[110] ($n = 51$)	CD19–28z	($n = 21$) Relapse, 2 of 21 (9%) LFS not reached ($P = .0006$)	($n = 7$) Relapse, 6 of 7 (86%) LFS, 4.9 months
Pan et al[20] ($n = 45$)	CD19-4-1BBz	($n = 27$) Relapse, 2 of 27 ($P = .023$); TRM, 2 of 27 6-mo LFS, 81.3%	($n = 18$) Relapse, 9 of 18
Pan et al[19] ($n = 23$)	CD22-4-1BBz	($n = 11$) Relapse, 1 of 11 (9%); TRM, 2 of 11 LFS at 1 year, 71.6%	($n = 7$) Relapse, 4 of 7
Jacoby et al[18] ($n = 20$)	CD19–28z	($n = 14$) Relapse, 2 of 14 1-year EFS, 73%; OS, 90%	($n = 4$) Relapse, 2 of 4
Shalabi et al[111] ($n = 85$)	CD19–28z ($n = 52$) CD22-4-1BBz ($n = 33$)	43 achieved MRD-negative CR 25 went on to allo-HCT 2-year relapse, 13.5%	N/A
Zhang et al ($n = 52$)[22]	CD19/CD22-4-1BB z	1-year OS, 87.8% 1-year EFS, 73.% 1-year TRM, 2·2%	N/A
Fabrizio et al[31]	19–28z/19-BBz	24-month relapse, 16% 24-month TRM 20% 24-month OS 80%	
Summers et al[32] No prior HCT ($n = 17$) Prior HCT ($n = 33$)	CD-19- 41BBz-EGFRt	No prior HCT: 2 of 14 relapsed, 1 TRM Prior HCT: 5 of 10 relapsed	No prior HCT: 3 of 3 relapsed Prior HCT: 15 of 23 relapsed

allo-HCT, allogeneic hematopoietic cell transplantation; CAR, chimeric antigen receptor; CR, complete remission; EFS, event-free survival; LFS, leukemia-free survival; MRD, minimal residual disease; N/A, not applicable. OS, overall survival; TRM, transplant-related mortality.

patients, 15 had B-cell aplasia of less than 63 days, and nine of these patients proceeded to transplant. Among the transplanted patients, only two relapsed, and all six patients with early reconstitution of B cells who did not proceed to transplant relapsed.[32]

Chimeric Antigen Receptor T-Cell Therapy After Allogeneic Transplant

Finally, sequencing CAR after an allogeneic HCT allows the production of donor-derived CAR T-cells if the patient remains chimeric. This allows the use of healthy T-cells for CAR production and provides a strategy to address relapse in these patients. A report on 18 patients with relapsed CD19+ ALL after allo-HCT had 13 of 18 patients achieving a CR (72%) and 11 of these not requiring further therapy at a median follow-up period of 7 months.[33] Importantly, full donor chimerism was restored for the responding patients, and only two patients had GVHD that responded to therapy. In another trial of 20 patients with relapsed B-cell malignancies after allogeneic HCT who received CAR T infusion, eight of the patients had a CR or partial response.[34] These patients did not receive any lymphodepletion before CAR T infusion, and importantly, no patients developed GVHD, despite 70% of patients having had a prior history of GVHD with their transplant. Similar findings have been reported from smaller series, importantly all without excess rates of GVHD.[35,36] A recent report of donor-derived cytokine-induced killer T-cells engineered with the Sleeping Beauty transposon to express CD19 CAR showed responses in four of five patients with refractory ALL, with no GVHD reported after treatment.[37]

Although most donor-derived CAR T trials investigated the use of CAR T-cells as therapy for relapse after transplant, a few have studied CAR T-cells as prophylactic therapy. Kebriaei et al used a nonviral approach for the production of CD19-directed CAR T-cells using

the Sleeping Beauty transposon–transposase system to incorporate the vector into the genome; this construct was tested in phase 1 clinical trials in 26 patients with B-cell malignancies in combination with allogeneic (n = 19) or autologous (n = 7) transplant.[38] Six of seven patients who had an autologous HCT followed by CAR T were in remission after a median follow-up period of 25.5 months; 11 of 19 patients receiving an allogeneic HCT were in remission after a median follow-up period of 7.5 months, with reported 1-year PFS and OS rates of 53% and 63%, respectively.[38] In another small study of two patients using a similar strategy of prophylactic donor-derived CAR T-cells after allogeneic HCT, investigators reported prolonged CAR T persistence, absence of GVHD, and continued remission at a follow-up period of 1 year.[39]

NATURAL KILLER CELLS

Natural killer (NK) cells have a number of advantages over T-cell therapy in the treatment of patients with cancer. Unlike T and B lymphocytes, NK cells do not express rearranged, antigen-specific receptors and as a consequence have a low risk for GVHD. This allows the use of allogeneic NK cells, thus providing an off-the-shelf product that decreases the cost and delay to treatment seen with autologous CAR T therapy. Furthermore, there is evidence that autologous immune cells are dysfunctional in cancer,[40] and thus it might be ideal to use allogeneic cells.

NK effector function is dictated by an integration of activating and inhibitory signals received through germline-encoded receptors that can recognize ligands on their cellular targets. This interplay between receptors is complex because certain ligands, such as CD155, can bind to both activating and inhibitory receptors, and certain receptors can be either activating or inhibitory.[41]

NK cells serve an important role in cancer immune surveillance. One method that cancer cells use to evade T-cells is to downregulate their HLA class I molecules. Because HLA class I molecules are some of the strongest inhibitors of NK cells, the lack of these molecules consequentially leads to NK cell activation, thus providing a balance to T-cell surveillance.[41] NK cells can also be activated by ligands such as major histocompatibility complex class I polypeptide-related sequence A (MICA), MICB, and UL16 binding proteins (ULBPs) that are upregulated in cells that have DNA damage or are stressed or infected, including cancer cells. Finally, NK cells can be activated by binding to the Fc portion of antibodies through its CD16 receptor and thus are involved in the body's antibody-dependent cellular cytotoxicity immune defense. This is believed to be integral, for example, in the efficacy observed with the anti-CD38 antibody therapy daratumumab in multiple myeloma.[42] After being activated, NK cells can directly kill cancer cells via secretion of granzymes and perforins, and they can also modulate the surrounding microenvironment by secreting cytokines such as IFN-γ and TNF-α (Fig. 22–3).

Early NK cell recovery (within 30 days) after allogeneic stem cell transplant has been associated with reduced rates of both relapse and acute GVHD (aGVHD), with resultant improved survival.[43] This dual benefit makes allogeneic NK cells an attractive option for adoptive cellular therapy peritransplant. Adoptive transfer of NK cells has previously been limited by the small numbers of circulating NK cells (5%–15% of the total lymphocytes) and consequently the low numbers obtained in an apheresis procedure.[44] Thus, techniques that have been used to expand NK cells ex vivo from hematopoietic or induced pluripotent stem cell–derived NK cells[45] or to use an immortalized NK cell line.[46] At MDACC, we have developed a novel method to expand cord blood NK cells in vitro by using engineered K562 "feeder cells" with IL-2 and are able to obtain clinically relevant cell numbers.[47] Furthermore, cord blood NK cells appear to have higher expression of genes for cell cycle and replication than peripheral blood (PB) NK cells.[48]

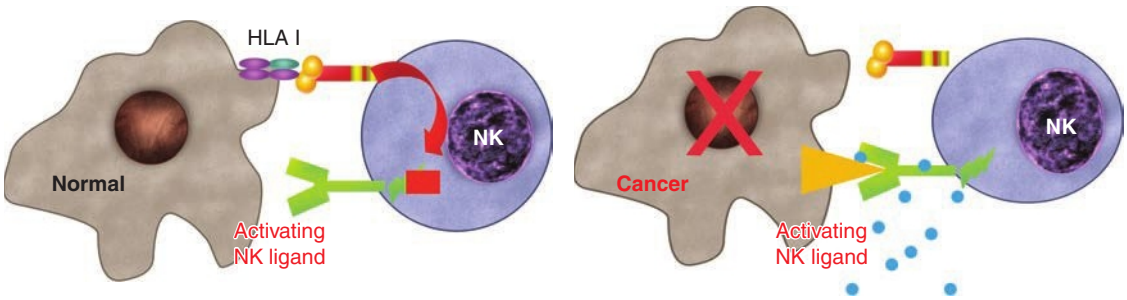


FIGURE 22–3 **Selective killing of transformed cells by natural killer (NK) cells. In normal cells, the inhibitory signals triggered by killer cell immunoglobulin-like receptor (KIR)–human leukocyte antigen (HLA) I molecule engagement overrides activating signals. In the context of cancer, expression of stress ligands for activating receptors, in conjunction with low expression of HLA I molecules, attenuates the triggering of inhibitory receptors and results in an activating signal.**

Optimizing Natural Killer Cell Efficacy

NK cells have a class of highly polymorphic receptors called killer cell immunoglobulin-like receptor (KIR) that can be divided into inhibitory and activating subtypes. The KIRs are inherited as haplotypes (KIR-A and KIR-B). The KIR-A haplotypes, found in one third of adults of European descent, have one activating receptor, but the KIR-B haplotypes have two or more. Transplantation in AML from a KIR-B haplotype donor is associated with lower relapse rates and superior survival.[49] Donor KIR2DS1 (an activating KIR) and recipient HLA-C type influence relapse risk. The KIR2DS1-associated reduction in the rate of AML relapse is restricted to donors with HLA-C1/C1 or C1/C2, in whom KIR2DS1-expressing NK cells are presumed to be "educated," and the benefit was eliminated in transplants from donors with HLA-C2/C2, in whom KIR2DS1-expressing NK cells are expected to be tolerized in the setting of self HLA-C2.[50] Selection of adult or cord blood donors for ex vivo NK cell expansion based on KIR genotype may therefore enhance NK cell efficacy.

Similar to T-cells, NK cells can be modified with a CAR to enhance their activation and specificity. This led to the first-in-human phase I/II trial of CAR-transduced NK cells at MDACC in which cord blood NK cells were modified to express a CAR against CD19 and to secrete IL-15 to support their in vivo proliferation and persistence.[51] In a heavily pretreated population of patients with B-cell malignancies who had received a median of four prior lines of therapy, 8 of 11 (73%) patients responded after only a single infusion, including patients with high-risk features such as Richter transformation or deletion 17p CLL. The infused CAR NK cells were detected as long as 1 year after treatment. The therapy was well tolerated, and the only grade 4 toxicity observed was neutropenia and leukopenia from the initial lymphodepleting chemotherapy. Unlike CAR T-cells, no CRS or neurotoxicity were observed, and there were no cases of GVHD. A phase II multicenter trial is planned.

Programmed Cell Death Protein 1 and Programmed Cell Death Protein Ligand 1 Antibodies

The interaction of PD-1 and PDL1 induces T-cell dysfunction, and manipulation of this pathway has offered a treatment strategy in a variety of malignancies. These therapies have been most extensively studies in metastatic solid tumors as monotherapy and in combination with the anti-CTLA4 antibody ipilimumab.[52] In one of the first studies in hematologic malignancies, 23 patients with refractory or relapsed HL received the PD-1–blocking antibody nivolumab with a reported overall response rate (ORR) of 87%[53]; these striking preliminary results were confirmed in larger trials[54] and led to the FDA approval of nivolumab for patients with relapsed HL.

The potential importance of immune checkpoints in AML has been demonstrated in preclinical studies,[55] and clinical studies are currently underway. Zeidner et al reported an ORR of 46% for patients with relapsed or refractory AML treated with high-dose cytarabine followed by pembrolizumab.[56]

REDUCING GRAFT-VERSUS-HOST DISEASE

Cellular Therapy for Treatment of Graft-versus-Host Disease

Grades II to IV aGVHD occur in 25% to 60% of MRDs and 45% to 70% of MUDs.[57] Corticosteroid-based therapy for grades II to IV aGVHD is unsatisfactory, with fewer than 50% of patients showing a durable complete response.[58] Increasing severity of aGVHD is associated with incremental TRM and inferior survival. Corticosteroid-refractory GVHD has a poor prognosis. Numerous additional agents have been studied in combination with corticosteroids or as second-line therapies and showed uniformly poor response rates and numerous complications, particularly viral reactivation.[58] Although mesenchymal stromal cells (MSCs) appear to show benefit in smaller, single-center trials for steroid-refractory GVHD,[59] there did not appear to be a clear benefit in the only phase 3 randomized controlled trial.[60] Some benefit was noted in post-hoc subset analyses of high-risk patients (day 28 OR, 58% MSC vs 37% placebo; $P = .03$) and pediatric patients (day 28, OR 64% MSC vs 23% placebo; $P = .05$), suggesting that MSCs may be a viable option for some patients. Further investigations are underway.[60]

T-Cell Depletion for Prevention of Graft-versus-Host Disease

A T-cell-replete transplant usually contains 1 to 5 × 10^7 T-cells/kg recipient weight.[61] T-cell depletion is the most potent method of preventing aGVHD but is associated with increased rates of graft rejection; delayed immune reconstitution; infectious complications, including Epstein-Barr virus (EBV)–driven post transplant lymphoproliferative disease (PTLD); and increased relapse risk.[62] T-cell depletion can be accomplished ex vivo immunologically (T-cell antibodies, positive CD34 selection) or by the use of physical separation (eg, density gradients) or in vivo by the use of anti-T-cell antibodies such as antithymocyte globulin (ATG) or alemtuzumab. In vivo T-cell depletion with

ATG reduces severe aGVHD and extensive cGVHD without increasing relapse but does not reduce TRM or improve survival,[62] likely because of increased infection risk. Alemtuzumab-based GVHD prophylaxis achieves low rates of severe aGVHD and extensive cGVHD but results in high rates of mixed chimerism and viral infections, particularly cytomegalovirus (CMV) reactivation.[63]

The alkylating agent cyclophosphamide is now being used more frequently as a method to eliminate cGVHD. Cyclophosphamide is metabolized by liver cytochrome P450 into phosphoramide mustard and acrolein and prevents cell division by crosslinking DNA strands. HSCs benefit from having a higher level of the enzyme aldehyde dehydrogenase, used to convert phosphoramide mustard into the inactive metabolite carboxycyclophosphamide. Administering cyclophosphamide a few days after transplant was first introduced into clinical practice on trials with haploidentical donor graft transplants at Johns Hopkins University[64] in an effort to reduce GVHD but has now extended across donor types as a mechanism to eliminate graft alloreactive CD4+ cells in donor grafts[65] and donor graft sources.[66] In a recent report of patients with AML or MDS who had checkpoint inhibitor therapy before proceeding with HCT, the use of posttransplant cyclophosphamide reduced severe acute GVHD and improved PFS.[67]

Adoptive Transfer of Regulatory T-Cells

The level of CD4+CD25+FOXP3+ T-reg cells in the graft and after HCT correlates inversely with aGVHD and cGVHD.[68] Therefore, adoptive transfer of T-reg cells could ameliorate GVHD. After sorting and expansion, adoptive transfer of T-reg cells has been shown in murine xenogenic GVHD models to prevent and treat GVHD, improving survival.[69]

Early-phase clinical trials have shown posttransplant adoptive transfer of T-reg cells to be safe, and they have been used for GVHD prevention, as well as treatment. In a study of 23 adult patients receiving double-unit cord blood–derived grafts, T-reg cells were administered for prevention of acute GVHD with a reduction in risk of grades II to IV aGVHD relative to historical control participants (43% vs 61%; $P = .05$) and, importantly, similar DFS rates.[70] A later report on 11 additional patients with higher dose levels showed very low incidence of 9% of acute GVHD and no patients with chronic GVHD at 1 year after transplant.[71] In a small case series with five patients receiving T-reg cells for as treatment for chronic GVHD, two patients had clinical improvement of symptoms, and three had a stable disease.[72] However, two of the patients developed skin cancers within 1 year of T-reg transfusion. Larger clinical trials are needed to validate these results and address safety issues as well as this therapy's impact on the graft-versus-leukemia effect.

Adoptive transfer of other immune-modulating cells, such as "veto" cells capable of inducing immune tolerance, are also being explored in preliminary clinical trials. These may also allow for more efficient "off-the-shelf" CAR T-cell therapy by inducing tolerance and preventing rejection of these allogeneic cells.[73]

PREVENTING AND TREATING INFECTION WITH VIRAL-SPECIFIC T-CELLS

Delayed recovery of cellular and humoral immunity results in morbidity and mortality from infection. Figure 22–4 shows the approximate time course of numeric recovery of immune cells after HCT; Figure 22–5 shows the time course of infections.

Viral infection is a major cause of death after HCT, resulting from cellular and humoral immune deficiency;

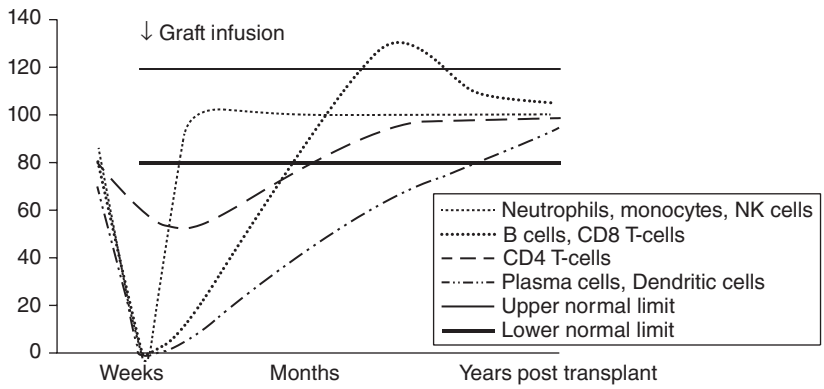


FIGURE 22–4 Time course of numeric cellular immune recovery posttransplant. (Reproduced with permission from Mackall C, Fry T, Gress R, et al. Background to hematopoietic cell transplantation, including post transplant immune recovery, *Bone Marrow Transplant* 2009 Oct;44(8):457-462.)

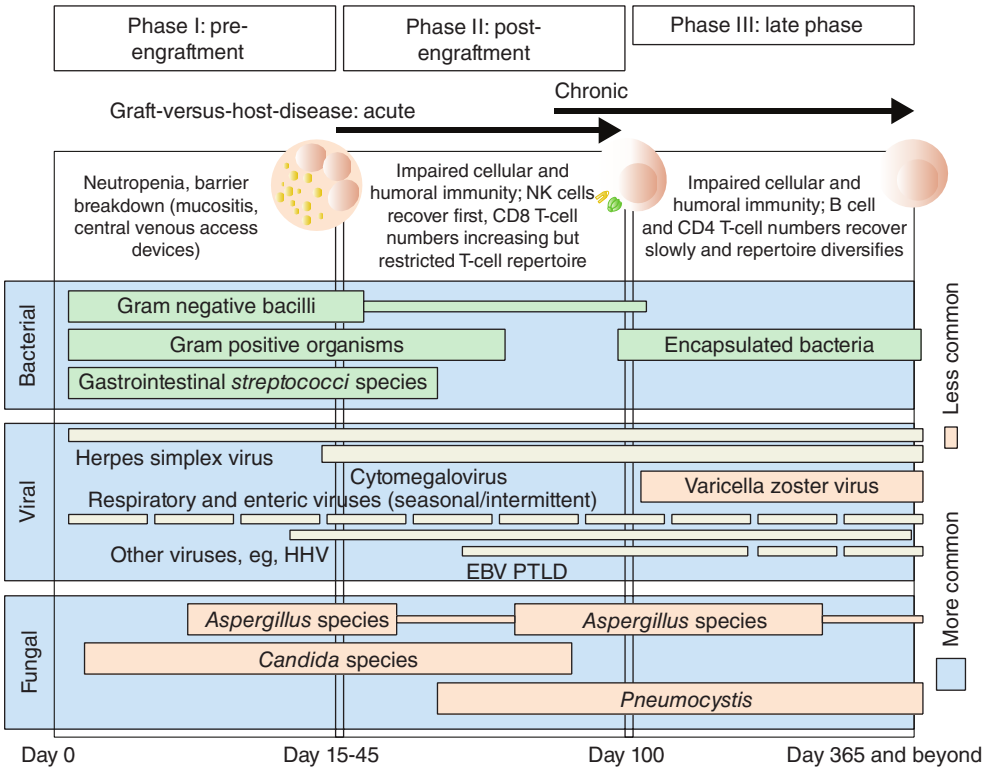


FIGURE 22–5 Time course of infections after transplant. (Reproduced with permission from Mackall C, Fry T, Gress R, et al. Background to hematopoietic cell transplantation, including post transplant immune recovery, *Bone Marrow Transplant* 2009 Oct;44(8):457-462.)

CHAPTER 22

risk factors include umbilical CB transplantation, T-cell depletion, and GVHD requiring systemic immunosuppression. Viral infections of particular relevance after HCT are CMV, EBV, the polyoma viruses BK and JC, adenovirus, and human herpesvirus 6 (HHV-6). Pharmacotherapy for these infections has limited efficacy and substantial toxicity Consequently, adoptive immunotherapy for the prevention and treatment of viral reactivation or infection after transplant is attractive.

Generation of viral-specific T-cells (VSTs)s is most straightforward from an immune-experienced adult donor who has viral-specific memory T-cells specific in the PB. The VSTs from such donors can be generated in two ways[74]:

1. T-cell co-culture, in the presence of specific cytokines, with an artificial APC modified to express the immune dominant antigens of the target virus and costimulatory molecules
2. Rapid selection strategies without ex vivo culture. These rely on the presence of sufficient numbers of VSTs in the donor PB and hence are limited to CMV and EBV.[75]

Generation of VSTs from immunologically naïve donors (eg, CB) is more challenging. However, multivirus-specific T-cells against EBV, CMV, and adenovirus can be generated from naïve CB cells by genetically modifying EBV lymphoblastoid cell lines transduced with an adenoviral vector expressing the CMVpp65 transgene.[76] These are highly active against virus despite recognition of noncanonical CMV and EBV epitopes,[76] and clinical results are encouraging.[77,78]

Third-party, banked VSTs from adult donors can also be used to treat viral reactivation in patients without an available adult donor or in whom rapid disease progression precludes waiting for generation of VSTs from their donor. Suitable lines (which are dependent on the recipient expressing immune dominant viral peptides on an HLA antigen shared by a donor VST line) are available in approximately 90% of patients and can be rapidly identified and made available. VSTs demonstrated high response rates in patients with refractory CMV, adenovirus, and EBV-related PTLD.[78–80]

In a recent review of 229 patients who received VST for viral infections occurring after transplant, the response rate was 91.3%.[81] Interestingly, despite the theoretical risk of inducing GVHD due to HLA mismatch, no severe cases of de novo aGVHD were seen in initial studies, and retreatment was successful in several cases despite initial immunologic rejection of the transferred cells.[78,79]

Treatment of Specific Infections with Viral-Specific T-Cells

Epstein-Barr Virus Reactivation and Posttransplant Lymphoproliferative Disorder

PTLD related to EBV occurs in the setting of severe transplant-related immunosuppression when the EBV-specific T-cell response is insufficient to control latent EBV infection within recipient or donor B cells. Risk factors for infection predominantly relate to the degree of immunosuppression in recipients of T-cell-depleted transplants. Patients typically present with high fever and lymphadenopathy with elevated serum lactate dehydrogenase levels. Initial therapy for EBV reactivation is reduction in immunosuppression. However, there are no randomized studies to guide the best therapy of established EBV-associated PTLD. In patients with frank PTLD, the largest study[82] showed a 70% complete response/complete response undefined rate with four weekly doses of rituximab monotherapy, but there were poor responses to subsequent treatment (chemotherapy, DLI, or both) in nonresponders. Chemotherapy is associated with greater toxicity in HCT recipients and may increase infection risk. Cellular therapy shows great promise in the management of EBV-related PTLD. Unmanipulated donor T-cell infusions can control established PTLD in approximately 70% of patients but can induce severe or fatal GVHD.[83] Therefore, when available, VSTs are preferred. The EBV-specific or polyvirus-specific cytotoxic T lymphocytes (CTLs) have proven successful in overt PTLD in 77.5% of patients, including patients with rituximab-refractory disease.[84] EBV CTLs have been administered in the prophylactic setting in more than 100 patients, and no patient has developed EBV-PTLD with up to 15-year follow-up.[75,85–91]

Cytomegalovirus Infection

Risk factors for CMV reactivation and disease after HCT include receiving umbilical CB grafts, T-cell-depleted grafts, T-cell antibody therapy for GVHD prophylaxis, or high-dose steroids.[92] In addition, CMV-seropositive patients with seronegative donors are at particularly high risk because of the lack of memory T-cells against CMV from the seronegative donor.[92] Although ganciclovir prophylaxis reduces the risk of CMV disease, it prolongs neutropenia, increases invasive bacterial and fungal infections, and does not improve survival.[92] Close monitoring for CMV reactivation in blood, followed by preemptive therapy with ganciclovir when assays in blood become positive, reduces the incidence of CMV disease. Overall, rates of CMV disease have declined from 30% to 35% to 8% to 10% with ganciclovir prophylaxis or preemptive therapy.[92] In 2017, letermovir, which targets the HCMV DNA terminase complex, was licensed for prophylaxis of HCMV infections in HCT recipients and has lowered the rate of reactivation. Use of letermovir is limited by emerging drug resistance and drug expense.[93] Gastrointestinal disease, pneumonia, and retinitis are the most common manifestations; pneumonia has a high mortality rate despite treatment with ganciclovir or foscarnet and CMV immunoglobulin.[92] Given the toxicity and expense associated with pharmacologic interventions and their imperfect efficacy, cellular therapy as treatment or prophylaxis of CMV in high-risk patients is attractive. In one study, 40 of 47 patients with CMV infection or disease refractory to antiviral therapy were treated with CMV CTLs and cleared the virus after one or two infusions. In another study, 110 patients received CMV CTLs as a prophylaxis 28 to 115 days after HCT. Reactivation of CMV in patients receiving CMV CTLs was 16% while reactivation in the control cohort was 66%. No statistically significant severe de novo GVHD has been reported after CMV CLT infusion.[94–99]

Adenovirus Infection

Adenovirus infection occurs in up to 21% of transplant recipients, with manifestations of adenovirus disease in 20% to 89% of infected patients.[100] Four clinically significant syndromes are seen: pneumonitis, nephritis, hemorrhagic colitis, and hemorrhagic cystitis. Disseminated disease with multiorgan failure also occurs and has a poor outcome despite antiviral therapy; most successfully treated cases are respiratory or urinary tract infections. Adenovirus-specific T-cells can now be generated from both CB[76,77] and adult donors,[77] with a high clinical response rate in cidofovir-refractory cases.[101] Donor-derived adenovirus-specific T-cells have been used recently in a high-risk pediatric trial with a 100% response rate with no serious toxicity noted.[91,102]

BK and JC Virus Infections

BK virus reactivation occurs in 5% to 68% of HCT recipients. It can cause severe hematuria, urinary obstruction, renal failure, and increased mortality. It is more frequent in patients with grades III and IV aGVHD and CB transplants.[103] Pharmacologic therapy is toxic and poorly efficacious. JC virus–associated progressive multifocal leukoencephalopathy (PML) occurs in immunosuppressed individuals and carries a grim prognosis with limited treatment options, although PD-1 inhibition does show some promise.[104,105] Because of the homology in immunogenic proteins between BK and JC, BK-0specific CTLs have been used in the treatment of patients with PML with

good response rates.[106] BKV CTLs have been included in multivirus-specific T-cell clinical trials with response rates approaching 100%.[91]

Human Herpes Virus 6 Infection

Infection with HHV-6 is virtually universal before age 2 years.[107] Reactivation occurs in more than 50% of allograft recipients and can result in encephalitis, delayed engraftment, and increased rate of GVHD, with increased mortality rates.[107] A response rate of 67% was reported in a clinical study in which HHV-6 was included in a multivirus-specific T-cell infusion.[91]

Multivirus Viral-Specific T-Cells

Some investigators have generated multiple-virus specific T-cells, with 2 ,3, 4, and 5 (EBV, CMV, adenovirus, BKV, and HHV-6) viruses included for use in both the prophylactic and treatment setting. Clinical studies have shown response rates from 67% to 100% with no increase in incidence of severe GVHD or other toxicity.[108,109]

CONCLUSION

Allogeneic HCT, initially performed in a twin patient with leukemia by Dr. E. Donnall Thomas in the late 1950s, was one of the first elegant demonstrations of the power of cellular therapy. Much has been learned since then, and our increased understanding of the immune system has translated into exciting new therapeutic approaches, especially relevant to transplantation and its complications, leading to continued better outcomes for patients.

MD ANDERSON PRACTICE TIPS

- Allogeneic HCT is curative for a subset of patients with hematologic malignancies.
- Adoptive infusion of CAR T-cells have shown remarkable efficacy for patients with refractory ALL and NHL; CAR T-cells in conjunction with transplant is under investigation.
- Infusion of allogeneic NK T-cells provide a readily available source of effective immunotherapy; trials are underway.
- The incorporation of post transplant cyclophosphamide has led to decreased rates of GVHD.
- Ruxolitinib is the first approved agent for steroid-refractory acute GVHD.
- VSTs can be very effective in patients with specific viral infections such as CMV, EBV, polyoma viruses BK and JC, adenovirus, and HHV-6.

REFERENCES

1. Clark EA, Ledbetter JA. How B and T cells talk to each other. *Nature*. 1994;367(6462):425-428.
2. Ferrara JL, Levine JE, Reddy P, Holler E. Graft-versus-host disease. *Lancet*. 2009;373(9674):1550-1561.
3. Fürst D, Müller C, Vucinic V, et al. High-resolution HLA matching in hematopoietic stem cell transplantation: a retrospective collaborative analysis. *Blood*. 2013;122(18):3220-3229.
4. Miller JS, Warren EH, van den Brink MR, et al. NCI first international workshop on the biology, prevention, and treatment of relapse after allogeneic hematopoietic stem cell transplantation: report from the committee on the biology underlying recurrence of malignant disease following allogeneic HSCT: graft-versus-tumor/leukemia reaction. *Biol Blood Marrow Transplant*. 2010;16(5):565-586.
5. Liu L, Chang Y-J, Xu L-P, et al. Reversal of T cell exhaustion by the first donor lymphocyte infusion is associated with the persistently effective antileukemic responses in patients with relapsed AML after Allo-HSCT. *Biol Blood Marrow Transplant*. 2018;24(7):1350-1359.
6. Schmidt S, Liu Y, Hu Z-H, et al. The role of donor lymphocyte infusion (DLI) in post-hematopoietic cell transplant (HCT) relapse for chronic myeloid leukemia (CML) in the tyrosine kinase inhibitor (TKI) era. *Biol Blood Marrow Transplant*. 2020;26(6):1137-1143.
7. Das-Gupta E, Thomson KJ, Bloor AJC, et al. Allo-HSCT in transplant-naïve patients with Hodgkin lymphoma: a single-arm, multicenter study. *Blood Adv*. 2019;3(24):4264-4270.
8. Sterling C, Webster J. Harnessing the immune system after allogeneic stem cell transplant in acute myeloid leukemia. *Am J Hematol*. 2020;95(5):529-547.
9. Dholaria B, Savani BN, Labopin M, et al. Clinical applications of donor lymphocyte infusion from an HLA-haploidentical donor: consensus recommendations from the acute leukemia working party of the EBMT. *Haematologica*. 2020;105(1):47-58.
10. Ghobadi A, Choi J, Fiala MA, et al. Phase I study of azacitidine following donor lymphocyte infusion for relapsed acute myeloid leukemia post allogeneic stem cell transplantation. *Leuk Res*. 2016;49:1-6.
11. Schroeder T, Rautenberg C, Krüger W, et al. Treatment of relapsed AML and MDS after allogeneic stem cell transplantation with decitabine and DLI—a retrospective multicenter analysis on behalf of the German Cooperative Transplant Study Group. *Ann Hematol*. 2018;97(2):335-342.
12. Kothari S, Artz AS, Lee SM, et al. Dose escalation prophylactic donor lymphocyte infusion after T-cell depleted matched related donor allogeneic hematopoietic cell transplantation is feasible and results in higher donor chimerism, faster immune re-constitution, and prolonged progression-free survival. *Bone Marrow Transplant*. 2020;55(6):1161-1168.
13. Guillaume T, Malard F, Magro L, et al. Prospective phase II study of prophylactic low-dose azacitidine and donor lymphocyte infusions following allogeneic hematopoietic stem cell transplantation for high-risk acute myeloid leukemia and myelodysplastic syndrome. *Bone Marrow Transplant*. 2019;54(11):1815-1826.
14. Ramos CA, Rouce R, Robertson CS, et al. In Vivo fate and activity of second-versus third-generation CD19-Specific CAR-T Cells in B Cell non-hodgkin's lymphomas. *Mol Ther*. 2018;26(12):2727-2737.
15. Greenbaum U, Kebriaei P, Srour SA, et al. Chimeric antigen receptor T-cell therapy toxicities. *Br J Clin Pharmacol*. 2020 May 28. doi: 10.1111/bcp.14403. Epub ahead of print.
16. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial. *Lancet Oncol*. 2019;20(1):31-42.
17. Schuster SJ, Bishop MR, Tam CS, et al. Long-term follow-up of tisagenlecleucel in adult patients with relapsed or refractory diffuse large B-cell lymphoma: updated analysis of juliet study. *Biol Blood Marrow Transplant*. 2019;25(suppl 3):S20-S21.
18. Jacoby E, Bielorai B, Avigdor A, et al. Locally produced CD19 CAR T cells leading to clinical remissions in medullary and extramedullary relapsed acute lymphoblastic leukemia. *Am J Hematol*. 2018;93(12):1485-1492.
19. Pan J, Niu Q, Deng B, et al. CD22 CAR T-cell therapy in refractory or relapsed B acute lymphoblastic leukemia. *Leukemia*. 2019;33(12):2854-2866. Epub 2019/05/22.
20. Pan J, Yang JF, Deng BP, et al. High efficacy and safety of low-dose CD19-directed CAR-T cell therapy in 51 refractory or relapsed B acute lymphoblastic leukemia patients. *Leukemia*. 2017;31(12):2587-2593.
21. Shadman M, Gauthier J, Hay KA, et al. Safety of allogeneic hematopoietic cell transplant in adults after CD19-targeted CAR T-cell therapy. *Blood Adv*. 2019;3(20):3062-3069. Epub 2019/10/28.
22. Zhang Y, Chen H, Song Y, et al. Post-chimeric antigen receptor T-cell therapy haematopoietic stem cell transplantation for 52 cases with refractory/relapsed B-cell acute lymphoblastic leukaemia. *Br J Haematol*. 2020;189(1):146-152.
23. Lee DW III, Stetler-Stevenson M, Yuan CM, et al. Long-term outcomes following CD19 CAR T cell therapy for B-ALL are superior in patients receiving a fludarabine/cyclophosphamide preparative regimen and post-CAR hematopoietic stem cell transplantation. *Blood*. 2016;128(22):218.
24. Grupp SA, Kalos M, Barrett D, et al. Chimeric antigen receptor–modified T cells for acute lymphoid leukemia. *N Engl J Med*. 2013;368(16):1509-1518.
25. Park JH, Rivière I, Gonen M, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. *N Engl J Med*. 2018;378(5):449-459.
26. Sauter CS, Senechal B, Rivière I, et al. CD19 CAR T cells following autologous transplantation in poor-risk relapsed and refractory B-cell non-Hodgkin lymphoma. *Blood*. 2019;134(7):626-635.
27. Srour SA, Singh H, McCarty J, et al. Long-term outcomes of Sleeping Beauty–generated CD19-specific CAR T-cell therapy for relapsed-refractory B-cell lymphomas. *Blood*. 2020;135(11):862-865.
28. Garfall AL, Stadtmauer EA, Hwang W-T, et al. Anti-CD19 CAR T cells with high-dose melphalan and autologous stem cell transplantation for refractory multiple myeloma. *JCI Insight*. 2018;3(8):e120505.
29. Shi X, Yan L, Shang J, et al. Tandom autologous transplantation and combined infusion of CD19 and Bcma-specific chimeric antigen receptor T cells for high risk MM: initial safety and efficacy report from a clinical pilot study. *Blood*. 2018;132(suppl 1):1009.
30. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med*.. 2018;378(5):439-448.
31. Fabrizio VA, Kernan NA, Boulad F, et al. Low toxicity and favorable overall survival in relapsed/refractory B-ALL following CAR T cells and CD34-selected T-cell depleted allogeneic hematopoietic cell transplant. *Bone Marrow Transplant*. 2020;55(11):2160-2169.
32. Summers C, Annesley C, Bleakley M, et al. Long Term Follow-up after SCRI-CAR19v1 Reveals late recurrences as well as a survival advantage to consolidation with HCT after CAR T Cell induced remission. *Blood*. 2018;132(suppl 1):967.
33. Zhang C, Gao L, Liu Y, et al. Role of donor-derived CD19. CAR-T cells in treating patients that relapsed after allogeneic

hematopoietic stem cell transplantation. *Blood*. 2019;134(suppl1):4561.
34. Brudno JN, Somerville RPT, Shi V, et al. Allogeneic T cells that express an anti-CD19 chimeric antigen receptor induce remissions of B-cell malignancies that progress after allogeneic hematopoietic stem-cell transplantation without causing graft-versus-host disease. *J Clin Oncol*. 2016;34(10):1112-1121.
35. Cheng Y, Chen Y, Yan C, et al. Donor-derived CD19-targeted T cell infusion eliminates B cell acute lymphoblastic leukemia minimal residual disease with no response to donor lymphocytes after allogeneic hematopoietic stem cell transplantation. *Engineering*. 2019;5(1):150-155.
36. Jain T, Sauter CS, Shah GL, et al. Safety and feasibility of chimeric antigen receptor T cell therapy after allogeneic hematopoietic cell transplantation in relapsed/ refractory B cell non-Hodgkin lymphoma. *Leukemia*. 2019;33(10):2540-2544.
37. Magnani CF, Gaipa G, Belotti D, et al. Donor-derived CD19 CAR cytokine induced killer (CIK) cells engineered with Sleeping Beauty transposon for relapsed B-cell acute lymphoblastic leukemia (B-ALL). *Blood*. 2019;134(suppl 1):200.
38. Kebriaei P, Singh H, Huls MH, et al. Phase I trials using Sleeping Beauty to generate CD19-specific CAR T cells. *J Clin Invest*. 2016;126(9):3363-3376.
39. Zhang C, Ma Y-Y, Liu J, et al. Preventive infusion of donor-derived CAR-T cells after haploidentical transplantation: two cases report. *Medicine (Baltimore)*. 2019;98(29):e16498-e.
40. Thommen DS, Schumacher TN. T cell dysfunction in cancer. *Cancer Cell*. 2018;33(4):547-562.
41. Shimasaki N, Jain A, Campana D. NK cells for cancer immunotherapy. *Nat Rev Drug Discov*. 2020:1-19.
42. Viola D, Dona A, Caserta E, et al. Daratumumab induces mechanisms of immune activation through CD38+ NK cell targeting. *Leukemia*. 2020:1-12.
43. Savani B, Mielke S, Adams S, et al. Rapid natural killer cell recovery determines outcome after T-cell-depleted HLA-identical stem cell transplantation in patients with myeloid leukemias but not with acute lymphoblastic leukemia. *Leukemia*. 2007;21(10):2145-2152.
44. Childs RW, Berg M. Bringing natural killer cells to the clinic: ex vivo manipulation. *Hematology Am Soc Hematol Educ Program*. 2013;2013(1):234-246.
45. Zhu H, Blum RH, Bjordahl R, et al. Pluripotent stem cell–derived NK cells with high-affinity noncleavable CD16a mediate improved antitumor activity. *Blood*. 2020;135(6):399-410.
46. Zhang C, Oberoi P, Oelsner S, et al. Chimeric antigen receptor-engineered NK-92 cells: an off-the-shelf cellular therapeutic for targeted elimination of cancer cells and induction of protective antitumor immunity. *Front Immunol*. 2017;8:533.
47. Liu E, Tong Y, Dotti G, et al. Cord blood NK cells engineered to express IL-15 and a CD19-targeted CAR show long-term persistence and potent antitumor activity. *Leukemia*. 2018;32(2):520-531.
48. Li L, Chen H, Marin D, et al. A novel immature natural killer cell subpopulation predicts relapse after cord blood transplantation. *Blood Adv*. 2019;3(23):4117-4130.
49. Cooley S, Trachtenberg E, Bergemann TL, et al. Donors with group B KIR haplotypes improve relapse-free survival after unrelated hematopoietic cell transplantation for acute myelogenous leukemia. *Blood*. 2009;113(3):726-732.
50. Venstrom JM, Pittari G, Gooley TA, et al. HLA-C–dependent prevention of leukemia relapse by donor activating KIR2DS1. *N Engl J Med*. 2012;367(9):805-816.
51. Liu E, Marin D, Banerjee P, et al. Use of CAR-Transduced Natural Killer Cells in CD19-Positive Lymphoid Tumors. *N Engl J Med*. 2020;382(6):545-553.
52. Reck M, Ciuleanu T-E, Dols MC, et al. Nivolumab (NIVO) + ipilimumab (IPI) + 2 cycles of platinum-doublet chemotherapy (chemo) vs 4 cycles chemo as first-line (1L) treatment (tx) for stage IV/recurrent non-small cell lung cancer (NSCLC): CheckMate 9LA. *J Clin Oncol*. 2020;38(15 suppl):9501.
53. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med*. 2015;372(4):311-319.
54. Armand P, Engert A, Younes A, et al. Nivolumab for relapsed/refractory classic Hodgkin lymphoma after failure of autologous hematopoietic cell transplantation: extended follow-up of the multicohort single-arm phase II CheckMate 205 trial. *J Clin Oncol*. 2018;36(14):1428.
55. Hutten TJA, Norde WJ, Woestenenk R, et al. Increased coexpression of PD-1, TIGIT, and KLRG-1 on tumor-reactive CD8+ T cells during relapse after allogeneic stem cell transplantation. *Biol Blood Marrow Transplant*. 2018;24(4):666-677.
56. Zeidner JF, Vincent BG, Esparza S, et al. Final clinical results of a phase II Study of high dose cytarabine followed by pembrolizumab in relapsed/refractory AML. *Blood*. 2019;134(suppl 1):831.
57. Harris AC, Young R, Devine S, et al. International, multicenter standardization of acute graft-versus-host disease clinical data collection: a report from the Mount Sinai Acute GVHD International Consortium. *Biol Blood Marrow Transplant*. 2016;22(1):4-10.
58. Jagasia M, Zeiser R, Arbushites M, et al. Ruxolitinib for the treatment of patients with steroid-refractory GVHD: an introduction to the REACH trials. *Immunotherapy*. 2018;10(5):391-402.
59. Hashmi S, Ahmed M, Murad MH, et al. Survival after mesenchymal stromal cell therapy in steroid-refractory acute graft-versus-host disease: systematic review and meta-analysis. *Lancet Haematol*. 2016;3(1):e45-e52.
60. Kebriaei P, Hayes J, Daly A, et al. A phase 3 randomized study of remestemcel-L versus placebo added to second-line therapy in patients with steroid-refractory acute graft-versus-host disease. *Biol Blood Marrow Transplant*. 2020;26(5):835-844.
61. Baron F, Mohty M, Blaise D, et al. Anti-thymocyte globulin as graft-versus-host disease prevention in the setting of allogeneic peripheral blood stem cell transplantation: a review from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *Haematologica*. 2017;102(2):224-234.
62. Cupit-Link MC, Nageswara Rao A, et al. EBV-PTLD, adenovirus, and CMV in pediatric allogeneic transplants with alemtuzumab as part of pretransplant conditioning: a retrospective single center study. *J Pediatr Hematol Oncol*. 2018;40(8).
63. Robin M, Raj K, Chevret S, et al. Alemtuzumab vs anti-thymocyte globulin in patients transplanted from an unrelated donor after a reduced intensity conditioning. *Eur J Haematol*. 2018;101(4):466-474.
64. O'Donnell PV, Luznik L, Jones RJ, et al. Nonmyeloablative bone marrow transplantation from partially HLA-mismatched related donors using posttransplantation cyclophosphamide. *Biol Blood Marrow Transplant*. 2002;8(7):377-386.
65. De Jong CN, Meijer E, Bakunina K, et al. Post-transplantation cyclophosphamide after allogeneic hematopoietic stem cell transplantation: results of the prospective randomized HOVON-96 Trial in recipients of matched related and unrelated donors. *Blood*. 2019;134(suppl 1):1.
66. Bashey A, Zhang M-J, McCurdy SR, et al. Mobilized peripheral blood stem cells versus unstimulated bone marrow as a graft source for T-cell–replete haploidentical donor transplantation using post-transplant cyclophosphamide. *J Clin Oncol*. 2017;35(26):3002-3009.
67. Oran B, Garcia-Manero G, Saliba RM, et al. Posttransplantation cyclophosphamide improves transplantation outcomes in patients with AML/MDS who are treated with checkpoint inhibitors. *Cancer*. 2020;126(10):2193-2205.

68. Rieger K, Loddenkemper C, Maul J, et al. Mucosal FOXP3+ regulatory T cells are numerically deficient in acute and chronic GvHD. *Blood*. 2006;107(4):1717-1723.
69. Riegel C, Boeld TJ, Doser K, et al. Efficient treatment of murine acute GvHD by in vitro expanded donor regulatory T cells. *Leukemia*. 2020;34(3):895-908.
70. Brunstein CG, Miller JS, Cao Q, et al. Infusion of ex vivo expanded T regulatory cells in adults transplanted with umbilical cord blood: safety profile and detection kinetics. *Blood*. 2011;117(3):1061-1070.
71. Brunstein CG, Miller JS, McKenna DH, et al. Umbilical cord blood–derived T regulatory cells to prevent GVHD: kinetics, toxicity profile, and clinical effect. *Blood*. 2016;127(8):1044-1051.
72. Theil A, Tuve S, Oelschlägel U, et al. Adoptive transfer of allogeneic regulatory T cells into patients with chronic graft-versus-host disease. *Cytotherapy*. 2015;17(4):473-486.
73. Reisner Y, Or-Geva N. Veto cells for safer nonmyeloablative haploidentical HSCT and CAR T cell therapy. *Semin Hematol*. 2019;56(3):173-182.
74. Papadopoulou A, Katari UL, Gerdemann U, et al. Safety and clinical efficacy of rapidly-generated virus-specific T cells with activity against Adv, EBV, CMV, HHV6 and BK Virus administered after allogeneic hematopoietic stem cell transplant. *Biol Blood Marrow Transplant*. 2014;20(suppl 2):S48.
75. Icheva V, Kayser S, Wolff D, et al. Adoptive transfer of epstein-barr virus (EBV) nuclear antigen 1-specific t cells as treatment for EBV reactivation and lymphoproliferative disorders after allogeneic stem-cell transplantation. *J Clin Oncol*. 2013;31(1):39-48.
76. Hanley PJ, Cruz CR, Savoldo B, et al. Functionally active virus-specific T cells that target CMV, adenovirus, and EBV can be expanded from naive T-cell populations in cord blood and will target a range of viral epitopes. *Blood*. 2009;114(9):1958-1967.
77. Hanley P, Leen A, Gee A, et al. Multi-virus-specific T-cell therapy for patients after hematopoietic stem cell and cord blood transplantation. *Blood*. 2013;122:140.
78. Hanley PJ. Build a bank: off-the-shelf virus-specific T cells. *Biol Blood Marrow Transplant*. 2018;24(12):e9-e10.8.
79. Leen AM, Bollard CM, Mendizabal AM, et al. Multicenter study of banked third-party virus-specific T cells to treat severe viral infections after hematopoietic stem cell transplantation. *Blood*. 2013;121(26):5113-5123.
80. Vasileiou S, Turney AM, Kuvalekar M, et al. Rapid generation of multivirus-specific T lymphocytes for the prevention and treatment of respiratory viral infections. *Haematologica*. 2020;105(1):235-243.
81. Qian C, Wang Y, Reppel L, et al. Viral-specific T-cell transfer from HSCT donor for the treatment of viral infections or diseases after HSCT. *Bone Marrow Transplant*. 2018;53(2):114-122.
82. Fox CP, Burns D, Parker AN, et al. EBV-associated post-transplant lymphoproliferative disorder following in vivo T-cell-depleted allogeneic transplantation: clinical features, viral load correlates and prognostic factors in the rituximab era. *Bone Marrow Transplant*. 2014;49(2):280-286.
83. Heslop HE, Leen AM. T-cell therapy for viral infections. *Hematology Am Soc Hematol Educ Program*. 2013;2013:342-347.
84. Mika T, Strate K, Ladigan S, et al. Refractory Epstein-Barr virus (EBV)-related post-transplant lymphoproliferative disease: cure by combined brentuximab vedotin and allogeneic EBV-specific T-lymphocytes. *Front Med*. 2019;6:295.
85. Heslop HE, Slobod KS, Pule MA, et al. Long-term outcome of EBV-specific T-cell infusions to prevent or treat EBV-related lymphoproliferative disease in transplant recipients. *Blood*. 2010;115(5):925-935.
86. Gustafsson A, Levitsky V, Zou JZ, et al. Epstein-Barr virus (EBV) load in bone marrow transplant recipients at risk to develop posttransplant lymphoproliferative disease: prophylactic infusion of EBV-specific cytotoxic T cells. *Blood*. 2000;95(3):807-814.
87. Imashuku S, Goto T, Matsumura T, et al. Unsuccessful CTL transfusion in a case of post-BMT Epstein-Barr virus-associated lymphoproliferative disorder (EBV-LPD). *Bone Marrow Transplant*. 1997;20(4):337-340.
88. Comoli P, Basso S, Labirio M, et al. T cell therapy of Epstein-Barr virus and adenovirus infections after hemopoietic stem cell transplant. *Blood Cells Mol Dis*. 2008;40(1):68-70.
89. Doubrovina E, Oflaz-Sozmen B, Prockop SE, et al. Adoptive immunotherapy with unselected or EBV-specific T cells for biopsy-proven EBV+ lymphomas after allogeneic hematopoietic cell transplantation. *Blood*. 2012;119(11):2644-2656.
90. Barker JN, Doubrovina E, Sauter C, et al. Successful treatment of EBV-associated posttransplantation lymphoma after cord blood transplantation using third-party EBV-specific cytotoxic T lymphocytes. *Blood*. 2010;116(23):5045-5049.
91. Tzannou I, Papadopoulou A, Naik S, et al. Off-the-shelf virus-specific t cells to treat bk virus, human herpesvirus 6, cytomegalovirus, Epstein-Barr virus, and adenovirus infections after allogeneic hematopoietic stem-cell transplantation. *J Clin Oncol*. 2017;35(31):3547-3557.
92. Boeckh M, Ljungman P. How we treat cytomegalovirus in hematopoietic cell transplant recipients. *Blood*. 2009;113(23):5711-5719.
93. Gerna G, Lilleri D, Baldanti F. An overview of letermovir: a cytomegalovirus prophylactic option. *Expert Opin Pharmacother*. 2019;20(12):1429-1438.
94. Micklethwaite K, Hansen A, Foster A, et al. Ex vivo expansion and prophylactic infusion of CMV-pp65 peptide-specific cytotoxic T-lymphocytes following allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2007;13(6):707-714.
95. Micklethwaite KP, Clancy L, Sandher U, et al. Prophylactic infusion of cytomegalovirus-specific cytotoxic T lymphocytes stimulated with Ad5f35pp65 gene-modified dendritic cells after allogeneic hemopoietic stem cell transplantation. *Blood*. 2008;112(10):3974-3981.
96. Mackinnon S, Thomson K, Verfuerth S, et al. Adoptive cellular therapy for cytomegalovirus infection following allogeneic stem cell transplantation using virus-specific T cells. *Blood Cells Mol Dis*. 2008;40(1):63-67.
97. Blyth E, Clancy L, Simms R, et al. Donor-derived CMV-specific T cells reduce the requirement for CMV-directed pharmacotherapy after allogeneic stem cell transplantation. *Blood*. 2013;121(18):3745-3758.
98. Koehne G, Hasan A, Doubrovina E, et al. Immunotherapy with donor T Cells sensitized with overlapping pentadecapeptides for treatment of persistent cytomegalovirus infection or viremia. *Biol Blood Marrow Transplant*. 2015;21(9):1663-1678.
99. Bao L, Cowan MJ, Dunham K, et al. Adoptive immunotherapy with CMV-specific cytotoxic T lymphocytes for stem cell transplant patients with refractory CMV infections. *J Immunother*. 2012;35(3):293-298.
100. Chakrabarti S, Mautner V, Osman H, et al. Adenovirus infections following allogeneic stem cell transplantation: incidence and outcome in relation to graft manipulation, immunosuppression, and immune recovery. *Blood*. 2002;100(5):1619-1627.
101. Geyeregger R, Freimuller C, Stemberger J, et al. First-in-man clinical results with good manufacturing practice (GMP)-compliant polypeptide-expanded adenovirus-specific T cells after haploidentical hematopoietic stem cell transplantation. *J Immunother*. 2014;37(4):245-249.
102. Ip W, Silva JMF, Gaspar H, et al. Multicenter phase 1/2 application of adenovirus-specific T cells in high-risk pediatric patients after allogeneic stem cell transplantation. *Cytotherapy*. 2018;20(6):830-838.
103. Rorije NM, Shea MM, Satyanarayana G, et al. BK virus disease after allogeneic stem cell transplantation: a cohort analysis. *Biol Blood Marrow Transplant*. 2014;20(4):564-570.

104. Walter O, Treiner E, Bonneville F, et al. Treatment of Progressive Multifocal Leukoencephalopathy with Nivolumab. *N Engl J Med*. 2019;380(17):1674-1676.
105. Cortese I, Muranski P, Enose-Akahata Y, Ha et al. Pembrolizumab Treatment for Progressive Multifocal Leukoencephalopathy. *N Engl J Med*. 2019;380(17):1597-1605.
106. Muftuoglu M, Olson A, Marin D, et al. Allogeneic BK virus-specific T cells for progressive multifocal leukoencephalopathy. *N Engl J Med*. 2018;379(15):1443-1451.
107. Gerdemann U, Keukens L, Keirnan JM, et al. Immunotherapeutic strategies to prevent and treat human herpesvirus 6 reactivation after allogeneic stem cell transplantation. *Blood*. 2013;121(1):207-218.
108. Ma CK, Blyth E, Clancy L, et al. Addition of varicella zoster virus-specific T cells to cytomegalovirus, Epstein-Barr virus and adenovirus tri-specific T cells as adoptive immunotherapy in patients undergoing allogeneic hematopoietic stem cell transplantation. *Cytotherapy*. 2015;17(10):1406-1420.
109. Papadopoulou A, Gerdemann U, Katari UL, et al. Activity of broad-spectrum T cells as treatment for AdV, EBV, CMV, BKV, and HHV6 infections after HSCT. *Sci Transl Med*. 2014;6(242):242ra83.
110. Lee DW, Kochenderfer JN, Stetler-Stevenson M, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. *Lancet*. 2015;385(9967):517-528.
111. Shalabi H, Delbrook C, Stetler-Stevenson M, et al. Chimeric antigen receptor T-cell (CAR-T) therapy can render patients with ALL into PCR-negative remission and can be an effective bridge to transplant (HCT). *Biol Blood Marrow Transplant*. 2018;24(suppl 3):S25-S26.

SECTION IV Lung Cancer

Section Editor: Bonnie S. Glisson

23 Small Cell Carcinoma of the Lung

24 Non–Small Cell Lung Cancer: General Principles, Management of Localized Disease, and Treatment of Metastatic Disease without Oncogene Drivers

25 Targeted Therapies in Non–Small Cell Lung Cancer

This page intentionally left blank

23 Small Cell Carcinoma of the Lung

Jeremy A. Ross
Lauren A. Byers
Carl M. Gay

KEY CONCEPTS

- Small cell lung cancer (SCLC) is an aggressive malignancy for which outcomes remain poor. The majority of patients present with metastatic disease, and few patients are cured, even among those that present with early-stage disease. There is an urgent need for more effective therapies for this disease.
- For patients with stage I disease, surgical resection should be considered if mediastinal staging is negative. Adjuvant chemotherapy with four cycles of etoposide–cisplatin (EP) should be considered for all patients with surgically resected SCLC and no lymph node metastases found at the time of resection.
- Most patients with limited-stage disease are treated with concurrent chemoradiotherapy. Although carboplatin is frequently used in patients with extensive-stage disease, EP with twice-daily radiation therapy remains the standard of care in patients without contraindications to cisplatin.
- Numerous clinical trials have established the effectiveness of prophylactic cranial irradiation (PCI) in decreasing the incidence of intracranial disease, although its impact on survival has been variable. All patients with limited-stage disease who respond to treatment should receive PCI. The use of PCI in patients with extensive-stage disease remains controversial.
- First-line chemoimmunotherapy has recently been shown to improve survival in patients with extensive-stage disease. The development and understanding of biomarkers for response to immunotherapy is progressing and may improve outcomes for some patients.
- Treatment options are limited for patients with recurrent disease, and clinical trials are recommended when feasible. There are no approved targeted agents for SCLC despite a plethora of trials.

Small cell lung cancer (SCLC) is an aggressive bronchogenic carcinoma representing 14% of all lung cancers, accounting for approximately 30,000 new cases annually in the United States.[1] It is distinguished from non–small cell lung cancer (NSCLC) by its rapid doubling time and early metastatic dissemination. Regional lymph node involvement or distant metastasis is present in 90% or more of patients at diagnosis. Historically, SCLC has been staged as limited disease (LD), which is confined to the ipsilateral thorax of origin and regional nodes, versus extensive disease (ED). The recent International Association for the Study of Lung Cancer (IASLC) staging project and American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC), eighth edition, suggest use of the tumor, node, metastasis (TNM) system for the staging of SCLC.[2] Clinically, the limited- and extensive-stage classification is practical given that most patients present with advanced disease (stages III–IV) and are rarely candidates for resection or other definitive therapies.

Standard treatment for patients with LD (stages I–IIIB) includes both chemotherapy and radiation; chemotherapy is the mainstay of treatment for ED (stage IV). Although a dramatic response to initial therapy is usually observed, more than 95% of patients with ED and 80% to 90% of those with LD eventually have a relapse and die of their disease.

Despite extensive research, few substantive advances in the systemic treatment of patients with SCLC have been made for decades. However, molecular profiling and preclinical models of SCLC

have increased our understanding of the biology and genomic changes in the pathogenesis of SCLC. The use of immune checkpoint inhibitors has improved survival, and the translation of preclinical research to the clinic has brought promising data with targeted therapies, providing hope that further improvements in outcomes for patients are on the horizon.

EPIDEMIOLOGY

SCLC is uncommon in never smokers, who constitute only 3% to 5% of cases, and is commonly associated with intense tobacco exposure.[3,4] However, transformation to SCLC has been documented in never smokers with epidermal growth factor receptor (*EGFR*) mutation–positive adenocarcinoma of the lung, in the setting of resistance to tyrosine kinase inhibitors.[5] The original *EGFR* mutation is maintained in the SCLC, supporting the notion that the tumor evolved from transformation and is not a second primary cancer.

The incidence of SCLC has steadily declined, as illustrated by an analysis of the Surveillance, Epidemiology, and End Results (SEER) database,[1] in which the proportion of SCLCs decreased from 17% in 1986 to 13% in 2002. However, this decrease was accompanied by an increase in SCLC cases arising in women (28% in 1973 vs 50% in 2002), attributed to increasing tobacco use among women starting in the 1960s. The reduced incidence is primarily due to decreased smoking in men and may also be due in part to changes in the pathologic criteria leading to the classification of cases as large cell neuroendocrine carcinoma (LCNEC) that would have been previously classified as SCLC.

RISK FACTORS

Of all lung cancer subtypes, SCLC shows the strongest association with tobacco exposure, which represents the most important risk factor.[4] The risk is related to both duration (>40 years) and intensity of tobacco use (>30 cigarettes/day). This risk is lower in former smokers versus current smokers, although the risk in former smokers still exceeds that of nonsmokers.[4] Additional risk factors include exposure to asbestos, benzene, coal tar, and radon gas, usually as co-carcinogens with tobacco. Smoking cessation should be encouraged as primary prevention. Patients with LD who continue to smoke during or after chemoradiation experience increased toxicity, have a high risk of second lung cancers, and have shorter survival times than those who quit.[6]

NATURAL HISTORY

The natural history of SCLC was documented in the placebo arm of a randomized trial from the Veterans Administration Lung Cancer Study Group (VALSG) reported in 1969, testing the effect of three doses of intravenous (IV) cyclophosphamide.[7] In this trial, the median survival periods for patients in the placebo arm were 6 weeks for those with ED and 12 weeks for those with LD, based on the primitive staging studies that were available at that time. Because of the availability of modern staging techniques, outcomes in both groups would be likely better today. Cyclophosphamide increased the median survival by 75 days in both groups, tripling the survival time of patients with metastases and doubling that of patients with LD. This was the first observation foretelling the important role chemotherapy would come to play in management of patients with SCLC.

The use of effective combination chemotherapy and, in the case of patients with tumor amenable to definitive radiation, the use of multimodality treatment have improved survival of patients with SCLC.[1]

PROGNOSTIC FACTORS

The most important prognostic factor for SCLC is the stage because patients with LD have improved survival compared with those with ED.[8] Among patients with LD, good performance status (PS), age younger than 70 years, female gender, and normal lactate dehydrogenase (LDH) levels are predictive of a favorable outcome.[8] Among these patients, a small subgroup with very LD (no mediastinal involvement) was found to have a longer median survival time when treated with surgery.[9] In patients with ED, normal LDH, multidrug regimen treatment, and a single metastasis predicted better outcomes. Liver or cerebral metastases confer significantly shorter survival compared with bone, soft tissue, or bone marrow involvement.[10] Paraneoplastic syndromes (PNSs) may also predict outcome. Patients with the syndrome of ectopic corticotrophin (ACTH) secretion producing clinical Cushing syndrome have a dismal prognosis, with a low response to chemotherapy and poor control of hypercortisolism after treatment.[8] Lambert-Eaton myasthenic syndrome (LEMS), an autoimmune PNS, confers a more favorable prognosis, presumably because of immunity against the cancer.[11]

PATHOBIOLOGY

SCLC is defined by light microscopy as a malignant epithelial tumor consisting of small cells, with a round to fusiform shape, scant cytoplasm, finely granular

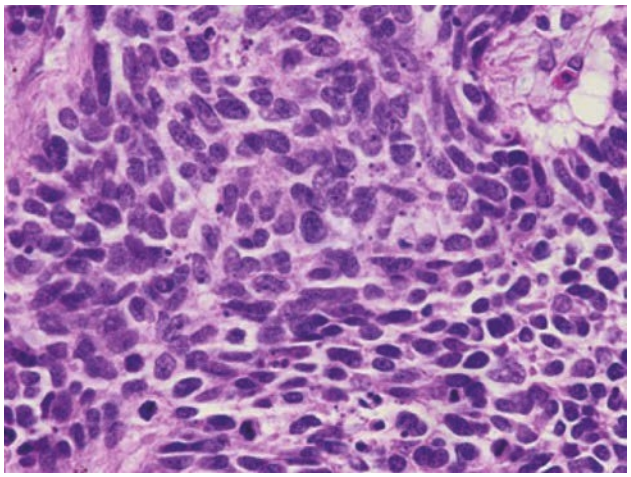


FIGURE 23–1 Light microscopic images of small cell lung cancer. Note the small, round, and spindle-shaped cells with hyperchromic nuclei and scant cytoplasm.

nuclear chromatin, and absent or inconspicuous nucleoli.[12] Nuclear molding and necrosis are frequent, and mitotic rates are high (Fig. 23–1). Tumors usually grow in diffuse sheets, but rosettes, peripheral palisading, organoid nesting, streams, ribbons, and rarely, tubules or ductules may be present. Typically, the diagnosis is made from small biopsies and cytology specimens because surgery is rarely performed. Because of significant crush artifact, biopsies are sometimes more problematic in diagnosis than cytology specimens.

SCLC is a "small, round, blue cell tumor" using a hematoxylin and eosin stain, and the differential diagnosis includes other small, round, blue cell tumors, including lymphomas and small cell sarcomas. Histologically, identical tumors can arise in other organs (eg, nasopharynx, larynx, genitourinary or gastrointestinal tract, and cervix) and are termed extrapulmonary small cell carcinomas. Both pulmonary and extrapulmonary small cell carcinomas have similar biological features and clinical behavior, with high potential for widespread disease. However, malignant cells from extrapulmonary small cell carcinomas do not exhibit 3p deletions, which are common in SCLCs, indicating, at least in part, differences in carcinogenesis.[13]

Immunohistochemical (IHC) markers are valuable in differential diagnosis of SCLC. Positive pancytokeratin (AE1/AE3) staining helps to identify the tumor as a carcinoma rather than a lymphoma or sarcoma.[12] Neural cell adhesion molecule (CD56), chromogranin, and synaptophysin are the most useful markers. Whereas CD56 expression is detectable in approximately 90% to 100% of cases, SCLC may be negative for expression of neuroendocrine markers, such as chromogranin and synaptophysin.[14] SCLC is a primitive undifferentiated high-grade neuroendocrine tumor (NET) and does not typically express these proteins as intensely as low-grade, well-differentiated NETs do, such as carcinoids. In 10% of cases, all neuroendocrine marker results may be negative, and the diagnosis can still be established if the morphology is diagnostic. Thyroid transcriptase factor 1 (TTF-1) is expressed in 70% to 90% of SCLCs; however, this marker may also be expressed in extrapulmonary small cell carcinomas and thus does not reflect lung origin.[15] The expression of TTF-1 may reflect molecular differences that could help guide treatment.[16] The Ki-67 staining index, reflecting proliferation, is generally greater than 50% in SCLC and can be used to differentiate SCLC from lower-grade NETs.[17]

MOLECULAR FEATURES

SCLC is characterized by genomic alterations, biology, and clinical behavior that are distinct from the intermediate- and low-grade pulmonary NETs. Loss of function alterations in the tumor suppressors tumor protein 53 (*TP53*) and the retinoblastoma 1 (*RB1*) gene at 13q14 occur in virtually all patients with SCLC.[18,19] Haploinsufficiency caused by allele loss in multiple areas on chromosome 3p, including 3p21.3,3p12,3p14.2, and 3p24.4, leads to absent or lower expression of several tumor-suppressor genes in more than 90% of SCLCs and is an early event in tumorigenesis.[13]

In addition to near-ubiquitous *TP53* and *RB1* inactivation, genomic profiling of SCLC tumors revealed frequent (25%) inactivating mutations in *NOTCH* family genes (PMID:26168399). Along with *NOTCH* family mutations, additional mutually exclusive alterations are frequent among histone acetyltransferase genes such as CREB-binding protein (*CREBBP*) and E1A binding protein P300 (*EP300*), as well as several genes related to *TP53* and *RB1* (tumor protein 73 (*TP73*), retinoblastoma-like 1 (*RBL1*), and retinoblastoma-like 2 (*RBL2*) ((PMID:26168399)). Amplification of MYC family members (v-myc avian myelocytomatosis viral oncogene homolog, MYC, MYCL1, and MYCN) is detected in 20% of SCLCs.[18] Loss of phosphatase and tensin homolog (PTEN) is observed in 2% to 4% of tumors[20]; however, the phosphoinositide 3-kinase (PI3K) pathway alteration rate be overall higher and promote SCLC tumorigenesis in preclinical models.

Differential patterns of gene expression underlie significant inter-tumoral diversity among SCLC (PMID: 20926931). The neuroendocrine-high (previously *classic*) SCLC subtype, now referred to as SCLC-A, is driven largely by the expression of the transcription factor achaete-scute homolog 1 (*ASCL1*) and its transcriptional targets (PMID: 2985258,27452466). Meanwhile, neuroendocrine-low (previously *variant*) SCLC is composed of several unique subtypes, including a neuronal differentiation 1 (*NEUROD1*)-regulated subtype

TABLE 23-1 Representative List of Common or Potentially Targetable Genomic and Proteomic Alterations According to Percentage in Small Cell Lung Cancer

Gene	Mutation Frequency (Type of Mutation)
TP53	75%–90% Loss of function (mutation, LOH, deletion)
RB1	~100% Loss of function (mutation, LOH, deletion)
PTEN	~5% Loss of function (mutation, LOH, deletion)
MYC	18%–31% MYC family alterations overall Gain of function (amplification or transcriptional dysregulation)
SOX2	27% Gain of function (amplification)
FGFR1	<10% Gain of function (amplification, mutation)
CCNE1	<10% Gain of function (amplification)
EPHA7	<10% Gain of function (amplification)
PARP1	>50% (overexpression of protein target)

CCNE1, cyclin E1; EPHA7, ephrin receptor A; FGFR1, fibroblast growth factor receptor 1; MYC, v-myc avian myelocytomatosis viral oncogene homolog; PARP, poly(ADP-ripose) polymerase 1; PTEN, phosphatase and tensin homolog; RB1, retinoblastoma 1; SOX2, sex-determining region Y box 2; TP53, tumor protein 53.

(SCLC-N) and a subtype originating in pulmonary tuft cells driven by the expression of POU domain, class 2, transcription factor 3 (*POU2F3*, SCLC-P) (PMID: 29852 58,27452466,28089889,29945888).

At the protein level, increased expression of cKit, and its ligand stem cell factor, is detected in up to 80% to 90% of SCLC surgical specimens.[21] The BCL-2 family proteins exert an antiapoptotic effect and may be upregulated in 75% to 95% of SCLCs.[18] More comprehensive proteomic profiling by reverse phase protein array has identified differences in protein expression between SCLC or LCNEC and other NSCLC cancers, including the DNA repair protein poly(ADP-ribose) polymerase 1 (PARP1).[22]

Alterations in epigenetic regulation of the genome may be involved in SCLC biology. Sequencing of SCLC exomes has led to the identification of histone modification as a major feature. Mutations in CREBBP and EP300 are common in SCLC and may clustered around the histone acetyltransferase (HAT) domain, significantly impacting the activity of these genes, and supports a role for the loss of their function in SCLC.[23,24] Table 23–1 describes common genomic and proteomic alterations that occur in SCLC.

CLINICAL PRESENTATION

SCLC typically arises in the central airways and infiltrates the submucosa, with a tendency to narrow the bronchial lumen through extrinsic or endobronchial spread, in contrast to squamous cell carcinomas, in which polypoid luminal occlusion is common. Rapid intrathoracic tumor growth, lymphatic and distant spread, and manifestation of PNSs can cause severe and progressive symptoms that lead to diagnosis generally within 3 months from onset. Common clinical manifestations include cough, dyspnea, weight loss, and debility. Hemoptysis and postobstructive pneumonia are relatively uncommon because of the submucosal growth pattern of the tumor. Bulky involvement of mediastinal lymph nodes is a hallmark of SCLC, and syndromes resulting from mass effects are commonly seen, including superior vena cava syndrome, hoarseness (from recurrent laryngeal nerve compression), phrenic nerve palsy, dysphagia (from esophageal compression), and stridor (from tracheal compression). SCLC is the most common malignant cause of superior vena cava obstruction. Radiographically, a large hilar mass with bulky mediastinal adenopathy is commonly observed (Fig. 23–2), although occasional peripheral satellite nodules may be found.

Most patients (60%–70%) present with overt metastatic disease; common sites of metastasis include liver, adrenals, bone, bone marrow, and brain. Symptoms of metastatic disease can include bone or abdominal pain, headache, seizures, fatigue, and anorexia. Occasionally, patients may present with PNSs, such as syndrome of inappropriate antidiuretic hormone (SIADH) or LEMS.

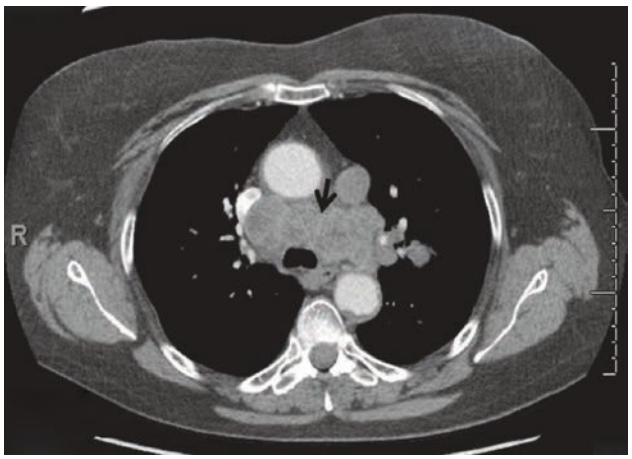


FIGURE 23–2 Bulky involvement of mediastinal adenopathy (*black arrow*) at computed tomography scan of chest in a patient with extensive-stage small cell lung cancer.

STAGING

The two-stage system originally proposed by the VALSG in the late 1950s and later modified by the IASLC is currently used for simplicity and practicality. LD is defined as a tumor confined to one hemithorax, with involvement of regional nodes, including contralateral mediastinal or ipsilateral supraclavicular nodes, that can be included in a single tolerable radiotherapy (RT) port (TNM stages I–IIIB). ED is defined as a tumor beyond the boundaries of LD, including distant metastases, malignant pericardial or pleural effusions, and contralateral supraclavicular and contralateral hilar node involvement (TNM stage IV, any T, any N, M1a/b). More recently, IASLC proposed changes to the TNM NSCLC staging system, mainly in T and M descriptors and stage groupings. These changes have been incorporated into the AJCC seventh and eighth editions, which recommend TNM staging for SCLC and NSCLC.[25] However, the two-stage system continues to be used in clinical practice because most patients present with advanced disease (stages III and IV) and are only rarely candidates for surgery. This system has prognostic significance and clinical implications because patients with LD are candidates for chemoradiation with curative intent, but patients with ED receive chemotherapy with or without immunotherapy and palliative radiation as clinically indicated. Approximately 30% to 40% of patients with SCLC present with LD; the remainder have ED.[1]

The initial clinical evaluation should include history and physical examination; chest radiography; pathology review; baseline laboratory tests, including complete blood cell count, a comprehensive metabolic profile, and LDH ;, computed tomography (CT) scans of the chest and abdomen with IV contrast; and brain magnetic resonance imaging (MRI) or CT scan with IV contrast. Brain MRI is more sensitive than CT in identifying metastases and is preferred. If LD is suspected, a positron emission tomography (PET)–CT scan may be indicated because it can identify distant disease and guide mediastinal evaluation. For most metastatic sites, a PET-CT scan is superior to other imaging modalities; however, it is inferior to MRI or CT of the brain for detection of brain metastases. Even though PET-CT may improve staging accuracy of SCLC, pathologic confirmation is still recommended for lesions depicted at PET-CT scan that may alter staging. If PET-CT scan is not available or is equivocal, bone imaging with a whole-body bone scan should be used to stage the skeleton.[26]

Staging should not focus only on symptomatic sites of disease or on altered laboratory data. For example, bone scans may be positive in up to 30% of asymptomatic patients without abnormal alkaline phosphatase levels. The goal of complete staging is to identify patients with LD who are candidates for definitive therapy. In the presence of obvious ED, staging may be clinically directed. Brain imaging should be obtained in all patients, given the morbidity of uncontrolled central nervous system (CNS) disease.[27] Imaging of the CNS reveals brain metastases in 10% to 15% of patients at diagnosis, with 30% of these individuals asymptomatic.

In patients with apparent stage I disease (T1-2N0), surgical resection should be considered if mediastinal staging results are negative[9] by conventional mediastinoscopy, transesophageal endoscopic ultrasound-guided fine-needle aspiration, endobronchial ultrasound-guided transbronchial needle aspiration, or video-assisted thoracoscopy. If a pleural effusion is present in a patient with otherwise LD, thoracentesis should be performed and fluid sent for cytology. If the fluid is exudative or if malignant cells are present, the patient should be considered to have ED (stage IV: M1a). Although most pleural effusions in lung cancer are related to the malignancy, there may be a few instances in which multiple cytopathological examinations are negative for malignancy and the pleural fluid is not an exudate. When these elements and clinical judgment indicate that a pleural effusion is not malignant, the effusion should be excluded as a staging element. Pericardial effusion is classified according to the same criteria.

Sampling of cerebrospinal fluid is indicated if leptomeningeal spread is suspected. Pulmonary function tests should be performed in patients who are candidates for definitive chemoradiation therapy. Severe anemia, nucleated red blood cells on peripheral smear, neutropenia, or thrombocytopenia, in the absence of other obvious causes are selection criteria for bone marrow aspiration and biopsy.[10,26] The presence of tumor cells in a marrow biopsy identifies ED. Treatment should be initiated as quickly as possible after diagnosis is confirmed, given the rapid rate of progression. If the patient is significantly symptomatic or the staging evaluation prolonged, staging should be completed while chemotherapy is started.

TREATMENT

Limited Disease

Patients with SCLC rarely survive more than a few months without treatment. The disease is highly responsive to both chemotherapy and radiation, and patients with LD are treated with curative intent. In LD, the overall response rates (RRs) to combined chemoradiation are typically 80% to 90%, including 50% to 60% complete RRs. Median overall survival (OS) is approximately 17 months, and the 5-year survival rate is approximately 12%.

Surgery

An autopsy series on patients who died from postoperative complications revealed that 90% of patients with SCLC had mediastinal metastasis within 30 days after surgical resection.[28] A randomized trial evaluating surgery versus thoracic RT (TRT) in patients with resectable disease revealed that the TRT group had significantly longer OS,[29] suggesting that even in absence of diagnosed metastases, surgery alone is an inadequate therapeutic strategy. However, surgery may play a role in multimodality therapy for patients (5%) with early T stage and without nodal involvement (T1-T2N0M0, very LD). A 5-year survival rate of 48% has been reported in patients with very LD when surgery was followed by adjuvant chemotherapy.[9] Adjuvant chemotherapy with four courses of etoposide–cisplatin (EP) should be considered for all patients with surgically resected SCLC. If nodal involvement is found at the time of surgery, chemoradiation and chemotherapy are recommended.

Combined Chemoradiation Therapy

Based on the results of a British Medical Research Council trial demonstrating surgery to be inferior to RT for the treatment of LD,[29] TRT became standard of care for local control for these patients. Although early studies indicated that RT could increase local control compared with chemotherapy alone, these studies did not consistently show significant survival benefits to combination therapy over chemotherapy.[30] Because of this controversy, randomized trials were performed. Two meta-analyses were performed that showed a significant 2-year survival benefit of 5.4% with the addition of RT to systemic chemotherapy for patients with LD.[30,31] Notably, the best outcomes from these older trials included concurrent as opposed to sequential approaches; in addition, the regimens used in this era were anthracycline- and alkylator-based therapies and were associated with excessive in-field toxicity when administered with concurrent radiation. The development of the EP regimen was critical to improving the tolerance and feasibility of concurrent chemoradiation. EP can be given at full dose with RT, leading to improved disease control.

An anthracycline-based regimen (cyclophosphamide, epirubicin, and vincristine [CEV]) was compared in a phase III trial with EP in patients with SCLC.[32] Patients received RT concurrently with the third cycle of chemotherapy, and prophylactic cranial irradiation (PCI) was administered to those who achieved complete remission (CR). The results showed that, in patients with LD, EP was superior to CEV for survival rates at 2 and 5 years (14% and 5% vs 6% and 2%, respectively; $P = .0001$), as well as median OS (14.5 vs 9.7 months; $P = .001$). In patients with ED, no survival difference was noted.

The addition of other chemotherapeutic agents to the EP regimen—either as a triplet with paclitaxel or alternating therapy with cyclophosphamide, doxorubicin, and vincristine—has also been studied, but to date a new standard in the treatment of LD has not emerged.[33,34]

Radiation Intensity

Based on the radiobiology of SCLC, the Intergroup (INT) trial 0096 studied accelerated hyperfractionated RT (AHRT) compared with conventional fractionation in a phase III trial.[35] More than 400 patients were randomized between the two arms. All patients received four cycles of EP, and TRT was administered concurrently, starting with the first cycle of chemotherapy. All patients received 45 Gy, either in once-daily 1.8-Gy fractions for 5 weeks or twice-daily 1.5-Gy fractions for 3 weeks. Patients in the twice-daily RT group had an improved median OS (23 vs 19 months) and 5-year survival (26% vs 16%), at the cost of increased weight loss and grade 3 esophagitis (27% vs 11%). Local failure rates were lower in the twice-daily RT arm, presumably the major reason for improved survival.

Intergroup trial 0096 convincingly showed an OS benefit to concurrent chemoradiation with hyperfractionation. However, because of concerns for side effects and the logistical difficulties involved in twice-daily treatment, the regimen was not widely adopted.[36] The control arm of the INT 0096 study used a relatively low total RT dose, and since the results of INT 0096 have become available, conventionally fractionated radiation in higher doses has also been studied. The Cancer and Leukemia Group B (CALGB) trial tested the regimen paclitaxel and topotecan for two cycles followed by TRT with 70 Gy in 35 daily fractions with concurrent carboplatin–etoposide (CE; total of three cycles) in a phase II study.[37] Median OS was 22.4 months, comparable to that found with AHRT in the INT 0096 study.

Another schedule of TRT tested was concomitant boost, in which patients received once-daily radiation through most of their course and then received hyperfractionated therapy at the end of treatment so that RT was accelerated without the need for twice-daily administration throughout the treatment course. The Radiation Therapy Oncology Group (RTOG) tested this approach in the phase II trial 0239. Patients received 61.2 Gy over 5 weeks, with twice-daily RT in the final 9 days.[38] RT started on day 1 of chemotherapy with four cycles of EP. The two-year survival rate was 37%, somewhat less than that found in both INT 0096 and the CALGB trial (2-year survival rates of 41% and 48%, respectively).

In the phase III CONVERT trial, patients were randomized to receive either 45-Gy RT in twice-daily fractions of 1.5 Gy over 19 days or 66-Gy RT in 33 once-daily fractions of 2 Gy over 45 days while receiving EP chemotherapy. The primary endpoint was OS, and there was no significant difference between the groups. Toxicities were similar between the groups, and twice-daily chemoradiotherapy continues to be the standard of care.[39]

Timing of Chemotherapy

Sequential, concurrent, and alternating chemotherapy have all been tested with TRT. Early studies did not show a survival benefit to concurrent chemotherapy, likely because of the increased toxicity when using cyclophosphamide- or doxorubicin-based chemotherapy. EP is better tolerated than these earlier regimens when administered concurrently with RT.

The National Cancer Institute of Canada reported a phase III trial of alternating CAV (cyclophosphamide, anthracycline, and vincristine)–EP with TRT in either the second or sixth cycle of chemotherapy.[40] The patients receiving early RT experienced improved OS (21.2 vs 16 months). The Japan Clinical Oncology Group compared RT (45 Gy in twice-daily 1.5-Gy fractions) starting with either the first cycle of EP or after completion of the chemotherapy course.[41] More myelosuppression was noted in the patients in the concurrent arm, but there was a significant reduction in risk of death for early concurrent therapy, with a hazard ratio (HR) of 0.70 (P = .02). Although not all trials have consistently shown a benefit for concurrent chemoradiation, the data strongly support this and its early integration in treatment when the regimen is EP. Furthermore, efficacy outcomes are consistently better with EP in the treatment of LD.

Given that SCLC is such a rapidly dividing malignancy, it has been hypothesized that accelerated proliferation of tumor clonogens can affect outcome and that treatment should be delivered in a condensed fashion.[42] A meta-analysis examined the impact of a novel parameter, time from the start of any treatment to the end of RT (SER), on OS in LD. A shorter SER was found to be a significant predictor of better outcome. For each week that the SER was lengthened, OS at 5 years showed an absolute decrease of almost 2%.[42] The data from INT 0096 had a strong influence on this result.

Carboplatin is frequently used in ED because of a more favorable toxicity profile, whereas cisplatin is preferred in patients with LD with curative intent. The efficacy of cisplatin versus carboplatin regimens in LD was evaluated in a meta-analysis of four trials,[43] which revealed no significant difference in terms of efficacy. Nevertheless, because of its use in trials for which the best 5-year survival rate has been observed in LD, EP should be given unless there is a significant contraindication to cisplatin use. Notably, the dose of cisplatin in INT 0096 was only 60 mg/m.[2] Figure 23–3 illustrates the treatment algorithm for management of limited-stage SCLC.

Extensive Disease

Systemic chemotherapy represents the primary therapeutic modality for patients with ED, although the addition of immunotherapy to first-line chemotherapy has been shown to improve survival.[44] Currently, TRT is used for symptom palliation; however, a potential role for radiation in patients with limited systemic disease and a good response to initial therapy has been suggested. Chemotherapy prolongs survival compared with best supportive care (BSC).[7] From the time of diagnosis, the median OS for patients with ED is 8 to 13 months, the 5-year survival rate is 1% to 2%, and the 2-year survival rate is 4% to 5%.[1] Figure 23–4 shows representative coronal PET-CT images in a patient with extensive-stage SCLC (ED).

Chemotherapy

In an early study, patients with SCLC had a highly significant improvement in survival with IV cyclophosphamide compared with placebo, increasing the median period survival from 12 weeks to almost 5 months.[7] As new cytotoxins became available, combination therapy was studied, and the CAV regimen became the standard of care for patients with ED. EP was initially evaluated in patients who had recurrent disease after or failed to respond to CAV, with RRs of 55%.[45] It was later evaluated as a first-line treatment in patients unable to tolerate CAV, demonstrating a median OS of 39 weeks in ED, with less toxicity.[46] In a phase III trial, the equivalent efficacy of EP and CAV was confirmed by randomizing 437 patients to receive four cycles of EP, six cycles of CAV, or alternation of these two regimens for 18 weeks (CAV/EP, three cycles each).[47] The RRs (61%, 51%, 59%, respectively) and median OS (8.6, 8.3, and 8.1 months, respectively) were equivalent across the arms. Myelosuppression was the dose-limiting toxicity, and four cycles of EP were better tolerated. Similar results were seen in a Japanese trial.[33]

Chemoimmunotherapy

The high mutation rate in SCLC led to the hypothesis that the addition of immunotherapy to chemotherapy could enhance the antitumor immune response. However, early trials of immune checkpoint inhibition did not improve outcomes. In a phase II study of 45

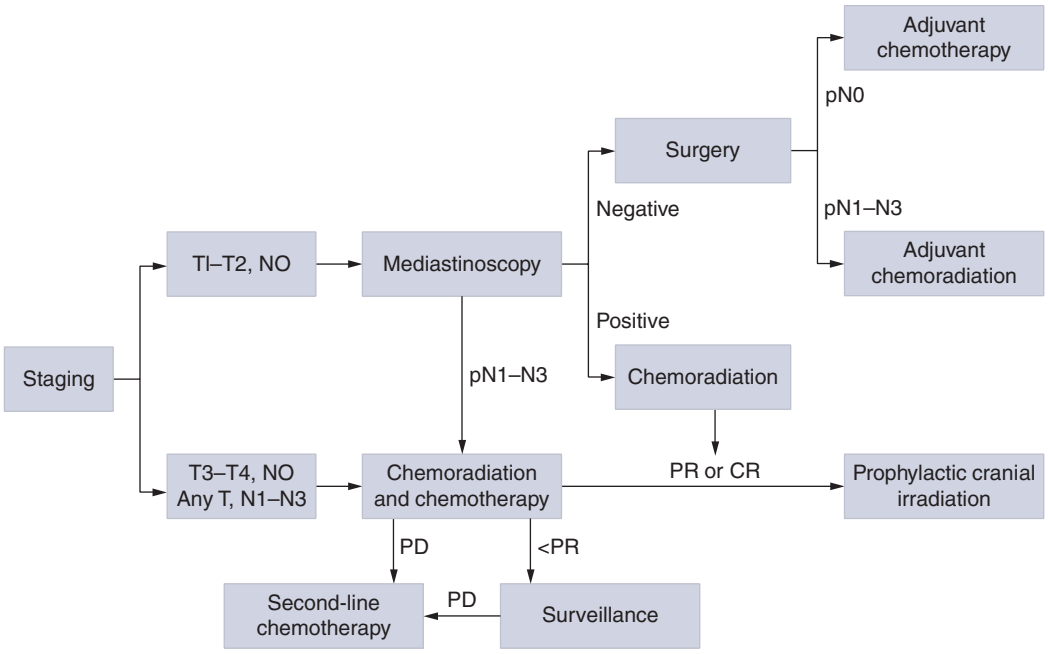
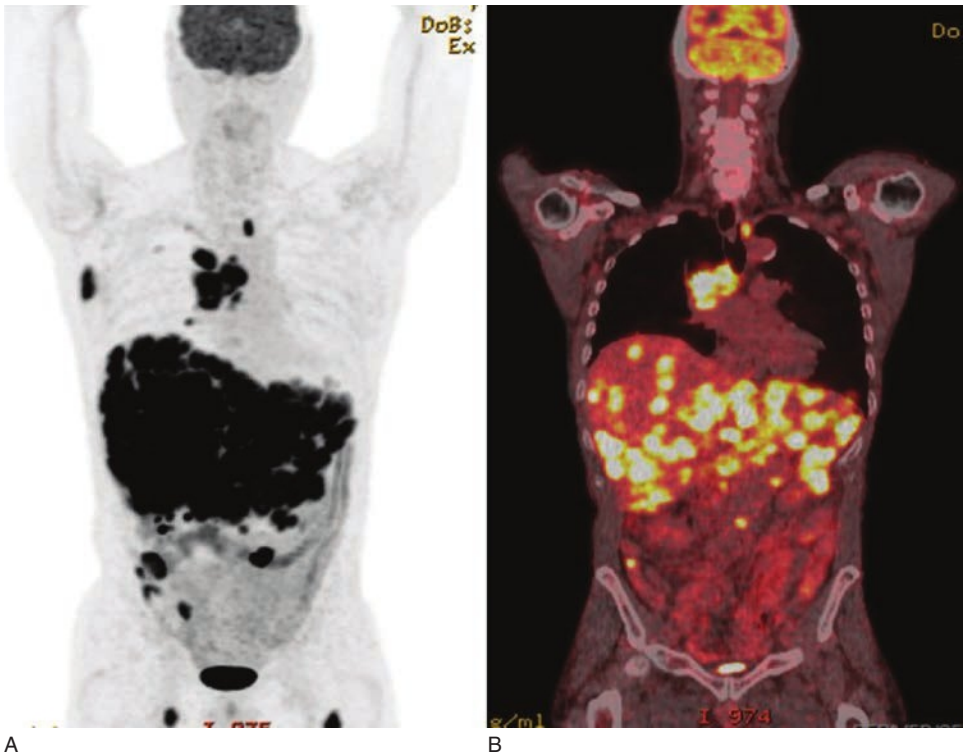


FIGURE 23–3 Treatment algorithm for management of patients with limited-stage small cell lung cancer. CR, complete remission; M, metastasis; N, node; PD, progressive disease; PR, partial remission; T, tumor.



A B

FIGURE 23–4 Representative positron emission tomography (PET)–computed tomography images in a patient with extensive-stage small cell lung cancer. Coronal PET (**A**) and fused coronal (**B**) images are shown.

patients with ED who had a response or stable disease with induction chemotherapy received maintenance therapy with pembrolizumab, a monoclonal antibody directed at programmed cell death protein 1 (PD-1). The median PFS was 1.4 months (95% confidence interval [CI], 1.3–2.8), which was not improved compared with historical data. However, 13% of patients had PFS of at least 1 year, and 37% of patients had OS of at least 1 year, suggesting that an unknown subset of patients could have benefitted from this therapy.[48] Ipilimumab, a monoclonal antibody directed against CTLA-4 (cytotoxic T lymphocyte-associated antigen 4), was given in sequential combination with carboplatin–paclitaxel in a randomized phase II of 130 untreated patients with SCLC. There was improved PFS (HR, 0.64; $P = .03$) but not OS (median, 12.5 vs 9.1 months for the sequential combination vs chemotherapy alone; $P = .13$).[49] In a subsequent phase III study of more than 1110 patients with newly diagnosed ED, the regimen of EP plus ipilimumab was compared with EP plus placebo. The addition of ipilimumab did not improve the median OS, which was approximately 11 months in both treatment groups.[50]

More recently, the IMpower133 study combined atezolizumab with chemotherapy in newly diagnosed ED. In this double-blind, placebo-controlled, phase III trial, patients were randomly assigned to receive EP plus atezolizumab followed by maintenance atezolizumab compared with EP plus placebo followed by maintenance placebo. The median OS was 12.3 months in the atezolizumab group compared with 10.3 months in the placebo group (HR, 0.70, $P = 0.007$).[44] The results of this study represented the first significant improvement in OS for patients with ED in multiple decades, and this regimen is now the standard-of-care regimen for the first-line treatment of ED.

The therapeutic value of immunotherapy as shown in the IMpower133 study was confirmed in another recent phase III clinical trial, the CASPIAN study. In this study, patients were randomly assigned to receive durvalumab, an inhibitor of PD-L1, plus platinum–etoposide, durvalumab plus tremelimumab, an inhibitor of CTLA-4, plus platinum–etoposide or platinum–etoposide alone. At a median follow-up period of 14.2 months, the median OS was 13.0 months with durvalumab plus chemotherapy (95% CI, 11.5–14.8) and 10.3 months (95% CI, 9.3–11.2) with chemotherapy alone. Furthermore, the objective RR was higher with durvalumab plus chemotherapy (79% vs 70%), although there was no difference in the median duration of response.[51] This trial is ongoing, and results for the durvalumab plus tremelimumab plus chemotherapy group have not yet been reported. The impact of the addition of immune checkpoint inhibitors to conventional chemotherapy on the survival of patients with ED will be clarified as data mature. As the development and understanding of biomarkers for response to immunotherapy progress, outcomes may continue to improve for some patients.

Thoracic Radiation Therapy

Prospective trials have evaluated the role of consolidative TRT in patients with ED who initially respond to systemic chemotherapy. In a single-center study, 206 patients received three cycles of EP,[52] and complete responders at distant sites and those with intrathoracic partial remission (PR) or CR ($n = 109$) were randomized to thoracic AHRT (54 Gy, 36 fractions over 18 days) combined with CE or four additional cycles of EP. Patients with brain metastases, stable disease, progressive disease, or only PR outside the thorax were not randomized. The addition of TRT to chemotherapy improved median OS (17 vs 11 months; 5-year survival rate, 9% vs 4%, respectively; $P = .041$). There was a trend toward reduced local recurrence in the radiation arm but no difference in metastasis-free survival. Acute high-grade toxicity was higher in the chemotherapy arm.

In the phase III multicenter European CREST trial, patients with ED were initially treated with four to six cycles of platinum-based chemotherapy. Patients with any response were then randomized to TRT (30 Gy in 10 fractions) plus PCI ($n = 247$) or to PCI alone ($n = 248$).[53] The study did not meet the primary end point of 1-year survival improvement (33% with thoracic RT vs 28% without; $P = .07$). However, 2-year survival and PFS rates were significantly longer for those receiving TRT after prolonged follow-up (2-year OS, 13% vs 3%; $P = .004$; PFS, 24% vs 7%, respectively, at 6 months). The most common grade 3 toxicities in the TRT group compared with the control group were fatigue (4.5% vs 3.2%) and dyspnea (1.2% vs 1.6%). Patients most likely to benefit were those with residual disease in the thorax.

The RTOG 0937 phase II study (NCT 01055197) comparing PCI alone versus PCI with consolidative RT to residual locoregional and metastatic disease in patients with ED who responded to platinum-based chemotherapy was closed early due to excess grade 5 toxicity in the experimental arm. Currently, it is our practice to consider consolidative TRT in selected patients with ED with excellent control of extrathoracic disease, residual disease in the thorax, and retained PS after chemotherapy. Thoracic RT should be limited to palliative dosing and conventional fractionation, and concurrent chemotherapy should not be given.

Figure 23–5 demonstrates metabolic response on PET in a patient with ED and extensive bone metastases after four cycles of CE. Figure 23–6 shows the treatment algorithm for the management of extensive-stage SCLC.

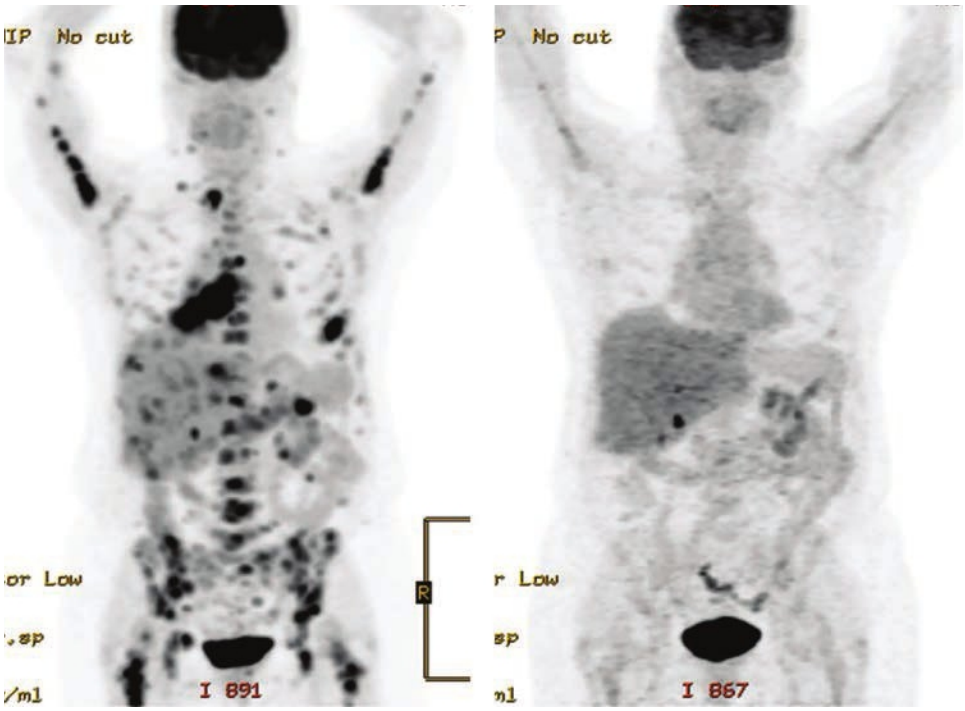


FIGURE 23–5 **Response of extensive-stage small cell lung cancer following treatment with platin–etoposide at positron emission tomography (PET)–computed tomography imaging. Baseline (A) and restaging coronal PET (B) images are shown.**

Recurrent Disease

Chemotherapy and Immunotherapy

Despite initial response to chemoradiation, approximately 11% of patients with LD and only 1% to 2% of those with ED are alive at 5 years, with the vast majority succumbing to recurrent SCLC.[1] Historically, recurrent disease is less responsive, and survival is limited, with the median survival period ranging from 2 to 6 months after relapse. The response to initial treatment and the time to relapse after induction chemotherapy are both important determinants of response to second-line chemotherapy. Patients with objective response to initial treatment and PFS at least 60 to 90 days after completion of induction chemotherapy are

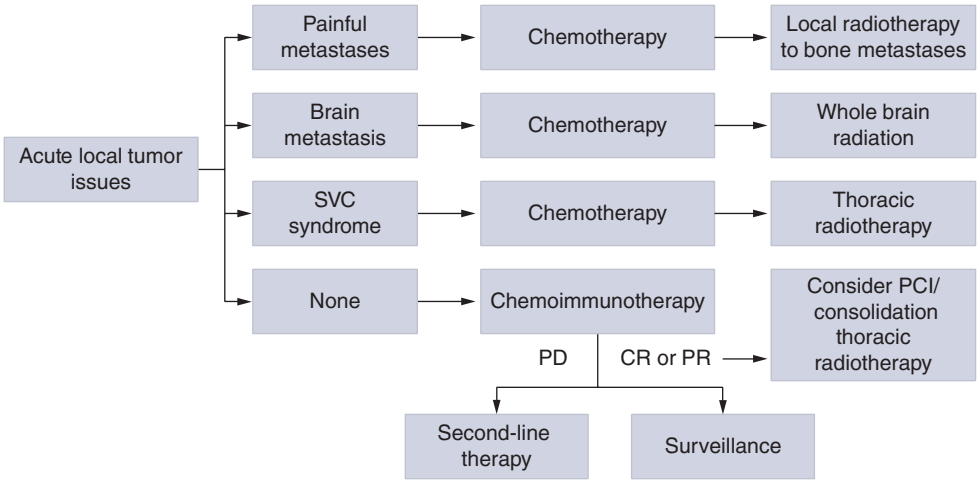


FIGURE 23–6 **Treatment algorithm for management of patients with extensive-stage small cell lung cancer. CR, complete remission; PCI, prophylactic cranial irradiation; PD, progressive disease; PR, partial remission; SVC, superior vena cava.**

more likely to respond to additional chemotherapy and are considered to have "sensitive" disease. Those who do not achieve disease regression with initial chemotherapy or with shorter duration of response after chemotherapy is discontinued are considered refractory.[54]

Reintroduction of the chemotherapy regimen used for induction has been a therapeutic strategy for relapse in patients with prolonged PFS after first-line therapy. The first evidence to support this was suggested in a series of six patients who had achieved a greater than 2-year remission after induction chemotherapy.[55] Five of these patients received some or all of the agents of their induction regimen, with four responses, lasting up to 18 months. Other studies also suggested responses when first-line therapy was reintroduced at relapse if patients had either a CR or a response longer than 34 weeks after induction.[56,57] In the modern era, when many patients receive just four courses of induction chemotherapy, retreatment with EP could be considered if initial response was dramatic and maintained PFS for 3 months or more.

Topotecan and irinotecan have been studied in recurrent disease. Topotecan is the only drug for which there are several randomized trials in this setting and is the only agent approved by the Food and Drug Administration (FDA) in the second-line setting for recurrent SCLC. Oral topotecan was found to have similar efficacy to IV topotecan, with less toxicity and ease of administration.[58] A phase III trial showed that IV topotecan had similar efficacy to the CAV regimen in patients with sensitive relapse, with an RR of 24% versus 18%, with a similar median TTP (13 vs 12 weeks) and OS (25 vs 24.7 weeks) for topotecan versus CAV, respectively.[54] The topotecan group had better symptom control, with less-severe neutropenia. The improvement in symptom control led to its FDA approval. In a phase III registration trial, oral topotecan was compared with BSC in patients who had relapsed 45 days or more after achieving a response to first-line therapy and were not candidates to receive IV topotecan.[59] Topotecan significantly improved OS (25.9 vs 13.9 weeks), including significant benefit in patients who relapsed 60 days or less after initial treatment, and was associated with a slower deterioration in quality of life. In a phase III trial, 304 patients with sensitive relapse were randomized to oral (2.3 mg/m^2 daily for 5 days) or IV (1.5 mg/m^2 daily for 5 days) topotecan every 3 weeks.[58] The RRs and the median and 1-year survival rates as well as the toxicity profiles were similar between the two arms (18% vs 22%, 33 vs 35 weeks, and 33% vs 29%, respectively). Topotecan is typically administered on days 1 to 5 of a 3-week cycle. Irinotecan has not been directly compared with topotecan, and phase III trials have not been performed; phase II studies suggested similar efficacy compared with topotecan in the recurrent setting.[60]

Temozolomide (TMZ) is a well-tolerated oral alkylating agent with an overall response rate (ORR) of 16% in a small phase II study.[61] In this study, the RRs were 23% in patients with platinum-sensitive disease, 13% in patients refractory to platinum, and 38% in brain metastases.

The CheckMate 032 study evaluated the efficacy and safety of nivolumab and nivolumab plus ipilimumab in patients with recurrent disease after the failure of platinum-based chemotherapy.[62] Patients were randomized to receive nivolumab or nivolumab plus ipilimumab for four cycles followed by nivolumab maintenance. The objective RR was 21.9% in patients receiving nivolumab plus ipilimumab compared with 11.6% with nivolumab alone. However, the median OS was similar between the two groups (5.7 months vs 4.7 months). This study has led to the inclusion of nivolumab with or without ipilimumab to the National Comprehensive Cancer Network SCLC Guidelines as an option for the treatment of recurrent, platinum-refractory disease. Furthermore, nivolumab monotherapy is FDA approved for use in the third-line setting. Pembrolizumab is also approved in the third-line setting based on the results of the KEYNOTE-158 study,[63] in which the ORR was 19%. Among patients that responded, the durations of response were greater than or equal to 18 months and 18 months in 56% and 63%, respectively.

BRAIN METASTASIS

The brain is a common site of metastasis in patients with SCLC, with 10% of patients presenting with brain involvement at diagnosis and an additional 40% to 50% developing CNS metastasis during the course of disease.

Whole-Brain Radiation Therapy

Whole-brain radiation therapy (WBRT) rapidly resolves symptoms of brain involvement from SCLC. RT with 30 Gy in 10 daily fractions has been shown equally effective as altered fractionation to a higher dose (54 Gy in 34 fractions) in the phase III trial RTOG 9104,[64] which evaluated these WBRT regimens in 429 patients with unresected brain metastases, including 39 patients with SCLC. Median OS was 4.5 months in both arms; the 1-year survival rate was also similar, at 19% with accelerated fractionation and 16% on the control arm.

Reirradiation of the CNS may be considered (20 Gy in 10 fractions) for symptom palliation in recurrent intracranial disease.[65] Stereotactic radiosurgery (SRS) represents a therapeutic option for progressive brain metastases following WBRT. The technique uses external irradiation beams that deliver a single high dose

of radiation to a small volume of tissue with minimal invasion of and injury to healthy tissue. SRS for brain metastases after WBRT from SCLC (fewer than four sites) is safe and achieves 1-year local control of 60% to 90%, especially in lesions smaller than 2 cm[66]; however, regional CNS recurrence risk approaches 60%.

Chemotherapy

In general, RRs to chemotherapy in brain metastases mirror those in extracranial disease sites, with higher rates in therapy-naïve patients. In a meta-analysis, a 36% RR in the CNS was revealed in the results of five trials in which 135 patients with brain metastases were treated after initial therapy with single-agent etoposide or carboplatin. Pooled data from another five studies conducted in 64 patients with brain metastases at diagnosis treated with various combination regimens showed a RR of 66%.[67]

In summary, for treatment-naïve patients who present with CNS involvement and are asymptomatic or minimally symptomatic, chemotherapy should be given initially, and if brain disease is controlled, WBRT may be given after completion of four cycles of chemotherapy. Brain irradiation should ultimately be administered given that it is associated with higher CR of brain metastases compared with chemotherapy alone. Symptomatic CNS involvement or progression of brain metastases during chemotherapy is an indication for WBRT. The approach of combining WBRT and induction chemotherapy must be considered in situations in which brain disease is bulky and symptomatic and there is also significant extracranial disease requiring urgent treatment. Myelosuppression is increased with concurrent modalities, and this should be expectantly managed. For patients who develop CNS involvement after initial chemotherapy, WBRT is indicated, and chemotherapy may have a palliative role in those who progress after receiving WBRT. Occasionally, previously irradiated patients with SCLC are candidates for SRS; however, the rate of brain failure is high.

PROPHYLACTIC CRANIAL IRRADIATION

Despite only 10% of patients with SCLC initially presenting with CNS involvement, there is a significant rate of occult brain disease in patients who lack neurologic symptoms; thus, staging of the brain is indicated in all patients. Approximately 15% to 20% of patients with LD SCLC who initially respond to therapy will develop brain metastases as the sole site of relapse, suggesting that brain radiation early in the treatment course might be curative in this group.[68] The risk of developing brain disease in patients alive at 2 years after diagnosis who did not receive PCI is between 50% and 80%.[68] PCI has been investigated as a means to control brain metastatic disease after chemotherapy before it becomes clinically evident, in an effort to prevent morbidity and mortality. Numerous clinical trials have established the effectiveness of PCI in decreasing the incidence of intracranial disease in patients who have responded to initial treatment for LD and ED, although its impact on survival has been variable.

Prophylactic Cranial Irradiation in Limited Disease

The PCI Overview Collaborative Group meta-analysis evaluated seven randomized trials comparing PCI (treatment group) versus no PCI (control group) in 987 patients with SCLC who achieved CR to initial therapy. Approximately 85% of the patients enrolled in both groups had LD. The PCI provided a 5.4% improvement in 3-year survival rate (15.3% vs 20.7% in control vs treatment group, respectively), increased disease-free survival (P <.001), and decreased the risk of developing brain disease (33% vs 59%, HR 0.46; P <.001).[68] A second meta-analysis evaluated 1547 patients from 12 randomized studies, five of whom required CR status for randomization.[69] The results of the second analysis confirmed the reduced rate of brain metastasis for all patients but improvement in OS only for patients in CR (HR, 0.82; 95% CI, 0.71–0.96). Based on these data, PCI became standard of care for patients with LD and disease control after chemoradiation.

Two large, randomized trials have investigated the effect of RT doses above 25 Gy. A multinational phase III trial randomized 720 patients with LD and CR after induction therapy to receive PCI at 25 Gy in 10 fractions or 36 Gy (18 fractions of 2 Gy each or 24 fractions of 1.5 Gy twice daily).[70] No significant differences were noted in the 2-year incidence rates of brain metastasis, and an increased mortality rate was noted with higher PCI doses (2-year survival rate 37% vs 42%; HR, 1.20). The phase II randomized RTOG 0212 study similarly showed no differences in the incidence of brain metastasis or OS benefit in patients with LD and CR after initial chemoradiation comparing PCI with 25 Gy to 36 Gy.[71]

Prophylactic Cranial Irradiation in Extensive Disease

An early European Organization for Research and Treatment of Cancer (EORTC) study suggested a benefit to PCI in ED, but this study had limitations in its design, and its conclusions were not supported

by a more recent study. The EORTC study randomized patients with ED with response to initial chemotherapy to either PCI (choice of three schedules) or observation.[72] Baseline imaging of the brain was required only for symptomatic patients. Overall, 286 patients were randomized. Patients in the PCI group had a lower risk of brain metastases (15% vs 40%; HR, 0.27; P <.001) and a longer median OS from time of randomization versus the observation group (6.7 vs 5.4 months, respectively). It is notable that more patients in the PCI group received second-line chemotherapy (68% vs 45%), possibly accounting for the OS improvement. Fatigue was significantly worse on the PCI arm in the first 24 weeks. Global health status and cognitive functioning were assessed only up to 9 months from randomization and were a mean of 8 points less (scale of 0–100) at 6 weeks and 3 months on the PCI arm.[73] These results are difficult to interpret given the lack of brain imaging at baseline and heterogeneity in both chemotherapy and PCI schedules. Furthermore, the 1.3-month OS improvement could be attributed to an imbalance in subsequent chemotherapy use, which is known to influence survival.

The more recent Japanese trial evaluated the efficacy of PCI versus observation in 224 patients with SCLC who had response to induction chemotherapy with either etoposide or irinotecan and cisplatin.[74] Before randomization, brain MRI was performed to rule out occult metastases, and patients on both arms were followed postrandomization with serial brain imaging. PCI was given as 25 Gy in 10 fractions. The accrual was stopped early for futility when analysis after 111 deaths revealed a trend toward shorter median survival with PCI (10.1 vs 15.1 months; HR, 1.38; P = .091). As expected, decreased incidence of brain metastases with PCI at 1 year (32% vs 58%; P <.001) was observed, and fewer patients treated with PCI required RT for symptomatic brain involvement (31% vs 80%). The high rate of brain metastases in both arms of this study (48% with PCI; 69% with observation) supports the need for MRI surveillance in all patients with ED.

In summary, PCI clearly decreased the incidence of symptomatic brain disease in SCLC, but the impact on OS in patients with ED was variable. It is reasonable to discuss PCI in patients with ED who have a CR or very good PR to initial treatment and good PS. The lack of definite survival benefit and the potential for at least short-term toxicity should be discussed. It should be used with caution in older adults and in patients with significant ischemic cerebrovascular disease because of a concern for increased acute and late brain toxicity. It is important to separate PCI from chemotherapy and to use radiation regimens that are safe in regard to late neurotoxic effects (e.g., 25 Gy in 10 daily fractions).

OLDER ADULT AND INFIRM PATIENTS

Approximately 25% of patients with SCLC are older than the age of 70 years. These patients have often been excluded from clinical trials because of concerns for greater toxicity because of lowered organ reserves, especially myelosuppression and frequently lowered functional status because of comorbidities. However, retrospective studies have shown that older adult patients with retained PS have improved outcomes with more aggressive treatment.[75] In a Canadian analysis, older adult patients 70 years of age or older who received four or more cycles of CAV or EP had a median survival time of 10.7 months; those patients who received three or fewer cycles had a median survival time of 3.9 months; and untreated patients survived a median time of 1.1 months.[76] Multivariate analysis showed that neither increasing age nor comorbidities was an adverse prognostic factor. This review reported that PS, stage, and treatment were the most important prognostic features. Additional studies have confirmed these conclusions, whereas only one retrospective Australian review reported that the complications from therapy adversely affected outcome in older adults.[77] In a retrospective cohort study examining the impact of chemotherapy on survival among patients 65 years and older with SCLC selected from the SEER database,[78]67% of the patients received chemotherapy, mainly EP or CE, which provided a 6.5-month improvement in median survival (P < .001), even in patients older than 80 years of age.

With regard to radiation tolerance in the case of LD, older adult patients have been reported to have increased toxicity. Analysis of the patients older than 70 years of age in the INT trial 0096 (EP with conventional TRT vs AHRT) showed that they experienced a higher rate of treatment-related death (older than 70 years vs 70 years or younger: 10% vs 1%, respectively).[79] However, the 5-year OS rate for older adult patients was 16%, similar to that in the control arm overall. Altered fractionation did not appear to benefit the older adult subgroup.

In summary, patients with good PS and no significant organ dysfunction should receive full-dose chemotherapy and RT. Their higher risk of treatment-related death implies a need for close monitoring and intense supportive care. Patients with severe comorbidities, a worse PS before diagnosis, or the very old may require a change in strategy from standard of care. A meta-analysis of randomized trials evaluating patients with "poor-risk" SCLC (generally ED) has shown a benefit of combination chemotherapy over single-agent oral etoposide.[80] These trials reported that IV combination regimens palliated symptoms better and improved median PFS and OS. Therefore, in patients with a poor

PS, initial treatment should be combination chemotherapy. EP is recommended over cyclophosphamide- or doxorubicin-based regimens in the older adult population because it is less myelosuppressive.[75] Several studies have evaluated the CE regimen in the older adult population.[81,82] With the exception of the trial reported by Samantas et al,[81] which used low doses of both agents, studies using CE have shown good RRs and tolerance in older adult patients.

In conclusion, carboplatin (area under the curve, 5) and etoposide (100 mg/m^2 for 3 days) can be recommended for most patients with SCLC considered "high risk" on the basis of age, comorbidities, or reduced functional status. The time of highest risk for treatment-related mortality is in the first cycle. Prophylactic use of bone marrow growth factors such as pegfilgrastim is recommended in this group when chemotherapy is given alone. The use of marrow growth factors is contraindicated during concurrent chemoradiation; thus, modest dose reduction and conventional fractionation should be considered. Continued research in this area, especially in the very old, is needed.

TARGETED AGENTS

There are no approved targeted agents for SCLC despite a plethora of trials over the past 15 years. Angiogenesis inhibitors, tyrosine kinase and other signal transduction inhibitors, and BH3 mimetics targeting apoptosis have not demonstrated substantial promise in early-phase trials, and none has been validated in phase III studies.[83–86] However, early experience with the Aurora A kinase inhibitor alisertib and inhibitors of poly(ADP-ribose) polymerase (PARP) showed promise.

Aurora A Kinase Inhibitors

Data in SCLC cell lines and xenografts indicate that expression of MYC is correlated with sensitivity to Aurora A kinase inhibition.[87] In a phase II study of alisertib (50 mg by mouth twice a day for 14 days every 21 days) in solid tumors, a partial RR of 15% was observed in 47 patients with relapsed SCLC.[88] In a randomized, double-blind, phase II study of alisertib plus paclitaxel as second-line treatment for SCLC, patients were randomized to alisertib plus paclitaxel or placebo plus paclitaxel. The median PFS was 3.3 months with alisertib plus paclitaxel compared with 2.17 months with placebo plus paclitaxel in the intent-to-treat population. However, among patients with cell cycle regular mutations, median PFS was improved to 3.68 months with the addition of alisertib compared with 1.80 months. In this group of patients, median OS was 7.2 months with alisertib plus paclitaxel and 4.5 months with placebo plus paclitaxel. Median PFS was also improved in patients with c-MYC expression.[89]

Poly(ADP-Ribose) Polymerase Inhibitors

Proteomic profiling of a large panel of SCLC cells showed high expression of PARP1 and other repair proteins. Several PARP inhibitors have shown single activity in in vitro and in vivo models of SCLC.[90] BMN-673 is the most potent PARP1/2 inhibitor, inducing synthetic lethality in tumors deficient in homologous recombination. In a phase I trial of BMN-673,2 of 11 patients with recurrent SCLC had PR. Veliparib, another PARP inhibitor, was studied in with TMZ in the second- or third-line setting in a randomized phase II study.[91] Patients were randomized to receive veliparib or placebo in combination with TMZ. There was no significant difference in the median PFS or OS between the groups. However, there was an improvement in the objective RR in patients receiving veliparib plus TMZ (39%) compared with placebo plus TMZ (14%). In patients who were positive for Schlafen-11 (SLFN11), a DNA/RNA helicase that regulates replication stress at sites of DNA damage, PFS was prolonged (5.7 months vs 3.6 months) as was OS (12.2 months vs 7.5 months) with veliparib plus TMZ. This study provided further evidence that a biomarker-driven selection of patients could improve outcomes in further clinical trials and suggested that SLFN11 may be predictive of response to PARP inhibitors.[92]

Delta-like Protein 3–Targeted Therapy

Delta-like protein 3 (DLL3) is a member of the NOTCH receptor ligand family and has been identified as a potential therapeutic target for SCLC and other high-grade neuroendocrine carcinomas. Rovalpituzumab tesirine is an antibody–drug conjugate targeting DLL3 that showed promising efficacy in a phase I clinical trial. The objective RRs were 18% in assessable patients and 38% in those with DLL3 expression in 50% or more of tumor cells.[93] Unfortunately, the phase III TRINITY showed only modest activity, including in patients with high DDL3 expression.[94] Furthermore, serious adverse events were seen in 63% of patients, and rovalpituzumab tesirine is unlikely to be tested further in SCLC.

PARANEOPLASTIC SYNDROMES

PNSs are a complex spectrum of symptoms secondary to hormones secreted from tumor cells not related to

their tissue or organ of origin or to immune-mediated tissue destruction through the production of autoantibodies against tumor cells. SCLC is one of the most common cancer types associated with such phenomena. Ectopic hormone production has been associated with ED and a poorer outcome, whereas the antibody-mediated PNSs are associated with more favorable outcomes.[8,11] It is critical to recognize the manifestations of PNSs because this may lead to the diagnosis of an underlying, previously unsuspected malignancy and be useful in monitoring the course of the underlying disease.

Endocrine Paraneoplastic Syndromes

Hyponatremia of malignancy occurs in 15% of patients with SCLC. This disorder is caused by ectopic production of antidiuretic hormone from tumor cells, resulting in the SIADH.[95] Fluid restriction, saline infusion with furosemide diuresis, hypertonic saline, and demeclocycline are options for acute management depending on the severity of symptoms. Chemotherapy should be started urgently.

The incidence of ectopic Cushing syndrome in SCLC is approximately 5%. Patients with SCLC with such a syndrome commonly present with signs and symptoms of rapid-onset hypercortisolism, including weight loss (83%), hypokalemia (87%), abnormal glucose tolerance (73%), and edema (58%) compared with the classic Cushingoid features of moon facies, central obesity, or hirsutism, which are more commonly seen in patients with carcinoid tumors.[95] This may be attributable to the slower growth rate of carcinoids, which causes a gradual, rather than acute, increase in ACTH levels. Patients with SCLC with Cushing syndrome have higher hydroxycorticosteroid (17-OHCS) and ACTH plasma levels than those seen in the Cushing disease of pituitary origin. These patients are immunosuppressed and at high risk for opportunistic infections from hypercortisolism; therefore, cortisol-suppressing agents, such as metyrapone or ketoconazole, are recommended before initiating myelosuppressive antineoplastic therapy. RT can also be used in these cases to palliate and temporize until hypercortisolism has been controlled. Endocrine syndromes parallel cancer control, subsiding with cytoreduction of tumor and recurring with progression.

Neurologic Paraneoplastic Syndromes

Neurologic PNS disorders occur as the result of onconeuronal antibodies recognizing tumor and neuronal cell antigens; thus, they are autoimmune in mechanism. LEMS, seen in 1% to 3% of patients with SCLC, is caused by autoantibodies directed against P/Q-type voltage-gated calcium channels on the tumor cells and at presynaptic nerve terminals. These antibodies impair acetylcholine release from the presynaptic motor terminal at the neuromuscular junction and cause transient cranial nerve palsies, upright presyncopal symptoms, proximal muscle weakness with lower extremity predominance, and depressed tendon reflexes.[11] The electromyographic findings of decreased baseline muscle action potential that increases with repeated stimulations are characteristic and allow for clear-cut diagnosis. LEMS represents a favorable prognostic factor presumably based on antitumor immunity.[11] Unfortunately, these patients frequently experience progressive neurologic decline despite tumor control with treatment because by the time neurologic symptoms and deficits emerge, permanent neuronal damage has occurred.

Additional paraneoplastic CNS disorders are associated with inflammation and neuronal loss. The most common syndromes in this group are paraneoplastic cerebellar degeneration, limbic encephalitis, opsoclonus-myoclonus, and diffuse encephalitis with multifocal neurologic symptoms.[95] It remains unclear whether these syndromes or the presence of antibodies can serve as predictive markers of tumor response or progression.

THE SPECTRUM OF NEUROENDOCRINE CARCINOMAS

Neuroendocrine carcinomas are a wide spectrum of diseases, including low-grade typical carcinoid (TC), intermediate-grade atypical carcinoid (AT), and high-grade neuroendocrine carcinomas (small cell carcinoma and LCNEC).[96] Carcinoid tumors are more often found in the gastrointestinal system than in the lungs. The behavior of these tumors is often dependent on grade of differentiation. The histopathological features of these tumors are identical regardless of their anatomic location; thus, the determination of a primary site often requires careful clinical evaluation.

Many of the same IHC markers are used to define NETs, regardless of primary site. Some IHC stains appear to be expressed in tumors in certain locations. For example, whereas TTF-1 is commonly positive in thoracic tumors, CDX2 is more commonly expressed in gastrointestinal tumors. On limited biopsies, definitive tumor grading may be challenging, especially in tumors of low and intermediate grade.

Pulmonary NETs comprise approximately 20% of all invasive lung malignancies. After SCLC, LCNEC accounts for 3% of resected lung cancers in surgical series, and TCs account for 1% to 2% of lung cancers. AT is the rarest lung NET because it comprises approximately 10% of all lung carcinoids, accounting

TABLE 23-2 Grading Criteria and Histologic Features of Pulmonary Neuroendocrine Tumors

Grade	Histology	Conventional Nomenclature
Low grade (well differentiated)	• < 3 mitotic figures × 10 hpf • Absent or only focal punctate necrosis • Absent or mild nuclear atypia	Carcinoid
Intermediate grade (moderately differentiated)	• 3–10 mitotic figures × 10 hpf • Comedonecrosis present • Moderate nuclear atypia	Atypical carcinoid
High grade, poorly differentiated (small cell carcinoma)	• >10 mitotic figures × 10 hpf • Necrosis present • Prominent nuclear atypia with or without positive NE markers	Small cell carcinoma
High grade, poorly differentiated (large cell neuroendocrine carcinoma)	• >10 mitotic figures × 10 hpf • Necrosis present • Prominent nuclear atypia with positive NE morphologic features and positive or negative NE markers	Large cell neuroendocrine carcinoma

hpf, high-power field; NE, neuroendocrine.
Data from Moran CA, Suster S, Coppola D, et al. Neuroendocrine carcinomas of the lung: a critical analysis, *Am J Clin Pathol.* 2009;131(2):206-221.

for 0.1% to 0.2% of invasive lung cancers. LCNEC has similar biology, behavior, and natural history to SCLC.[12] Table 23–2 shows the grading criteria and the histopathological features for pulmonary NETs.[97] The different types of NETs possess diverse epidemiologic, clinical, pathologic, and molecular features.[98]

Surgical resection is recommended for localized pulmonary NETs if pulmonary reserve is adequate. For surgically unfit patients or for exceptional low-grade cases, transbronchoscopic resection may be considered. Approximately 5% to 20% of bronchial TCs and 30% to 70% of ATs metastasize to lymph nodes; thus, a complete mediastinal lymph node sampling or dissection at the time of surgery is recommended. The 5-year survival rates of surgically resected pulmonary TCs and ATs range between 87% and 100% and 30% and 95%, respectively.[98] Patients with TCs are unlikely to benefit from adjuvant systemic therapy even if lymph node involvement is present. The ATs have higher recurrence rates; therefore, despite the lack of consensus, adjuvant EP with or without RT for patients with stage II or III may be considered.[99]

Because of the rarity of LCNEC, most of the data regarding treatment are retrospective in nature. In general, there is a worse prognosis for patients with resected LCNEC compared with those with stage-matched other NSCLC. Treatment recommendations for this entity are extrapolated from treatment paradigms for SCLC. For resected stage I and II LCNEC, four cycles of adjuvant EP are recommended. For locally advanced disease (stage III), concurrent chemoradiation or chemotherapy is recommended (one or two cycles of EP concurrent with RT followed by additional chemotherapy to complete a total of four courses). For stage IV disease, four to six cycles of EP and palliative RT, if clinically indicated, are recommended. PCI cannot be routinely recommended because of limited data on the incidence of brain metastases in patients with LCNEC.[96]

SUMMARY

SCLC is a very aggressive malignancy, affecting 30,000 or more individuals annually in the United States. Most patients present with widespread disease at diagnosis, and despite the initial high sensitivity to chemotherapy and RT, resistance emerges rapidly. Extensive research over the past few decades has not significantly impacted the therapeutic paradigm of SCLC. The standard of care for both LD and ED is etoposide–platin chemotherapy for a minimum of four courses. Early integration of concurrent TRT is indicated for LD. PCI can be offered to patients who have excellent disease control after initial therapy. Major advances in treatment will require greater understanding of the drivers of the pan-resistant phenotype that characterizes recurrent disease and development of therapy to which these cells will be vulnerable. Recent discoveries from bench research and early-phase clinical investigation fuel the hope that outcomes for patients with SCLC will continue to improve in the next decade.

MD ANDERSON PRACTICE TIPS

- Clinical trials should be considered for all patients with SCLC, especially after relapse.
- The use of PCI in extensive-stage patients with SCLC should be restricted to *highly selected* cases, such as patients with low burdens of metastatic disease; good PS; *and* a complete, or near-complete, metabolic response to frontline systemic therapy. All patients with extensive-stage disease should have surveillance brain imaging.
- Consider the use of the TMZ for patients with relapsed disease, which is a convenient (oral) agent with good tolerability and excellent blood–brain barrier penetration. In particular, this agent is useful for patients with a history of CNS metastases.
- Although both the IMpower133 and CASPIAN trials excluded use of consolidative thoracic irradiation after chemoimmunotherapy, we continue to deploy this treatment modality for appropriate patients treated with chemoimmunotherapy.
- As with all malignancies, but especially true in light of SCLC's poor prognosis, early establishment of realistic prognostic expectations and goals of care is critical.
- Although nivolumab and pembrolizumab are FDA approved for third-line treatment of relapsed SCLC, we do not recommend repeat use of immune checkpoint blockade in patients who failed frontline chemoimmunotherapy unless within a clinical trial. On the other hand, if a newly relapsed patient did not previously receive immunotherapy, off-label use of nivolumab or pembrolizumab even in the second line should be considered, in light of durable, albeit rare, responses.

REFERENCES

1. Govindan R, Page N, Morgensztern D, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. *J Clin Oncol*. 2006;24(28):4539-4544.
2. Nicholson AG, Chansky K, Crowley J, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: proposals for the revision of the clinical and pathologic staging of small cell lung cancer in the forthcoming eighth edition of the TNM Classification for Lung Cancer. *J Thorac Oncol*. 2016;11(3):300-311.
3. Muscat JE, Wynder EL. Lung cancer pathology in smokers, ex-smokers and never smokers. *Cancer Lett*. 1995;88(1):1-5.
4. Barbone F, Bovenzi M, Cavallieri F, Stanta G. Cigarette smoking and histologic type of lung cancer in men. *Chest*. 1997;112(6):1474-1479.
5. Dowlati A, Wildey G. Defining subgroups of small-cell lung cancer. *J Thorac Oncol*. 2014;9(6):750-751.
6. Videtic GM, Stitt LW, Dar AR, et al. Continued cigarette smoking by patients receiving concurrent chemoradiotherapy for limited-stage small-cell lung cancer is associated with decreased survival. *J Clin Oncol*. 2003;21(8):1544-1549.
7. Green RA, Humphrey E, Close H, Patno ME. Alkylating agents in bronchogenic carcinoma. *Am J Med*. 1969;46(4):516-525.
8. Yip D, Harper PG. Predictive and prognostic factors in small cell lung cancer: current status. *Lung Cancer*. 2000;28(3):173-185.
9. Shepherd FA, Evans WK, Feld R, et al. Adjuvant chemotherapy following surgical resection for small-cell carcinoma of the lung. *J Clin Oncol*. 1988;6(5):832-838.
10. Ihde DC, Makuch RW, Carney DN, et al. Prognostic implications of stage of disease and sites of metastases in patients with small cell carcinoma of the lung treated with intensive combination chemotherapy. *Am Rev Respir Dis*. 1981;123(5):500-507.
11. Maddison P, Newsom-Davis J, Mills KR, Souhami RL. Favourable prognosis in Lambert-Eaton myasthenic syndrome and small-cell lung carcinoma. *Lancet*. 1999;353(9147):117-118.
12. Zakowski MF. Pathology of small cell carcinoma of the lung. *Semin Oncol*. 2003;30(1):3-8.
13. Johnson BE, Whang-Peng J, Naylor SL, et al. Retention of chromosome 3 in extrapulmonary small cell cancer shown by molecular and cytogenetic studies. *J Natl Cancer Inst*. 1989;81(16):1223-1228.
14. Hiroshima K, Iyoda A, Shida T, et al. Distinction of pulmonary large cell neuroendocrine carcinoma from small cell lung carcinoma: a morphological, immunohistochemical, and molecular analysis. *Mod Pathol*. 2006;19(10):1358-1368.
15. Agoff SN, Lamps LW, Philip AT, et al. Thyroid transcription factor-1 is expressed in extrapulmonary small cell carcinomas but not in other extrapulmonary neuroendocrine tumors. *Mod Pathol*. 2000;13(3):238-242.
16. Cardnell RJ, Li L, Sen T, et al. Protein expression of TTF1 and cMYC define distinct molecular subgroups of small cell lung cancer with unique vulnerabilities to aurora kinase inhibition, DLL3 targeting, and other targeted therapies. *Oncotarget*. 2017;8(43):73419-73432.
17. Travis WD. Update on small cell carcinoma and its differentiation from squamous cell carcinoma and other non-small cell carcinomas. *Mod Pathol*. 2012;25(suppl 1):S18-S30.
18. Wistuba II, Gazdar AF, Minna JD. Molecular genetics of small cell lung carcinoma. *Semin Oncol*. 2001;28(2 suppl 4):3-13.
19. George J, Lim JS, Jang SJ, et al. Comprehensive genomic profiles of small cell lung cancer. *Nature*. 2015;524(7563):47-53.
20. D'Angelo SP, Pietanza MC. The molecular pathogenesis of small cell lung cancer. *Cancer Biol Ther*. 2010;10(1):1-10.
21. Tamborini E, Bonadiman L, Negri T, et al. Detection of overexpressed and phosphorylated wild-type kit receptor in surgical specimens of small cell lung cancer. *Clin Cancer Res*. 2004;10(24):8214-8219.
22. Byers LA, Rudin CM. Small cell lung cancer: where do we go from here? *Cancer*. 2015;121(5):664-672.
23. Peifer M, Fernández-Cuesta L, Sos ML, et al. Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. *Nat Genet*. 2012;44(10):1104-1110.
24. Jia D, Augert A, Kim DW, et al. Crebbp Loss drives small cell lung cancer and increases sensitivity to HDAC inhibition. *Cancer Discov*. 2018;8(11):1422-1437.
25. Vallières E, Shepherd FA, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals regarding the relevance of TNM in the pathologic staging of small cell lung cancer in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2009;4(9):1049-1059.
26. Levitan N, Byrne RE, Bromer RH, et al. The value of the bone scan and bone marrow biopsy staging small cell lung cancer. *Cancer*. 1985;56(3):652-654.
27. Hochstenbag MM, Twijnstra A, Wilmink JT, et al. Asymptomatic brain metastases (BM) in small cell lung cancer (SCLC): MR-imaging is useful at initial diagnosis. *J Neurooncol*. 2000;48(3):243-248.
28. Matthews MJ, Kanhouwa S, Pickren J, Robinette D. Frequency of residual and metastatic tumor in patients undergoing curative surgical resection for lung cancer. *Cancer Chemother Rep 3*. 1973;4(2):63-67.
29. Fox W, Scadding JG. Treatment of oat-celled carcinoma of the bronchus. *Lancet*. 1973;2(7829):616-617.
30. Warde P, Payne D. Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. *J Clin Oncol*. 1992;10(6):890-895.
31. Pignon JP, Arriagada R, Ihde DC, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med*. 1992;327(23):1618-1624.
32. Sundstrøm S, Bremnes RM, Kaasa S, et al. Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: results from a randomized phase III trial with 5 years' follow-up. *J Clin Oncol*. 2002;20(24):4665-4672.
33. Fukuoka M, Furuse K, Saijo N, et al. Randomized trial of cyclophosphamide, doxorubicin, and vincristine versus cisplatin and etoposide versus alternation of these regimens in small-cell lung cancer. *J Natl Cancer Inst*. 1991;83(12):855-861.
34. Levitan N, Dowlati A, Shina D, et al. Multi-institutional phase I/II trial of paclitaxel, cisplatin, and etoposide with concurrent radiation for limited-stage small-cell lung carcinoma. *J Clin Oncol*. 2000;18(5):1102-1109.
35. Turrisi AT 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med*. 1999;340(4):265-271.
36. Movsas B, Moughan J, Komaki R, et al. Radiotherapy patterns of care study in lung carcinoma. *J Clin Oncol*. 2003;21(24):4553-4559.
37. Bogart JA, Herndon JE 2nd, Lyss AP, et al. 70 Gy thoracic radiotherapy is feasible concurrent with chemotherapy for limited-stage small-cell lung cancer: analysis of Cancer and Leukemia Group B study 39808. *Int J Radiat Oncol Biol Phys*. 2004;59(2):460-468.
38. Komaki R, Paulus R, Ettinger DS, et al. Phase II study of accelerated high-dose radiotherapy with concurrent chemotherapy for patients with limited small-cell lung cancer: Radiation Therapy Oncology Group protocol 0239. *Int J Radiat Oncol Biol Phys*. 2012;83(4):e531-e536.

39. Faivre-Finn C, Snee M, Ashcroft L, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. *Lancet Oncol*. 2017;18(8):1116-1125.
40. Murray N, Coy P, Pater JL, et al. Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*. 1993;11(2):336-344.
41. Takada M, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. *J Clin Oncol*. 2002;20(14):3054-3060.
42. De Ruysscher D, Pijls-Johannesma M, Bentzen SM, et al. Time between the first day of chemotherapy and the last day of chest radiation is the most important predictor of survival in limited-disease small-cell lung cancer. *J Clin Oncol*. 2006;24(7):1057-1063.
43. Rossi A, Di Maio M, Chiodini P, et al. Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data. *J Clin Oncol*. 2012;30(14):1692-1698.
44. Horn L, Mansfield AS, Szcz sna A, et al. First-Line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med*. 2018;379(23):2220-2229.
45. Evans WK, Osoba D, Feld R, et al. Etoposide (VP-16) and cisplatin: an effective treatment for relapse in small-cell lung cancer. *J Clin Oncol*. 1985;3(1):65-71.
46. Evans WK, Shepherd FA, Feld R, et al. VP-16 and cisplatin as first-line therapy for small-cell lung cancer. *J Clin Oncol*. 1985;3(11):1471-1477.
47. Roth BJ, Johnson DH, Einhorn LH, et al. Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. *J Clin Oncol*. 1992;10(2):282-291.
48. Gadgeel SM, Pennell NA, Fidler MJ, et al. Phase II study of maintenance pembrolizumab in patients with extensive-stage small cell lung cancer (SCLC). *J Thorac Oncol*. 2018;13(9):1393-1399.
49. Reck M, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial. *Ann Oncol*. 2013;24(1):75-83.
50. Reck M, Luft A, Szczesna A, et al. Phase III randomized trial of ipilimumab plus etoposide and platinum versus placebo plus etoposide and platinum in extensive-stage small-cell lung cancer. *J Clin Oncol*. 2016;34(31):3740-3748.
51. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2019;394(10212):1929-1939.
52. Jeremic B, Shibamoto Y, Nikolic N, et al. Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: a randomized study. *J Clin Oncol*. 1999;17(7):2092-2099.
53. Slotman BJ, van Tinteren H, Praag JO, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. *Lancet*. 2015;385(9962):36-42.
54. von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. *J Clin Oncol*. 1999;17(2):658-667.
55. Batist G, Ihde DC, Zabell A, et al. Small-cell carcinoma of lung: reinduction therapy after late relapse. *Ann Intern Med*. 1983;98(4):472-474.
56. Giaccone G, Ferrati P, Donadio M, et al. Reinduction chemotherapy in small cell lung cancer. *Eur J Cancer Clin Oncol*. 1987;23(11):1697-1699.
57. Vincent M, Evans B, Smith I. First-line chemotherapy rechallenge after relapse in small cell lung cancer. *Cancer Chemother Pharmacol*. 1988;21(1):45-48.
58. Eckardt JR, von Pawel J, Pujol JL, et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. *J Clin Oncol*. 2007;25(15):2086-2092.
59. O'Brien ME, Ciuleanu TE, Tsekov H, et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. *J Clin Oncol*. 2006;24(34):5441-5447.
60. Masuda N, Fukuoka M, Kusunoki Y, et al. CPT-11: a new derivative of camptothecin for the treatment of refractory or relapsed small-cell lung cancer. *J Clin Oncol*. 1992;10(8):1225-1229.
61. Pietanza MC, Kadota K, Huberman K, et al. Phase II trial of temozolomide in patients with relapsed sensitive or refractory small cell lung cancer, with assessment of methylguanine-DNA methyltransferase as a potential biomarker. *Clin Cancer Res*. 2012;18(4):1138-1145.
62. Ready NE, Ott PA, Hellmann MD, et al. Nivolumab monotherapy and nivolumab plus ipilimumab in recurrent small cell lung cancer: results from the CheckMate 032 randomized cohort. *J Thorac Oncol*. 2020;15(3):426-435.
63. Chung HC, Lopez-Martin JA, Kao SCH, et al. Phase 2 study of pembrolizumab in advanced small-cell lung cancer: KEYNOTE-158. *J Clin Oncol*. 2018;36:8506-8506.
64. Murray KJ, Scott C, Greenberg HM, et al. A randomized phase III study of accelerated hyperfractionation versus standard in patients with unresected brain metastases: a report of the Radiation Therapy Oncology Group (RTOG) 9104. *Int J Radiat Oncol Biol Phys*. 1997;39(3):571-574.
65. Imanaka K, Sugimoto K, Obayashi Y, et al. Reirradiation therapy for brain metastases from small cell lung cancer. *Radiat Med*. 1998;16(2):153-156.
66. Sneed PK, Suh JH, Goetsch SJ, et al. A multi-institutional review of radiosurgery alone vs. radiosurgery with whole brain radiotherapy as the initial management of brain metastases. *Int J Radiat Oncol Biol Phys*. 2002;53(3):519-526.
67. Grossi F, Scolaro T, Tixi L, et al. The role of systemic chemotherapy in the treatment of brain metastases from small-cell lung cancer. *Crit Rev Oncol Hematol*. 2001;37(1):61-67.
68. Aupérin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med*. 1999;341(7):476-484.
69. Meert AP, Paesmans M, Berghmans T, et al. Prophylactic cranial irradiation in small cell lung cancer: a systematic review of the literature with meta-analysis. *BMC Cancer*. 2001;1:5.
70. Le Péchoux C, Dunant A, Senan S, et al. Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial. *Lancet Oncol*. 2009;10(5):467-474.
71. Wolfson A, Quoix E, Faivre-Finn C, et al. Primary analysis of a phase II randomized trial Radiation Therapy Oncology Group (RTOG) 0212: impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2011;81(1):77-84.

72. Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med*. 2007;357(7):664-672.
73. Slotman BJ, Mauer ME, Bottomley A, et al. Prophylactic cranial irradiation in extensive disease small-cell lung cancer: short-term health-related quality of life and patient reported symptoms: results of an international phase III randomized controlled trial by the EORTC Radiation Oncology and Lung Cancer Groups. *J Clin Oncol*. 2009;27(1):78-84.
74. Takahashi T, Yamanaka T, Seto T, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017;18(5):663-671.
75. Johnson DH. Small cell lung cancer in the elderly patient. *Semin Oncol*. 1997;24(4):484-491.
76. Shepherd FA, Amdemichael E, Evans WK, et al. Treatment of small cell lung cancer in the elderly. *J Am Geriatr Soc*. 1994;42(1):64-70.
77. Findlay MP, Griffin AM, Raghavan D, et al. Retrospective review of chemotherapy for small cell lung cancer in the elderly: does the end justify the means? *Eur J Cancer*. 1991;27(12):1597-1601.
78. Caprario LC, Kent DM, Strauss GM. Effects of chemotherapy on survival of elderly patients with small-cell lung cancer: analysis of the SEER-medicare database. *J Thorac Oncol*. 2013;8(10):1272-1281.
79. Yuen AR, Zou G, Turrisi AT, et al. Similar outcome of elderly patients in intergroup trial 0096: cisplatin, etoposide, and thoracic radiotherapy administered once or twice daily in limited stage small cell lung carcinoma. *Cancer*. 2000;89(9):1953-1960.
80. Girling DJ. Comparison of oral etoposide and standard intravenous multidrug chemotherapy for small-cell lung cancer: a stopped multicentre randomised trial. Medical Research Council Lung Cancer Working Party. *Lancet*. 1996;348(9027):563-566.
81. Samantas E, Skarlos DV, Pectasides D, et al. Combination chemotherapy with low doses of weekly carboplatin and oral etoposide in poor risk small cell lung cancer. *Lung Cancer*. 1999;23(2):159-168.
82. Okamoto H, Watanabe K, Nishiwaki Y, et al. Phase II study of area under the plasma-concentration-versus-time curve-based carboplatin plus standard-dose intravenous etoposide in elderly patients with small-cell lung cancer. *J Clin Oncol*. 1999;17(11):3540-3545.
83. Pujol JL, Lavole A, Quoix E, et al. Randomized phase II-III study of bevacizumab in combination with chemotherapy in previously untreated extensive small-cell lung cancer: results from the IFCT-0802 trialdagger. *Ann Oncol*. 2015;26(5):908-914.
84. Pujol JL, Breton JL, Gervais R, et al. Phase III double-blind, placebo-controlled study of thalidomide in extensive-disease small-cell lung cancer after response to chemotherapy: an intergroup study FNCLCC cleo04 IFCT 00-01. *J Clin Oncol*. 2007;25(25):3945-3951.
85. Rudin CM, Salgia R, Wang X, et al. Randomized phase II study of carboplatin and etoposide with or without the bcl-2 antisense oligonucleotide oblimersen for extensive-stage small-cell lung cancer: CALGB 30103. *J Clin Oncol*. 2008;26(6):870-876.
86. Dy GK, Miller AA, Mandrekar SJ, et al. A phase II trial of imatinib (ST1571) in patients with c-kit expressing relapsed small-cell lung cancer: a CALGB and NCCTG study. *Ann Oncol*. 2005;16(11):1811-1816.
87. Hook KE, Garza SJ, Lira ME, et al. An integrated genomic approach to identify predictive biomarkers of response to the aurora kinase inhibitor PF-03814735. *Mol Cancer Ther*. 2012;11(3):710-719.
88. Melichar B, Adenis A, Lockhart AC, et al. Safety and activity of alisertib, an investigational aurora kinase A inhibitor, in patients with breast cancer, small-cell lung cancer, non-small-cell lung cancer, head and neck squamous-cell carcinoma, and gastro-oesophageal adenocarcinoma: a five-arm phase 2 study. *Lancet Oncol*. 2015;16(4):395-405.
89. Owonikoko TK, Niu H, Nackaerts K, et al. Randomized phase II study of paclitaxel plus alisertib versus paclitaxel plus placebo as second-line therapy for SCLC: primary and correlative biomarker analyses. *J Thorac Oncol*. 2020;15(2):274-287.
90. Byers LA, Wang J, Nilsson MB, et al. Proteomic profiling identifies dysregulated pathways in small cell lung cancer and novel therapeutic targets including PARP1. *Cancer Discov*. 2012;2(9):798-811.
91. Pietanza MC, Waqar SN, Krug LM, et al. Randomized, double-blind, phase II study of temozolomide in combination with either veliparib or placebo in patients with relapsed-sensitive or refractory small-cell lung cancer. *J Clin Oncol*. 2018;36(23):2386-2394.
92. Inno A, Stagno A, Gori S. Schlafen-11 (SLFN11): a step forward towards personalized medicine in small-cell lung cancer? *Transl Lung Cancer Res*. 2018;7(suppl 4):S341-S345.
93. Rudin CM, Pietanza MC, Bauer TM, et al. Rovalpituzumab tesirine, a DLL3-targeted antibody-drug conjugate, in recurrent small-cell lung cancer: a first-in-human, first-in-class, open-label, phase 1 study. *Lancet Oncol*. 2017;18(1):42-51.
94. Morgensztern D, Besse B, Greillier L, et al. Efficacy and safety of rovalpituzumab tesirine in third-line and beyond patients with DLL3-expressing, relapsed/refractory small-cell lung cancer: results from the phase II TRINITY study. *Clin Cancer Res*. 2019;25(23):6958-6966.
95. Gandhi L, Johnson BE. Paraneoplastic syndromes associated with small cell lung cancer. *J Natl Compr Canc Netw*. 2006;4(6):631-638.
96. Glisson BS, Moran CA. Large-cell neuroendocrine carcinoma: controversies in diagnosis and treatment. *J Natl Compr Canc Netw*. 2011;9(10):1122-1129.
97. Moran CA, Suster S, Coppola D, Wick MR. Neuroendocrine carcinomas of the lung: a critical analysis. *Am J Clin Pathol*. 2009;131(2):206-221.
98. Ferguson MK, Landreneau RJ, Hazelrigg SR, et al. Long-term outcome after resection for bronchial carcinoid tumors. *Eur J Cardiothorac Surg*. 2000;18(2):156-161.
99. Kunz PL. Carcinoid and neuroendocrine tumors: building on success. *J Clin Oncol*. 2015;33(16):1855-1863.

24

Non–Small Cell Lung Cancer: General Principles, Management of Localized Disease, and Treatment of Metastatic Disease without Oncogene Drivers

Mehmet Altan
Joshua M Gulvin
George Simon
Bonnie Glisson

KEY CONCEPTS

- Lung cancer is the leading cause of cancer-related death in the United States. However, patients with early lung cancer have lower lung cancer–related mortality, and screening with low-dose computed tomography in high-risk groups correlates with a reduction in overall mortality.
- Multidisciplinary evaluation, including early integration of palliative care, for patients with locally advanced or metastatic non–small cell lung cancer (NSCLC), improves patient outcomes and quality of life.
- Immune checkpoint therapies, particularly therapies targeting the programmed cell death protein 1–programmed cell death ligand 1 pathway are now the standard (as a single agent or as a part of combination) therapy for first-line treatment of metastatic NSCLC that does not harbor targetable mutations and should be considered for all patients if there are no contraindications.

Lung cancer is the second most common cancer in women (after breast cancer) and in men (after prostate cancer) but is the most common cause of cancer-related death.[1] Every year, more than 1.7 million patients die of lung cancer worldwide.[2] About 70% of patients are diagnosed in advanced stages of disease, when the probability of cure is low. Over the years, lung cancer screening efforts and technological advancements in imaging studies have increased the detection of lung cancer in earlier stages; advances in minimally invasive techniques for diagnosis, radiation therapy, and multimodality approaches in locally advanced disease in non–small cell lung cancer (NSCLC) have improved clinical outcomes. Furthermore, in the metastatic setting, advances in targeted therapies in patients with actionable mutations and introduction of immune checkpoint inhibitors (ICIs) used as single agents or in combination have contributed to significant improvements in overall survival (OS). The eventual survival of a patient depends on factors such as presence or absence of comorbidities, stage, tumor characteristics, and performance status as discussed in this chapter.

Lung cancer is broadly divided into small cell lung cancer (SCLC) and NSCLC. Approximately 85% of lung cancers are NSCLC. This chapter describes the epidemiology, etiology, histology, prevention, and molecular biology of NSCLC. The multidisciplinary management of stages I to III is described followed by treatment of stage IV NSCLC without an oncogene driver. Chapter 25 focuses on treatment of patients with NSCLC with a targetable mutation. We will review current clinical knowledge in these areas, with an emphasis on our approach at the University of Texas MD Anderson Cancer Center (MDACC).

EPIDEMIOLOGY

Lung cancer is rarely diagnosed in people younger than 35 years old. Indeed, the median age for lung cancer in the United States in 70 years of age. Incidence and

death rates rise exponentially until age 75 years, when a plateau is reached. NSCLC accounts for the greatest number of deaths from cancer in both men and women over age 60 years.

The geographic, social, and temporal trends of the incidence of NSCLC are closely related to tobacco consumption. In developed Western countries, the incidence of NSCLC has been declining; however, it has been increasing in Asia, Eastern Europe, and developing countries.[3]

Worldwide, NSCLC is more common in men, and this difference has been attributed to higher tobacco consumption. In some regions, such as Eastern Europe and South America, there was an uptake of smoking by women in the 1980s, and these areas are currently experiencing a rise in NSCLC cases in women. In the United States, the incidence has been declining for both men and women as tobacco use declines; the male-to-female ratio from 2007 to 2011 was 1.4 to 1.[4]

ETIOLOGY

Smoking

The causal relationship between tobacco smoke and lung cancer was established in the 1950s in case-control and cohort studies. This led to the 1964 report of the US Surgeon General, concluding that smoking can cause lung cancer. Currently, it is estimated that 83% to 85% of lung cancers in the United States are caused by smoking. Nonsmokers who are exposed to secondhand smoke are also at an increased risk. There is a dose–response relationship between smoking and lung cancer risk, and smoking cessation leads to a significant risk reduction (Table 24–1).[5]

Tobacco smoke is a complex mixture of chemicals that includes multiple carcinogens, most important, the *N*-nitrosamines (nicotine-derived nitrosamino ketone and N′-nitrosonornicotine [NNN]) and polycyclic aromatic hydrocarbons [benzo(a)pyrene and dimethylbenz(a)anthracene]. They are activated through hydroxylation by the P450 enzyme system and exert their action through the formation of DNA adducts.

Smokeless tobacco is frequently advocated as a safer alternative. There has not been a clear association between smokeless tobacco and lung cancer; however, it increases the risk of head and neck, pancreatic, and gastric cancer. E-cigarettes deliver water vapor with scents and different amounts of nicotine, which is addictive and contains nitrosamines. They also contain high levels of propylene glycol and glycerin, and their long-term effects on health are unknown. Their use should not be recommended to nonsmokers, and use as part of a smoking cessation approach needs further study.[6]

Approximately 15% of cases of NSCLC occur in never smokers, corresponding to approximately 20,000 deaths annually. In addition to secondhand smoke exposure, several other agents have also been linked to the development of lung cancer (Table 24–2).

Asbestos

Asbestos exists in many natural forms. The silicate fiber has been implicated in carcinogenesis, is chemically inert, and can remain in a person's lungs for a lifetime. Epidemiologic studies have confirmed the association between asbestos exposure and certain lung diseases, such as pulmonary fibrosis, mesothelioma, and lung cancer.[7] Most exposure occurs in the workplace. When smoking is combined with asbestos exposure, the relative risk of lung cancer is strikingly increased.[7]

TABLE 24–1 Approximate 10-Year Risk of Developing Lung Cancer[a]

	Duration of Smoking					
	25 Years		40 Years		50 Years	
Age (years)	Quit (%)	Still Smoking (%)	Quit (%)	Still Smoking (%)	Quit (%)	Still Smoking (%)
One-Pack-Per-Day Smokers						
55	<1	1	3	5	NA	NA
65	<1	2	4	7	7	10
75	1	2	5	8	8	11
Two-Packs-Per-Day Smokers						
55	<1	2	4	7	NA	NA
65	1	3	6	9	10	14
75	2	3	7	10	11	15

[a]This table assumes that people who have quit smoking will continue to abstain for the next 10 years and those who are still smoking will keep smoking the same amount for the next 10 years.
NA, not available.
Adapted with permission from Bach PB, Kattan MW, Thornquist MD, et al. Variations in lung cancer risk among smokers, *Cancer* 2003 Mar 19;95(6):470-478.

TABLE 24–2 Relative Risk of Developing Lung Cancer

Risk Factor	Relative Risk	Reference
Cigarette smoking in males	17.4	(Garfinkel & Silverberg, 1991)
Cigarette smoking in females	10.8	(Garfinkel & Silverberg, 1991)
Passive smoking	1.5	(Samet et al., 2009)
Asbestos	1.2–2.6	(Bach et al., 2003; Hodgson & Jones, 1986)
Asbestos and smoking	28.8	(Kjuus, Skjaerven, Langård, Lien, & Aamodt, 1986)
Mining	3–8	(Harley et al., 1986; Samet et al., 2009)
Radon (residential)	1.1–2	(Samet et al., 2009)

Bach PB, Kattan MW, Thornquist MD, et al. Variations in lung cancer risk among smokers. *J Natl Cancer Inst*. 2003;95:470-478. doi:10.1093/jnci/95.6.470
Garfinkel L, Silverberg E. Lung cancer and smoking trends in the United States over the past 25 years. *CA Cancer J Clin*. 1991;41(3):137-145. doi:10.3322/canjclin.41.3.137
Harley N, Samet JM, Cross FT, Hess T, Muller J, Thomas D. Contribution of radon and radon daughters to respiratory cancer. *Environ Health Perspect*. 1986;70:17-21. doi:10.1289/ehp.867017
Hodgson JT, Jones RD. Mortality of asbestos workers in England and Wales 1971-81. *Br J Ind Med*. 1986;43(3):158-164. doi:10.1136/oem.43.3.158
Kjuus H, Skjaerven R, Langård S, Lien JT, Aamodt T. A case-referent study of lung cancer, occupational exposures and smoking. II. Role of asbestos exposure. *Scand J Work Environ Health*. 1986;12(3):203-209. doi:10.5271/sjweh.2157
Samet JM, Avila-Tang E, Boffetta P, Hannan LM, Olivo-Marston S, Thun MJ, Rudin CM. Lung cancer in never smokers: clinical epidemiology and environmental risk factors. *Clin Cancer Res*. 2009; 15(18):5626-5645. doi:10.1158/1078-0432.Ccr-09-0376

Radon

Radon is a naturally occurring decay product of uranium. It is a colorless, odorless, chemically inert gas that can penetrate the earth's crust and accumulate in buildings. It emits heavy ionizing alpha particles, which may damage DNA. It was shown that many households in Europe, Canada, and the United States have some degree of radon radiation that may increase NSCLC risk among smokers and nonsmokers.[8]

Diet

The majority of studies that have examined vegetable consumption in relation to lung cancer have shown a protective effect,[9] but there are inherent biases in these population studies. There is also epidemiologic evidence that dietary intake of certain vitamins decreases lung cancer risk; however, trials of vitamin supplementation for cancer prevention have ultimately been unsuccessful (see later Chemoprevention section).

Other Factors

Environmental or industrial exposure to arsenic, chromium, chloromethyl ether, vinyl chloride, and polycyclic aromatic hydrocarbons increases lung cancer risk.[10] Preexisting lung disease such as tuberculosis, silicosis, pulmonary fibrosis, and chronic obstructive pulmonary disease are also associated with an increased lung cancer incidence even when correcting for the degree of cigarette consumption. This suggests that common pathways to these conditions, such as chronic inflammation, may drive the tumorigenic process.

Genetic Predisposition

Family history of lung cancer is associated with a two- to threefold increase in lung cancer risk, even after correction for smoking, and this risk seems to be inherited in a Mendelian co-dominant fashion.[11]

Many studies describe weak but consistent associations between some polymorphisms and lung cancer risk. The cytochrome P450 (CYP) family is responsible for the metabolism of tobacco smoke, and the polymorphism CYP1A1 $Ile^{462}Val$ is associated with a higher risk in Asians (odds ratio [OR], 1.61).[12] The glutathione *S*-transferase enzyme prevents oxidative damage, and the polymorphism GSTM1 increases risk in Asians (OR, 1.17).[13] Finally, individuals with impaired DNA repair capacity are at higher risk of developing lung cancer, even if they are nonsmokers, and the polymorphism $Lys^{751}Gln$ in the DNA-repairing enzyme ERCC2 is associated with lung cancer (OR, 1.15).[14]

Large genome-wide association studies (GWAS)[15] have identified three loci strongly associated with lung cancer risk in different populations: 15q25, 5p15, and 6p21. The 15q25 susceptibility region encodes three cholinergic nicotine receptor genes (*CHRNA3*, *CHRNA5*, *CHRNB4*), and alterations in those regions have been associated with a higher risk for nicotine dependence and higher smoking burden. In nonsmokers, they have also been associated with impaired healing of the respiratory mucosa, suggesting a higher sensitivity to toxin-induced airway damage. The 5p15 region encodes the *TERT* gene, responsible for telomerase function, which is altered in many cancers.[16]

PREVENTION OF LUNG CANCER

Smoking Cessation and Prevention

The most effective method of preventing lung cancer is reducing tobacco exposure, either through encouraging smoking cessation or preventing young people from starting to smoke. In the United States, campaigns to reduce smoking rates have been successful.

The estimated percentage of Americans who actively smoke decreased from 42.4% in 1965 to 25% in 1990 and to 18.1% in 2012.[17] However, former smokers retain an increased risk of lung cancer, and there are still a considerable number of smokers, highlighting the need for better education and prevention strategies, especially those targeted to youths.

Early Detection and Screening

Previous studies examined the role of chest radiography, with or without cytologic analysis of sputum, to screen for lung cancer, and none showed a clear benefit. Most of them were confounded by lead time, length time, and overdiagnosis biases.

Spiral computed tomography (CT)—also called helical CT or low-dose CT—is much more sensitive to detect early NSCLC than chest radiography. In 2011, the results of the National Lung Screening Trial were published.[18] In this trial, 53,454 current or former smokers ages 55 to 74 years old with at least a 30-pack-year smoking history and no symptoms that could be related to lung cancer were randomized to undergo yearly chest radiographs or low-dose CT for 3 years. After a median follow-up of 6.5 years, the low-dose CT group had a 20% reduction in the rate of lung cancer–specific mortality, from 309 to 247 per 100,000 person-years, as well as a 6.7% reduction in overall mortality. In the CT group, 39% of patients had suspicious lung nodules (vs 16% in the control arm), and the majority of these (96%) were considered false-positive results. Sensitivity and specificity of low-dose CT were 93.8% and 73.4%, respectively, compared with 73.5% and 91.3% for chest radiography. Cost-effectiveness analysis showed a median cost of $43,000 per quality-adjusted life-year gained for current smokers assigned to the low-dose CT group. Another trial that supported the surveillance with CT scans had been conducted in Belgium and the Netherlands (the NELSON study) looking at the 10-year impact of lung cancer screening using low-dose CT scan. In this study, A total of 13,195 male participants at high risk for lung cancer were randomly assigned to either the screening group (6583 men) or the control group (6612 men). CT screening performed at baseline, year 1, year 3, and year 5.5 or no screening. At 10 years of follow-up, the incidences of lung cancer were 5.58 cases per 1000 person-years in the screening group and 4.91 cases per 1000 person-years in the control group; lung cancer mortality was 2.5 deaths versus 3.3 deaths per 1000 person-years, respectively. The cumulative rate ratio for death from lung cancer at 10 years was 0.76 (95% confidence interval [CI], 0.61–0.94; P = .01) in the screening group compared with the control group. CT scanning decreased the mortality rate by 26% in high-risk men and up to 61% in high-risk women over a 10-year period.[19] Based on these results, the US Preventive Services Task Force currently recommends lung cancer screening with yearly low-dose CT for current or past smokers, age 55 to 80 years, with a smoking history of at least 30 pack-years. (In late 2020. this screening recommendation is expected to revise and to be extended to include adults ages 50 to 80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years.[20]) Screening should be discontinued when a person has not smoked for 15 years.

Despite recent developments, low-dose CT screening still has significant limitations, including high false-positive ratios and the development of interval lung cancers, which can be aggressive. Positron emission tomography (PET)–CT scan, epigenetic markers, and cell-free tumor DNA are additional approaches under investigation, which are only recommended in the setting of a clinical trial.

Chemoprevention

Cigarette smoking has an effect of field cancerization, with the accumulation of genetic mutations and other premalignant changes throughout the lung and the aerodigestive tract lining. Patients treated and cured of early-stage lung cancer have a high risk of developing second primary tumors. Therefore, a series of chemoprevention trials has focused on smokers and survivors of lung and head and neck cancers.

Multiple studies evaluated supplementation with vitamins and oligo-elements, but none showed a benefit to supplementation, and several studies showed risk, with increased lung cancer incidence and mortality (Table 24–3).[21–27]

Given the potential connection between inflammation and tumorigenesis, phase II studies have used anti-inflammatory agents, such as celecoxib, and prostaglandin analogues, such as iloprost. These agents have been able to reduce proliferation and dysplasia of oral and bronchial epithelium in smokers and former smokers, but their benefit in cancer prevention remains to be proven. There are currently no proven agents for the chemoprevention of lung cancer.

HISTOLOGY AND MOLECULAR PATHOLOGY

NSCLCs include three major types: adenocarcinoma, squamous cell carcinoma (SCC), and large cell carcinoma.

The most current histologic classification of NSCLC was proposed by the International Association for the Study of Lung Cancer/American Thoracic

TABLE 24–3 Large Randomized Lung Cancer Chemoprevention Trials

Study	Intervention	Population	Size	Endpoint	Outcome
ATBC[21]	β-Carotene; α-tocopherol	Male smokers	29,133	Lung cancer incidence	Harmful
CARET[22]	β-Carotene; retinol	Current and former smokers	18,314	Lung cancer incidence	Harmful
Intergroup Lung Trial[23]	Isotretinoin	Resected NSCLC	1166	Second malignancies	Harmful
Euroscan[24]	Retinol, *N*-acetylcysteine	Resected NSCLC and head and neck cancer	2592	Second malignancies	Negative
ECOG 5597[25]	Selenium	Resected NSCLC	1772	Second malignancies	Negative
Physicians' Health Study II[26]	Vitamin C and vitamin E	Healthy male physicians	14,641	Cancer incidence	Negative
NORVIT and WENBIT[27]	Vitamin B_{12} and folic acid	Patients with ischemic heart disease	6845	Cancer incidence	Harmful

ATBC, The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study; CARET, The Beta-Carotene and Retinol Efficacy Trial (CARET); ECOG, Eastern Cooperative Oncology Group; NORVIT, The Norwegian Vitamin (NORVIT) trial; NSCLC, non–small cell lung cancer; WENBIT, Western Norway B Vitamin Intervention Trial (WENBIT).

Society/European Respiratory Society in 2011[28] and uses immunohistochemistry (IHC) to identify subgroups with different molecular profiles and clinical behaviors (Tables 24–4 and 24–5). Adenocarcinomas usually stain positive for cytokeratin 7, thyroid transcription factor 1 (TTF-1), and Napsin A and are negative for cytokeratin 20. TTF-1 is a marker to determine if a tumor is arising from the lung or thyroid origin and is expected to be negative if adenocarcinoma is originating from other organ systems.[29] All carcinoids and most SCLCs stain positive for chromogranin and synaptophysin, whereas NSCLC is usually negative for these two markers. Mesothelioma is distinguished from adenocarcinoma by the presence of calretinin, WT-1, and cytokeratin 5/6 staining and the absence of carcinoembryonic antigen (CEA), B72.3, Ber-EP4, and MOC-31.[29,30]

Adenocarcinoma

Adenocarcinoma is the most common subtype of NSCLC in the United States, representing 40% of cases in men and 50% in women. It is predominant in nonsmokers, and its incidence has been rising. These tumors are classically peripheral and, on histologic examination, demonstrate gland formation, papillary structures, or mucin production (Fig. 24–1).

NSCLC is one of the cancer types with the highest mutation burden, with an average of 360 exonic mutations per sample.[31] However, the patterns of mutations are different for adenocarcinomas and SCCs.

About 75% of lung adenocarcinomas have alterations in driver genes that activate intracellular pathways leading to proliferation, cell survival, and oxidative stress response.[32] Up to 79% of those alterations are in the Receptor Tyrosine Kinase (RTK)–Rat sarcoma (RAS)–Rapidly Accelerated Fibrosarcoma (RAF) pathway, including mutations in the ErbB family member *EGFR* (ErbB1).The prevalence of *EGFR* mutations ranges from 5% to 10% in smokers to 40% to 50% in nonsmokers in the Western population.[33] The alterations are usually in the tyrosine kinase domain of the gene within exons 18 to 24, most specifically in the intracellular adenosine triphosphate (ATP)-binding domain.[33–35]

Frequencies of *EGFR*, *KRAS*, *ALK*, *ROS1*, and other driver genetic alterations commonly found in lung adenocarcinoma samples are listed in Table 24–6.[32,33,36–40] This is a rapidly changing landscape that is defining the many molecular subsets of this heterogeneous disease.

Squamous Cell Carcinoma

SCC is now the second most frequent histology, accounting for 30% of cases of NSCLC in men and 20% in women. This tumor arises most frequently in the proximal bronchi and has the stronger association with smoking than adenocarcinomas. Pathologically, it is characterized by visible keratinization, with prominent desmosomes and intercellular bridges (Fig. 24–2).

SCCs frequently have amplifications in chromosome 3q, which contains genes involved in squamous differentiation (*SOX2* and *TP53*) and cell proliferation (*PI3K*). About 81% to 90% of patients with SCCs have *TP53* mutations, and 47% have alterations in the PI3K–AKT–mTOR pathway, whereas only 26% of SCCs have activations of the RTK/RAS/RAF pathway.[31] Whereas the prevalence of *EGFR* mutations is 1% to 3%, 6% of patients have *EGFR* amplifications, and 1% to 6% have *KRAS* mutations.[31]

TABLE 24–4 The 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society Histologic Classification of Invasive Malignant Epithelial Tumors

Squamous cell carcinoma
Small cell carcinoma
Adenocarcinoma Lepidic predominant (formerly nonmucinous bronchoalveolar carcinoma pattern with >5 mm invasion) Acinar predominant Papillary predominant Micropapillary predominant Solid predominant with mucin production
Variants of invasive adenocarcinoma Invasive mucinous adenocarcinoma (formerly mucinous bronchoalveolar carcinoma) Colloid Fetal (low and high grade) Enteric
Large cell carcinoma Variants: large cell neuroendocrine; large cell neuroendocrine (NE) carcinoma (positive NE markers); large cell carcinoma with NE morphology (morphology suggestive of NE carcinoma but negative stains)
Adenosquamous carcinoma or NSCLC with squamous cell and adenocarcinoma patterns
Carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements Carcinoma with spindle or giant cells Pleomorphic carcinoma Spindle cell carcinoma Giant cell carcinoma
Carcinosarcoma Blastoma (pulmonary blastoma) Others
Carcinoid tumor Typical carcinoid Atypical carcinoid
Carcinomas of salivary gland type Mucoepidermoid carcinoma Adenocystic carcinoma, others
Unclassified carcinoma

NSCLC, non–small cell lung cancer.
Adapted with permission from Travis WD, Brambilla E, Noguchi M, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma, *J Thorac Oncol* 2011 Feb;6(2):244-285.

Large Cell Carcinoma

The least common subtype of NSCLC, large cell carcinoma, accounts for approximately 8% of all NSCLCs (Fig. 24–3). Refinements in histopathologic techniques have led to the diagnosis of adenocarcinoma or SCC in cases previously diagnosed as undifferentiated large cell carcinoma.

CLINICAL PRESENTATION

NSCLC is often asymptomatic at diagnosis and may be found incidentally on imaging performed for other reasons. If symptoms are present, they are often related to the specific locations of tumor masses and the occurrence of paraneoplastic syndromes. The symptoms of centrally located lesions include cough, hemoptysis, wheezing, stridor, dyspnea, and postobstructive pneumonia. Peripheral lesions can cause pain because of pleural or chest wall invasion, cough, or restrictive dyspnea. Loss of appetite, loss of weight, and bone pain are other common systemic symptoms.

The involvement of thoracic and cervical structures can also lead to classical clinical presentations:

- **Pancoast syndrome:** shoulder pain radiating to the arm in an ulnar distribution caused by invasion of the eighth cervical and first thoracic nerves in the superior sulcus
- **Horner syndrome:** enophthalmos, ptosis, miosis, and ipsilateral dyshidrosis caused by involvement of the paravertebral sympathetic nerves, typically from a superior sulcus tumor
- **Hoarseness:** compression or invasion of the left recurrent laryngeal nerve as it passes through the aortopulmonary window by metastatic adenopathy
- **Elevation of the hemidiaphragm:** involvement of phrenic nerve from mediastinal adenopathy
- **Superior vena cava syndrome:** swelling of the face and arm and superficial venous engorgement caused by compression of the superior vena cava either directly by the primary tumor or by metastatic adenopathy

The production of hormones or hormone-like substances can lead to paraneoplastic syndromes:

- **Cancer cachexia:** The most common paraneoplastic syndrome, characterized by weight loss, impaired immune function, and weakness that are not completely explained by poor oral intake. The exact mechanism for development of cachexia is unknown, but tumor-elaborated cytokines have been implicated.
- **Hypercalcemia:** The second most common paraneoplastic syndrome in NSCLC, hypercalcemia is caused by ectopic production of a parathyroid hormone–related protein or bone metastases. Ectopic secretion is more common in the squamous cell subtype.
- **Hypertrophic pulmonary osteoarthropathy:** Arthropathy and clubbing of the fingers and toes with evidence of periostitis of the long bones (Fig. 24–4). Its cause is unknown, and it is more common in adenocarcinomas and large cell carcinoma.

NSCLC is frequently metastatic at diagnosis, and symptoms secondary to metastases are common. The most common sites for metastases are intrathoracic nodes, pleura, contralateral lung, liver, adrenal glands, bone, and brain.

TABLE 24–5 Adenocarcinoma Histologic Subtypes and Molecular and Radiologic Associations

Predominant Histologic Subtype	Molecular Features	Computed Tomography Scan Appearance	Relative Risk of Recurrence After Resection
Lepidic	TTF-1 positive: 100% *EGFR* amplification: 20%–50% *EGFR* mutation (nonsmokers): 10%–30% *KRAS* mutations (smokers): 10% *BRAF* mutations: 5%	Ground glass or solid nodule	1.0
Papillary	TTF-1 positive: 90%–100% *EGFR* amplification: 20%–60% *EGFR* mutation: 10%–30% *KRAS* mutations: 3% *BRAF* mutations: 5% *ERBB2* mutations: 3% *P53* mutations: 30%	Solid nodule	2.7 (95% CI, 1.1–6.8)
Acinar	TTF-1 positive or negative *EGFR* amplification: 10% *EGFR* mutation (nonsmokers): <10% *KRAS* mutation (smokers): 20% *P53* mutation: 40% *EML4/ALK* translocation: >5%	Solid nodule	2.3 (95% CI, 0.9–5.7)
Micropapillary	*EGFR* mutation: 20% *KRAS* mutation: 33% *BRAF* mutation: 20%	Unknown	4.4 (95% CI, 1.8–11.2)
Solid	TTF-1 positive: 70% MUC1 positive *EGFR* amplification: 20%–50% *EGFR* mutation (nonsmokers): 10%–30% *KRAS* mutation (smokers): 10%-30% *EML4/ALK* translocations: >5% *P53* mutations: 50% *LRP1B* mutations *INHBA* mutations	Solid nodule	5.7 (95% CI, 2.2–14.7)
Invasive mucinous adenocarcinoma	TTF-1 negative (0%–33% positive) No *EGFR* mutation *KRAS* mutation: 80%–100% MUC5, MUC6, MUC2, CK20 positive	Consolidation; air bronchograms	Unknown

CI, confidence interval; TTF-1, thyroid transcription factor 1.
Adapted with permission from Travis WD, Brambilla E, Noguchi M, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma, *J Thorac Oncol* 2011 Feb;6(2):244-285.

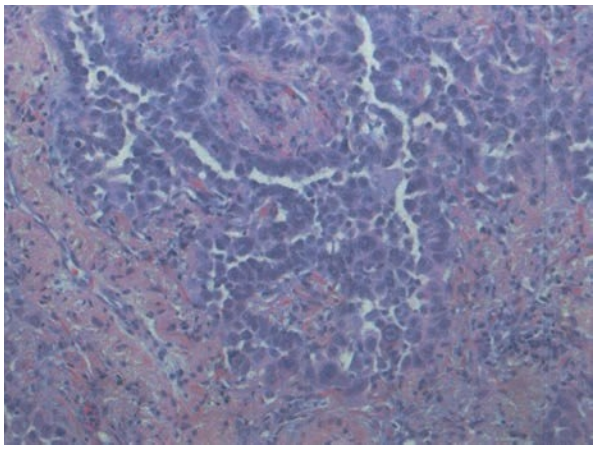


FIGURE 24–1 Adenocarcinoma. Photomicrograph of adenocarcinoma of the lung stained with hematoxylin and eosin. (Used with permission from Cesar Moran, MD.)

DIAGNOSIS

Solitary Pulmonary Nodule

A solitary pulmonary nodule is a single asymptomatic mass that is surrounded by lung tissue, is well circumscribed, measures less than 3 cm, and does not show evidence of mediastinal or hilar adenopathy. The differential diagnosis includes primary cancer, metastatic cancer, infection, benign tumors (eg, hamartomas), vascular abnormalities, and inflammation (eg, granulomatous disease). The American College of Chest Physicians and National Comprehensive Cancer Network (NCCN) have issued guidelines on the evaluation of solitary lung nodules, based on their size, the clinical probability of malignancy, and the patient's surgical risk41 (Table 24–7 and Fig. 24–5).

TABLE 24–6 Common Driver Genes Altered in Lung Adenocarcinoma

Name	Alteration	Main Effects	Incidence
KRAS mutations	Multiple; usually in codons 12 and 13; most common, G12D (nonsmokers) and G12C (smokers)	Activation of RAS–RAF–MEK–ERK pathway	30%–35% (mostly in smokers)[33]
EGFR mutations	Several alterations in the ATP-binding domain of the receptor	Activation of RAS/RAF/MEK and PI3K–AKT–mTOR pathways	10%–15% (40%–50% in nonsmokers)[36]
BRAF mutations	~50% are the V600E mutation also described in other cancers	Activation of RAS–RAF–MEK–ERK pathway	7%–10%[32]
MET mutations	Exon 14 skipping; can occur with or without *MET* amplification	Activation of MET	7%[32]
PIK3CA	Many activating mutations	AKT, TSC, and mTOR	7%[32]
EML4/ALK and other *ALK* translocations	Inversion within chromosome 2p	Constitutively activates the anaplastic lymphoma kinase (*ALK*) gene leading to downstream activation of RAS and PI3K	1%–4%[37,38]
ROS1 fusions	Multiple rearrangements of the *ROS1* gene with different genes	Related to the ALK protein, also activates RAS and PIK3CA	1%–2%[37]
RET fusions	Multiple rearrangements of the *RET* gene with different genes	Activation of the *RET* proto-oncogene and RAS pathway	1%[39]
ERBB2 (*HER2*) mutations	Various mutations; in ~50% of cases co-occurrence with *HER2* amplification	Activation of RAS–RAF–MEK and PI3K–AKT–mTOR pathways	2%–4%[40]

AKT, Protein kinase B (PKB); ERK: extracellular signal-regulated kinase; MEK, Mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; RAS, Rat sarcoma; RAF, Rapidly Accelerated Fibrosarcoma; TSC, Tuberous Sclerosis Complex.

A detailed description of the management of solitary pulmonary nodules is beyond the scope of this book chapter. Readers referred to the updated Fleischner Society guidelines (2017)[42] and the NCCN guidelines.[43]

Pulmonary Mass

Lesions that are large (>3 cm), multiple, or with enlarged hilar, mediastinal, and/or supraclavicular lymph nodes should undergo complete lung cancer staging and a

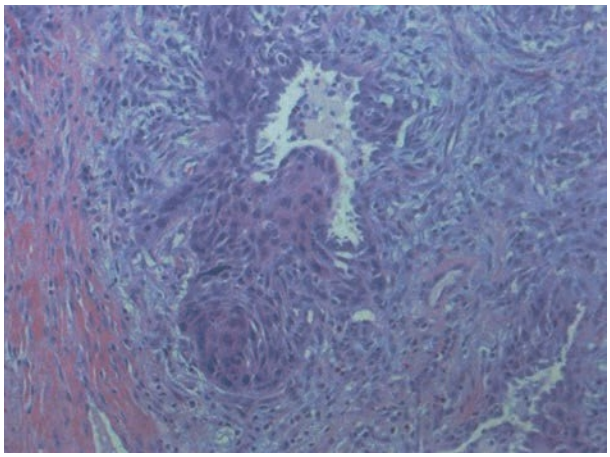


FIGURE 24–2 Squamous cell carcinoma. Photomicrograph of squamous cell carcinoma of the lung stained with hematoxylin and eosin. (Used with permission from Cesar Moran, MD.)

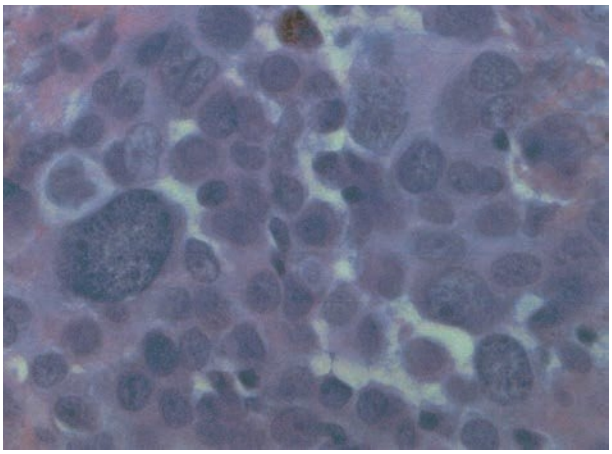


FIGURE 24–3 Large cell carcinoma. Photomicrograph of large cell carcinoma of the lung stained with hematoxylin and eosin. (Used with permission from Cesar Moran, MD.)

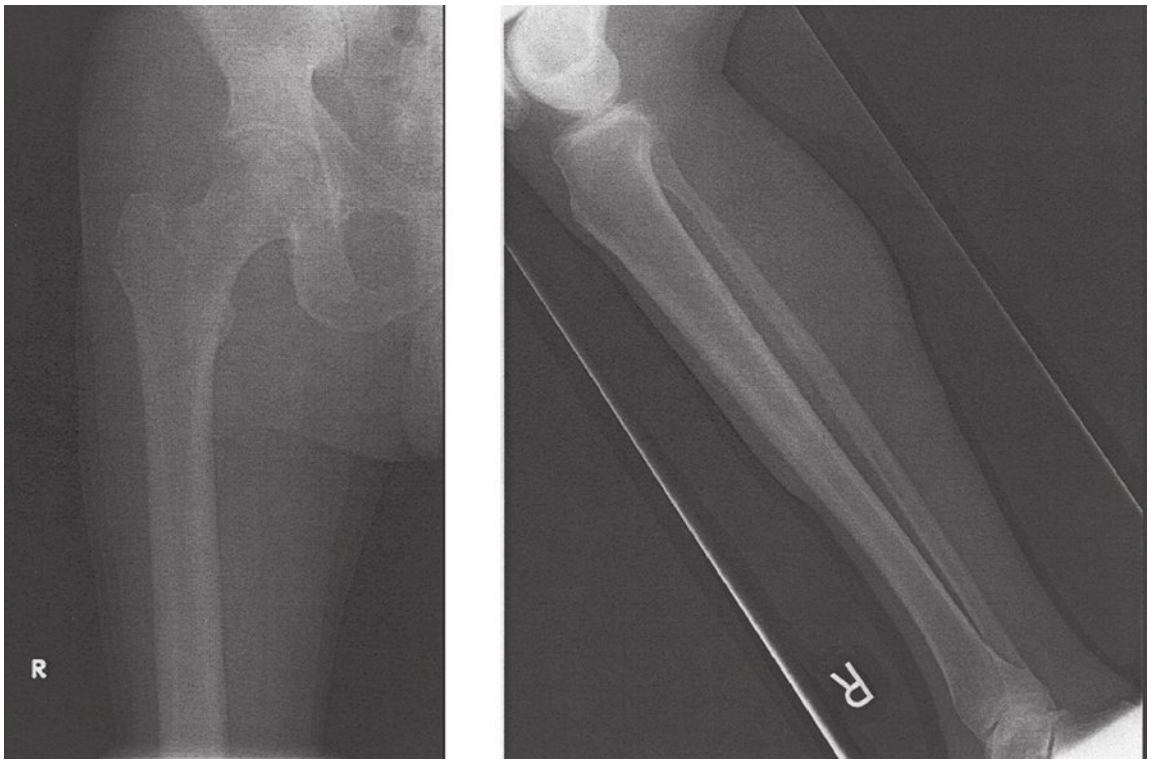


FIGURE 24–4 Hypertrophic pulmonary osteoarthropathy (HPO). This 62-year-old man with non–small cell lung cancer reported a 1-month history of finger clubbing and arthritic lower extremity pain. Plain radiographs of the lower extremities show a periosteal reaction in both femora as well as in bilateral tibias and fibulas that is consistent with HPO.

TABLE 24–7 Clinical Probability of Malignancy of Solitary Lung Nodules

	Low Probability (<5%)	Intermediate Probability (6%–65%)	High Probability (>65%)
Patient	Young, low smoking burden, no previous history of cancer	Mixture of low- and high-probability features	Older, heavy smoker, previous cancer
Nodule (CT scan)	Small, regular margins, non–upper lobe location, enhancement <15 HU in the contrast phase	Mixture of low- and high-probability features	Large, irregular or spiculated, upper lobe location; enhancement >15 HU in the contrast phase
FDG-PET results	Low or moderate clinical probability with low PET probability	Weak or moderate PET activity	Intense hypermetabolic nodule
Nonsurgical biopsy results (bronchoscopy or transthoracic biopsy)	Specific benign diagnostic	Nondiagnostic	Suspicious for malignancy
Behavior on CT surveillance	Progressive decrease in size or resolution; no growth over ≥2 years (solid nodules) or over ≥3 years (semisolid nodules)	NA	Clear evidence of growth

CT, computed tomography; FDG-PET, ^{18}F-fluorodeoxyglucose–positron emission tomography; NA, not applicable.

nonsurgical biopsy. Fiberoptic bronchoscopy is appropriate for central lesions and is able to establish the diagnosis in 97% of cases. For peripheral lesions, the diagnostic yield of bronchoscopy is only 55%, and percutaneous transthoracic biopsies can be considered. Because of the tissue requirements for IHC and molecular marker testing of lung cancers, at MDACC, we usually perform an image-guided core-needle

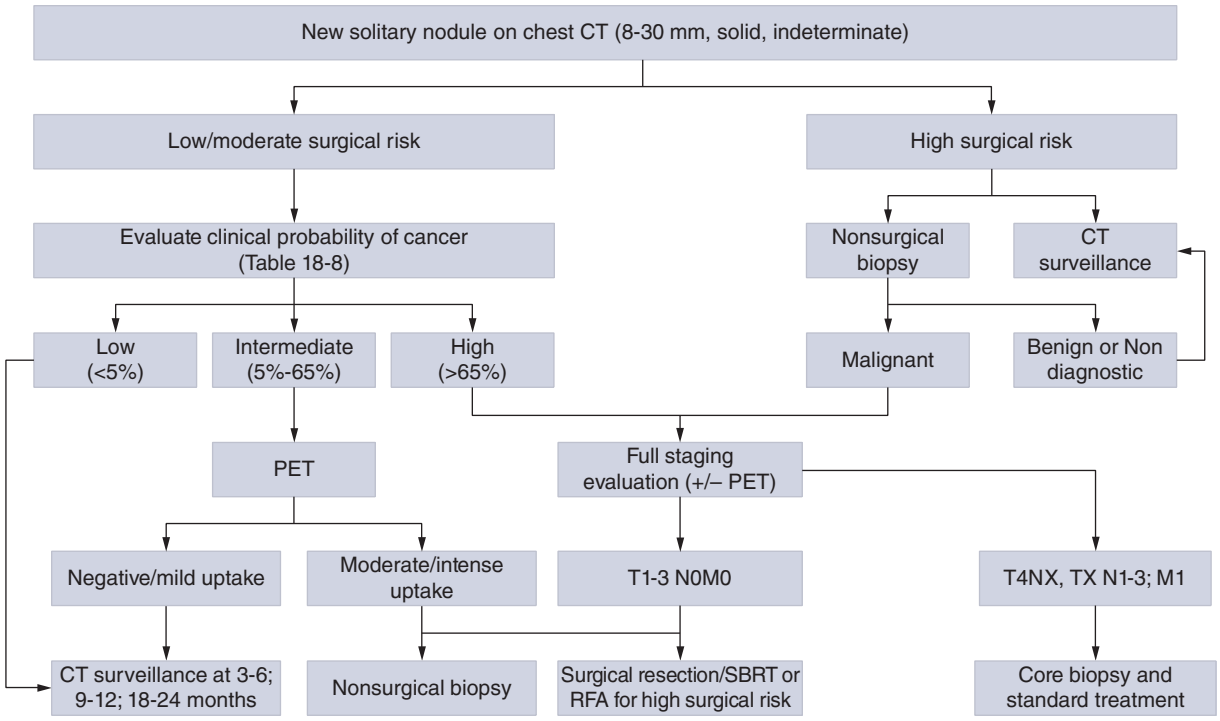


FIGURE 24–5 Management algorithm for individuals with solitary nodules (8–30 mm). CT, computed tomography; PET, positron emission tomography; RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy. (Adapted with permission from Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines., *Chest* 2013 ;143(5 suppl):e93S-120S.)

biopsy. Mediastinoscopy or bronchoscopic endobronchial ultrasound (EBUS) can be used to obtain biopsy samples from mediastinal and hilar nodes.

Staging

After the histologic diagnosis of NSCLC has been established, the extent of disease must be determined. The stage of disease dictates therapy and prognosis (Tables 24–8 and 24–9). All patients must undergo a complete history and physical examination, PET-CT, a complete blood count, and blood chemistry tests that assess renal and hepatic function, electrolytes, and calcium levels. All patients with stage II to IV disease should have evaluation of the brain, with magnetic resonance imaging (MRI) if possible. Central nervous system imaging may also be considered for patients with stage I disease. For stage I to IV NSCLC,[18]F-fluorodeoxyglucose (FDG)-PET should be performed to evaluate mediastinal nodes and for distant metastases. Because the involvement of mediastinal lymph nodes will influence surgical decisions (see the Treatment section), the presence of FDG-avid mediastinal lymph nodes in a PET-CT scan should be confirmed with either mediastinoscopy or EBUS. In the setting of a normal-appearing mediastinum on PET-CT, invasive mediastinal assessment should also be encouraged as a part of the initial evaluation in the preoperative setting and preradiation settings (stages I–III) In one series, occult N2 disease was found in 20% of patients with T1 to T2 NSCLC, node negative by PET-CT.[44]

After completion of the staging evaluation, the disease is assigned a TNM stage as outlined in Tables 24–8, 24–9. The eighth edition TNM staging a was adopted in 2017.[45]

Key T Descriptors (Fig. 24–6)

Primary Tumor

T1 disease: T1 tumors are divided into T1a (≤1 cm), T1b (>1 to ≤2 cm), and T1c (>2 to ≤3 cm).

T2 disease: T2a is larger than 3 cm to 4 cm, and T2b is larger than 4 cm but not larger than 5 cm. Or it is a tumor with any of the following features. involvement of the mainstem bronchus, regardless of the distance from the carina; visceral pleura involvement; and partial or total atelectasis that extends to the hilar region either involving part of the lung or the entire lung.

T3 disease: T3 is larger than 5 to 7 cm. Or the tumor directly invades any of the following: chest wall, phrenic nerve, parietal pericardium, or associated spate tumor nodule(s) in the same node as the primary.

TABLE 24–8 Definitions for Tumor (T), Node (N), and Metastasis (M) Descriptors (Stage Grouping for the TNM Classification for Lung Cancer)

Descriptor	Subgroup	Definition
T		Primary tumor
Tx		Primary tumor cannot be assessed or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0		No evidence of primary tumor
Tis		Carcinoma in situ
T1		Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (ie, not in the main bronchus)[a]
	T1mi	Minimally invasive adenocarcinoma[b]
	T1a	Tumor ≤1 cm in greatest dimension[a]
	T1b	Tumor >1 cm but not >2 cm in greatest dimension[a]
	T1c	Tumor >2 cm but not >3 cm in greatest dimension[a]
T2		Tumor >3 cm but not >5 cm or tumor with any of the following features[c] • Involves main bronchus regardless of distance to the carina but without involving the carina • Invades the visceral pleura • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, either involving part of the lung or the entire lung
	T2a	Tumor >3 cm but not >4 cm in greatest dimension
	T2b	Tumor >4 cm but not >5 cm in greatest dimension
T3		Tumor >5 cm but not >7 cm in greatest dimension or one that directly invades any of the following: chest wall (including superior sulcus tumors), phrenic nerve, or parietal pericardium; or associated separate tumor nodule(s) in the same lobe as the primary
T4		Tumor >7 cm or one that invades any of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; separate tumor nodule(s) in a different ipsilateral lobe to that of the primary
N		Regional lymph nodes
Nx		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in ipsilateral peribronchial or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2		Metastasis in ipsilateral mediastinal or subcarinal lymph node(s)
N3		Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M		Distant metastasis
M0		No distant metastasis
M1		Distant metastasis
	M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodules or malignant pleural or pericardial effusion[d]
	M1b	Single extrathoracic metastasis in a single organ[e]
	M1c	Multiple extrathoracic metastasis in one or several organs

[a]The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a.
[b]Solitary adenocarcinoma (≤3 cm), with a predominantly lepidic pattern and ≤5 mm invasion in the greatest dimension in any one focus.
[c]T2 tumors with these features are classified T2a if ≤4 cm or if size cannot be determined and T2b if >4 cm but not >5 cm.
[d]Most pleural (pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. When these elements and clinical judgement dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.
[e]This includes involvement of a single distant (nonregional) node.
Reproduced with permission from Goldstraw P, Chansky K, Crowley J, et al: The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer, *J Thorac Oncol* 2016 Jan;11(1):39-51.

TABLE 24–9 Staging Grouping for the 8th Edition of the Tumor (T), Node (N), and Metastasis (M) Classification for Lung Cancer

Stage	T	N	M
Occult carcinoma	Tx	N0	M0
0	Tis	N0	M0
IA1	T1mi	N0	M0
	T1a	N0	M0
IA2	T1b	N0	M0
IA3	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB	T1a	N1	M0
	T1b	N1	M0
	T1c	N1	M0
	T2a	N1	M0
	T2b	N1	M0
	T3	N0	M0
IIIA	T1a	N2	M0
	T1b	N2	M0
	T1c	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
IIIB	T1a	N3	M0
	T1b	N3	M0
	T1c	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N2	M0
	T4	N2	M0
IIIC	T3	N3	M0
	T4	N3	M0
IVA	Any T	Any N	M1a
	Any T	Any N	M1b
IVB	Any T	Any N	M1c

Reproduced with permission from Goldstraw P, Chansky K, Crowley J, et al: The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer, *J Thorac Oncol* 2016 Jan;11(1):39-51.

T4 disease: T4 is larger than 7 cm. Or the tumor that invades any of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina or it is a separate tumor nodule(s) in a different ipsilateral lobe to that of the primary.

Regional Lymph Nodes (Fig. 24–7):

N0: no nodal metastases

N1: metastasis in ipsilateral peribronchial or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension

N2: metastasis in ipsilateral mediastinal or subcarinal nodal disease

N3: metastasis in contralateral mediastinal, contralateral hilar, ipsilateral, or contralateral scalene or supraclavicular lymph node(s)

Distant Metastasis (Fig. 24–8)

M1a: metastatic disease confined to the chest is classified as M1a, which includes contralateral lung nodule(s) (notably, nodules in the ipsilateral lung are classified as T3 disease if they are in the same lobe as the primary or T4 disease if they are in a different lobe as the primary), malignant pleural or pericardial effusions, or pleural or pericardial nodules. MIa disease is grouped as stage IVA disease.

M1b: a solitary metastasis outside the chest. M1b disease is grouped as stage IVA.

M1c: multiple metastases outside the chest in one or several organs. M1c disease is grouped as stage IVB. Please see Table 24–10 for stage groupings and prognosis by stage.[45]

Clinical staging has inherent inaccuracies and therefore typically underestimates the true extent of disease. In patients who undergo surgical tumor resection, surgical or pathologic staging should be done to predict recurrence and to evaluate the need for adjuvant therapy. Patients' 5-year survival rates by tumor stage per American Joint Committee on Cancer (AJCC) eighth edition are shown in Table 24–10.

TREATMENT

Stage I and II Disease

Surgery

Surgery is standard treatment for stage I and II NSCLC if there are no contraindications (Figs. 24–9 and 24–10). For patients who cannot be safely operated on or refuse surgery, radiation therapy can be considered.

The extent of lung resection is dictated by the size and location of the tumor. The entire tumor must be removed, with margins negative for cancer. Wedge resection and segmentectomy are associated with higher rates of local recurrence than lobectomy and pneumonectomy and are not considered standard of

care, although they may be an option for patients who cannot tolerate a larger surgery due to poor pulmonary function.[46] All patients should also undergo complete ipsilateral mediastinal lymph node dissection or systematic mediastinal sampling for accurate pathologic staging.[47]

Any patient who is being considered for surgery must undergo pulmonary function tests to assess the ability to withstand pulmonary resection. Split-lung function studies can further help to predict lung function after the planned resection. There is no single accepted value, criterion, or cutoff for pulmonary resection. Published criteria that have been shown to predict high risk for lung resection include estimated posttreatment forced vital capacity less than 2 L, forced expiratory volume in 1 second less than 1 L, and diffusing capacity of the lungs for carbon dioxide less than 40% to 60%.[48]

Radiation Therapy

For patients with early-stage lung cancer who cannot undergo surgery because of poor pulmonary reserve or medical comorbidities, stereotactic radiosurgery (SRS) is a reasonable and even a desirable option with local control rates of 90% and a cancer-specific survival rate of 88% at 3 years.[49]

There is controversy regarding whether SRS should be considered in patients who are candidates for surgery and who have small primary tumors and no lymph node involvement. Retrospective series suggest that outcomes with radiation may be similar to those

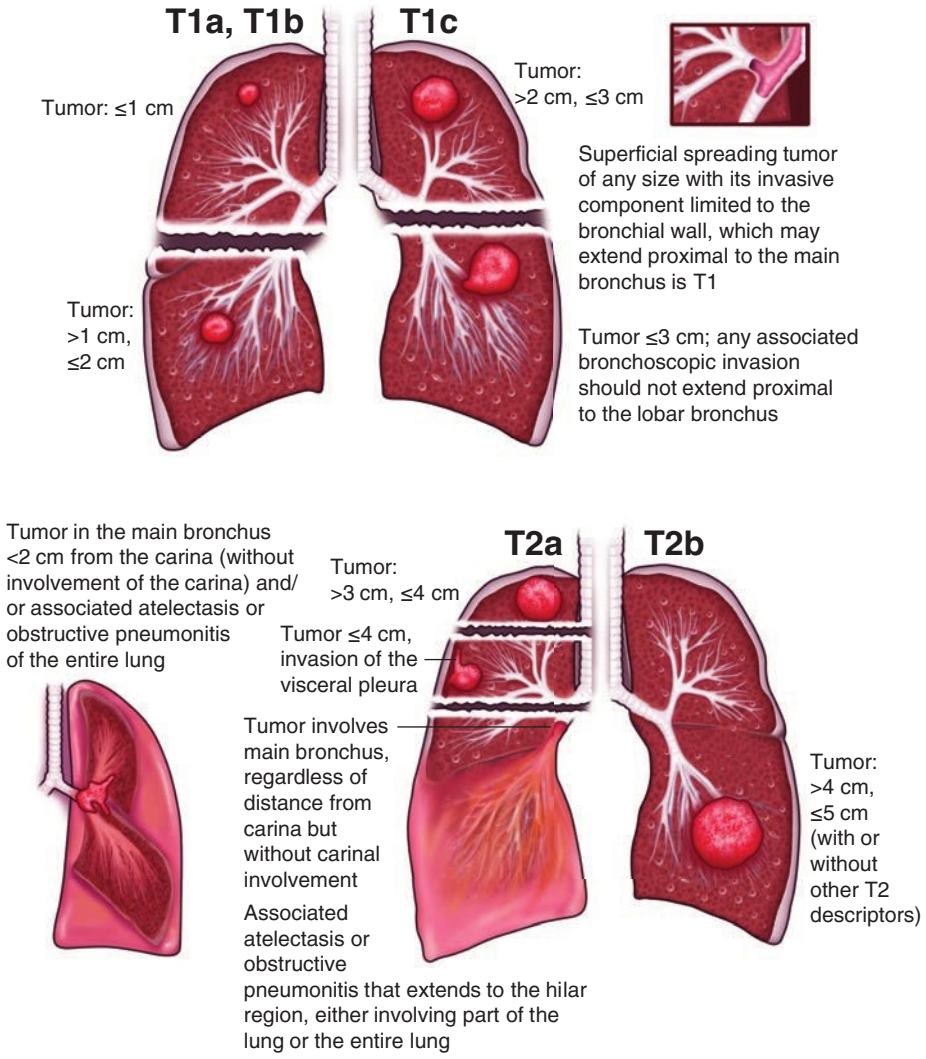


FIGURE 24–6 Lung cancer staging for tumor (T). SVC, superior vena cava.

(*Continued*)

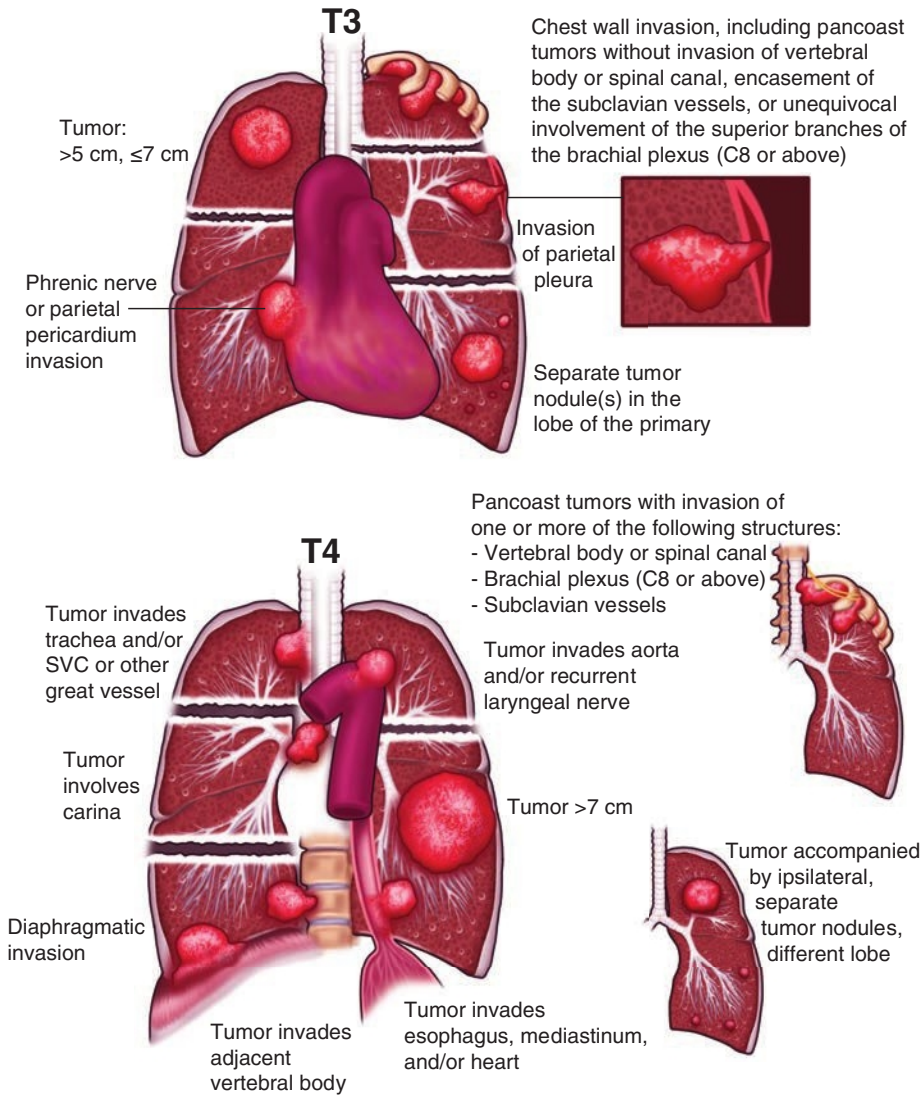


FIGURE 24–6 (*Continued*)

of surgery.[49] Surgery, however, remains the standard of care for patients who can tolerate it.

Concurrent chemotherapy and radiotherapy are recommended for patients who are medically inoperable with stage II (node-positive) and stage III NSCLC.[50–53]

Adjuvant Chemotherapy

Even after complete resection, rates of recurrence of NSCLC are high, prompting the study of adjuvant chemotherapy in this disease. The potential benefit of adjuvant chemotherapy is the eradication of micrometastatic disease before it becomes clinically evident, thus potentially increasing cure rates. For patients with completely resected stage II or III NSCLC, multiple meta-analyses demonstrate that adjuvant platinum-based chemotherapy is associated with an absolute benefit in 5-year survival rate of about 5%.[54] In a pooled analysis of five largest trials of cisplatin-based chemotherapy in patients with completely resected NSCLC showed that this benefit is greater with increasing stage, with a hazard ratio (HR) for stage II of 0.83; (95% CI, 0.73–0.95) and HR for stage III of 0.83; (95% CI, 0.72–0.94).[55] Thus, adjuvant chemotherapy should be offered to all patients with good performance status, with completely resected stage II and III NSCLC (Table 24–11).[55–60] For patients with no lymph node involvement and a primary tumor smaller than 4 cm, adjuvant chemotherapy is not recommended. For node-negative tumors larger than 4 cm, the Cancer and Leukemia Group B 9633 trial suggested a benefit of adjuvant platinum-based chemotherapy, and it should be considered particularly in the setting of high-risk factors such as vascular invasion, visceral

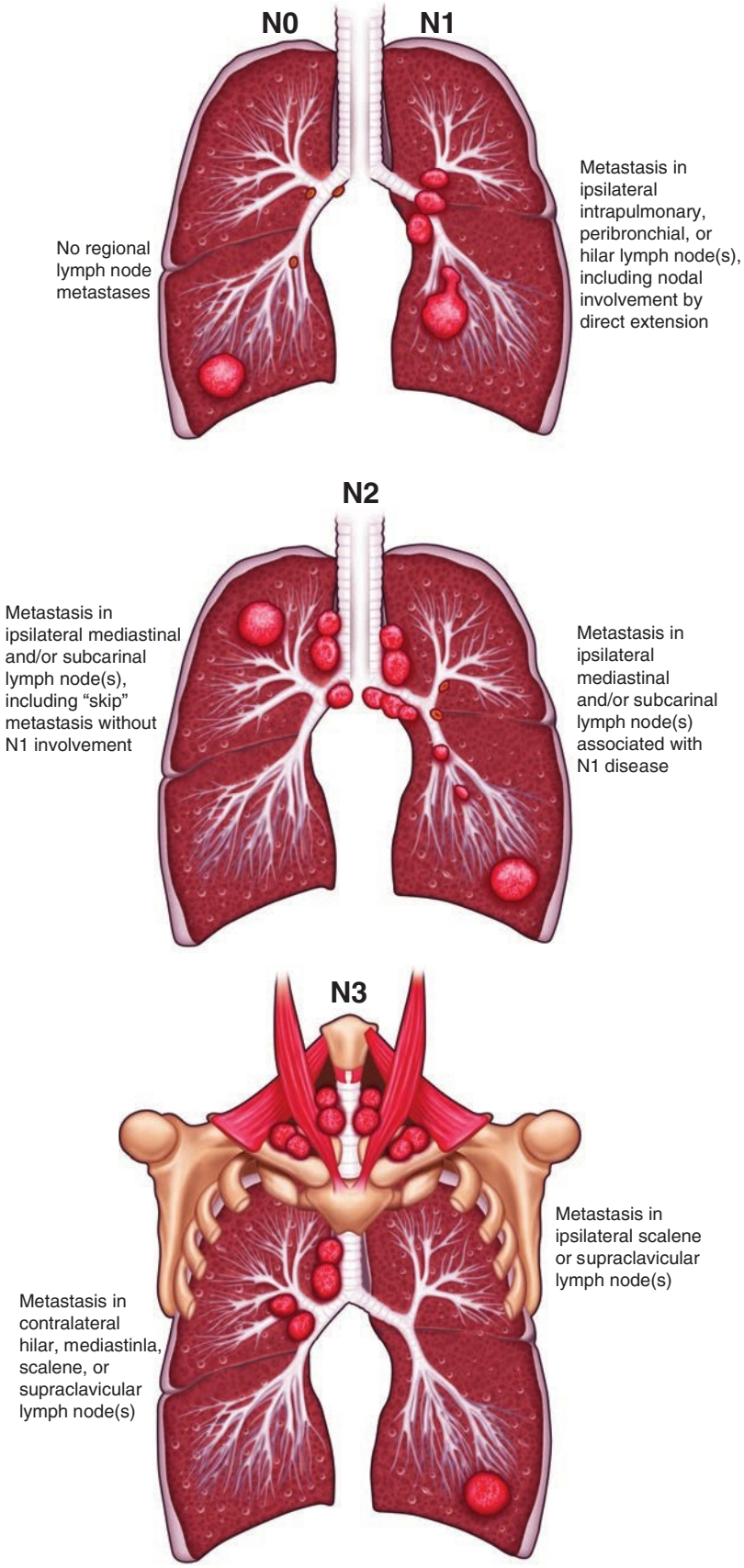


FIGURE 24–7 Lung cancer staging for node (N).

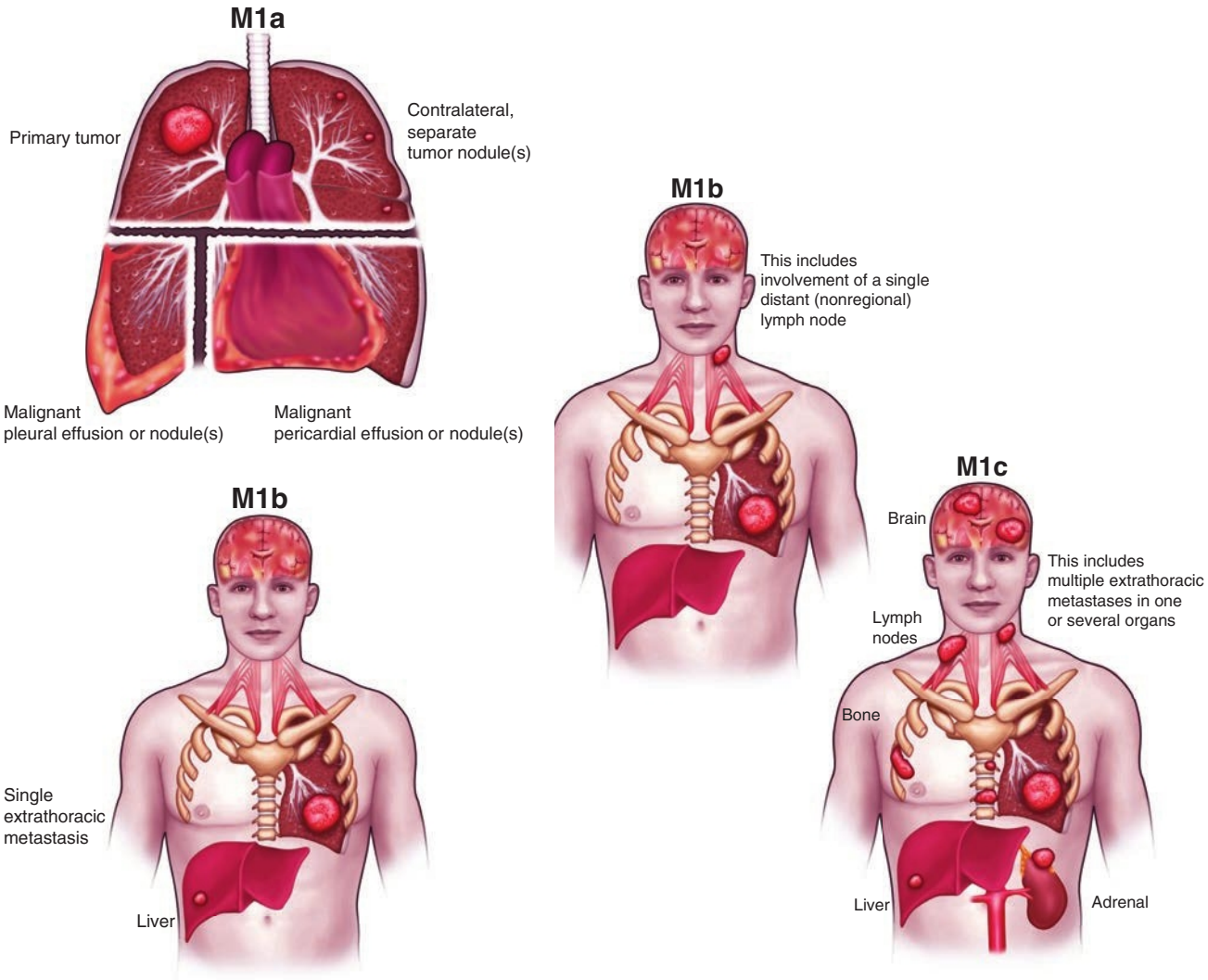


FIGURE 24–8 Lung cancer staging for metastasis (M).

TABLE 24–10 Five-Year Survival for Non–Small Cell Lung Cancer by Pathologic Clinical Stage

Stage	MST	24 Months (%)	60 Months (%)
IA1	NR	97	92
IA2	NR	94	83
IA3	NR	90	77
IB	NR	87	68
IIA	NR	79	60
IIB	66.0	72	53
IIIA	29.3	55	36
IIIB	19.0	44	26
IIIC	12.6	24	13
IVA	11.5	23	10
IVB	6.0	10	0

MST, median survival time in months; NR, not reached.
Data from Goldstraw P, Chansky K, Crowley J, et al: The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer, *J Thorac Oncol* 2016 Jan;11(1):39-51.

pleural involvement, wedge resection, poorly differentiated tumors, and unknown lymph node status[56,61] (see Table 24–11).

Cisplatin–vinorelbine is the most studied regimen for adjuvant chemotherapy; in practice, other cisplatin-based doublets are frequently used. Acceptable second agents include pemetrexed (for nonsquamous NSCLC), docetaxel, paclitaxel, etoposide, and gemcitabine. Cisplatin is preferred over carboplatin, but if cisplatin is not feasible, carboplatin–paclitaxel is an appropriate alternative.[56] Neoadjuvant chemotherapy offers several real and theoretical advantages over postoperative therapy, including better patient compliance, improved tumor resectability, earlier treatment of micrometastatic disease, and earlier assessment of clinical and pathologic response. There has been one randomized trial and one meta-analysis[62] that suggest the equivalence of the neoadjuvant and adjuvant approaches. Adjuvant treatment is the standard of care, but neoadjuvant chemotherapy could be

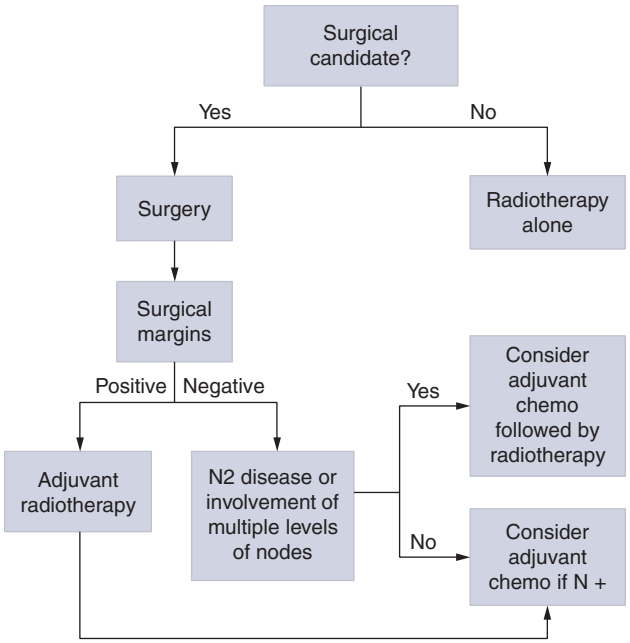


FIGURE 24–9 Treatment algorithm for stage I non–small cell lung cancer. See text for details.

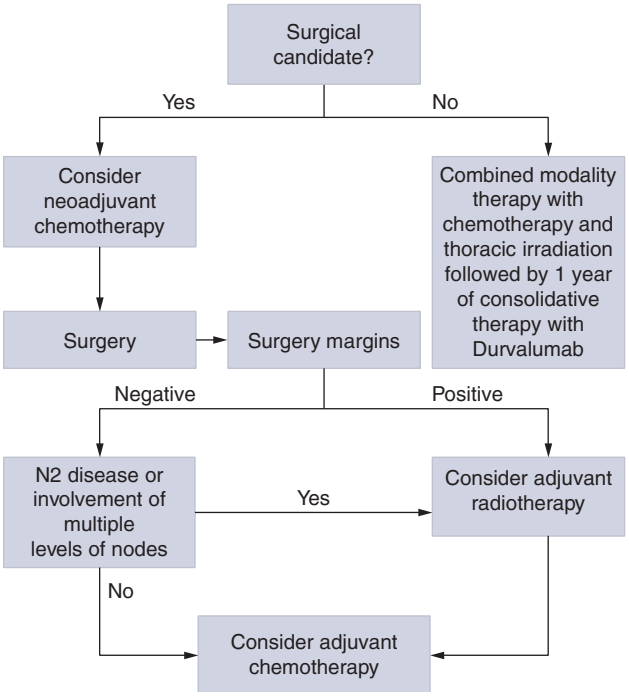


FIGURE 24–10 Treatment algorithm for stage II, incidental III non–small cell lung cancer. See text for details.

considered in special situations, such as for stage III disease when response to chemotherapy may help to determine whether a patient should undergo surgery or chemoradiation.

Adjuvant radiation or chemoradiation for resected stage I and II NSCLC has been shown to be detrimental and is not recommended.[63]

Stage III Disease

Patients with stage III disease have better outcomes with multimodality rather than single-modality therapy, and their care should be managed by an experienced multidisciplinary team. For patients with stage IIIB disease, chemoradiation represents the standard of care.

TABLE 24–11 Chemotherapy Regimens for Adjuvant Treatment of Patients with Non–Small Cell Lung Cancer

Trial	Regimen
IALT[57]	Cisplatin 80–120 mg/m^2 every 3 of 4 weeks for three or four cycles, with
	Vinorelbine 30 mg/m^2 weekly or
	Vinblastine 4 mg/m^2 every week for 5 weeks; then every 2 weeks or
	Etoposide 100 mg/m,^{2} days 1–3, with each cisplatin
ANITA[58]	Cisplatin 100 mg/m,^{2} day 1, every 4 weeks and vinorelbine 30 mg/m^2 weekly for four cycles
NCIC-CTG JBR.10[62]	Cisplatin 50 mg/m,^{2} days 1 and 8, every 4 weeks for four cycles; vinorelbine 25 mg/m^2 every week for 16 cycles
TREAT[60] (nonsquamous histology)	Cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 every 3 weeks for four cycles
CALGB 9633[56]	Carboplatin AUC 6 and paclitaxel 200 mg/m^2 every 3 weeks for four cycles
Others	Cisplatin 75 mg/m^2 and docetaxel 75 mg/m,^{2} day 1, every 3 weeks for four cycles Cisplatin 75–80 mg/m,^{2} day 1; vinorelbine 25–30 mg/m,^{2} days 1 and 8, every 3 weeks for four cycles Cisplatin 75 mg/m,^{2} day 1, and gemcitabine 1250 mg/m,^{2} days 1 and 8, every 3 weeks for four cycles Carboplatin AUC 6 and pemetrexed 500 mg/m^2 every 3 weeks for four cycles (nonsquamous histology)

ANITA, Adjuvant Navelbine International Trialist Association [ANITA); AUC, area under the curve; CALGB, Cancer and Leukemia Group B; NCIC-CTG JBR.10, National Cancer Institute of Canada Clinical Trials Group JBR.10; NSCLC, non–small cell lung cancer; TREAT, Trial on Refinement of Early Stage Lung Cancer Adjuvant Therapy.

Chemoradiation is often used for patients with stage IIIA disease as well, but surgery with adjuvant treatment can be considered for carefully selected patients.

In a randomized trial of chemoradiation alone versus chemoradiation followed by resection, the patients who benefited from the surgical approach were those with stage IIIA disease who had limited involvement of mediastinal lymph nodes and who underwent lobectomy (as opposed to pneumectomy).[64] Neoadjuvant chemoradiation followed by surgery has been compared with neoadjuvant chemotherapy followed by surgery and adjuvant radiation[65] and was associated with more toxicity with no survival benefit. At MDACC, we consider surgical treatment in patients with stage IIIA disease with good performance status and without multistation or bulky (>2 cm) mediastinal adenopathy. These patients are typically treated with neoadjuvant chemotherapy followed by consideration of surgery. Adjuvant radiation therapy is typically given if there is evidence of mediastinal node involvement based on assessment of surgical pathology (Fig. 24–11).

Patients with stage IIIA disease and extensive mediastinal involvement or IIIB disease should be treated with concurrent chemoradiation and followed by consolidative ICI therapy. Concurrent chemoradiotherapy (CRT), when compared with sequential radiotherapy and chemotherapy, is associated with higher survival rates (23.8% vs 18.1% at 3 years; HR, 0.84; P =.004) with increased, but manageable, acute esophageal toxicity (grade 3–4 from 4% to 18% vs 4%; relative risk [RR], 4.9; P =.001) without a significant difference regarding acute pulmonary toxicity.[50]

Standard radiotherapy for stage III NSCLC consists of radiation given once daily for 6 weeks (30 fractions) to a total dose of 60 Gy. Attempts to increase efficacy through increased radiation dose have failed. In The Radiation Therapy Oncology Group 0617 trial, patients receiving high-dose radiation (74 Gy) had higher rates of locoregional failure (44% vs 35.3%; P =.04) and worse median survival times (19.5 vs 28.7 months; P =.0007) than those receiving standard-dose radiation (60 Gy).[66] Proton therapy is a newer technique that is able to deliver a higher dose to the tumor while delivering lower doses to normal surrounding tissue; it is currently being compared with standard radiation in a randomized phase III trial.

Multiple concurrent chemotherapy regimens have been tested against radiation alone with proven benefit[53]; however, these regimens have not been directly compared with each other, and multiple regimens are considered acceptable (Table 24–12). At MDACC, we favor carboplatin and paclitaxel based on our experience and retrospective data that suggest that this regimen is less toxic than cisplatin and etoposide.[67]

ICI therapy is standard as consolidation after CRT based on a landmark study, the A Phase III, Randomised, Double-blind, Placebo-controlled, Multicentre, International Study of MEDI4736 as Sequential Therapy in Patients With Locally Advanced, Unresectable Non-Small Cell Lung Cancer (Stage III) Who Have Not Progressed Following Definitive, Platinum-based, Concurrent Chemoradiation Therapy (PACIFIC) trial. For patients with unresectable, stage III NSCLC without progression after CRT, durvalumab demonstrated increased survival rates versus placebo leading to its approval by the Food and Drug Administration (FDA). Patients included in the PACIFIC study had stage III unresectable disease, received two or more cycles of platinum-based chemotherapy (containing etoposide, vinblastine, vinorelbine, paclitaxel, docetaxel, pemetrexed) concurrently with definitive radiation, without progression.[68] Patients previously treated with programmed cell death (ligand) 1 (PD-(L)1 inhibitors or grade 2 or greater pneumonitis from previous chemoradiation were excluded.[68] Patients were enrolled irrespective of PD-L1 status. Patients were randomized within

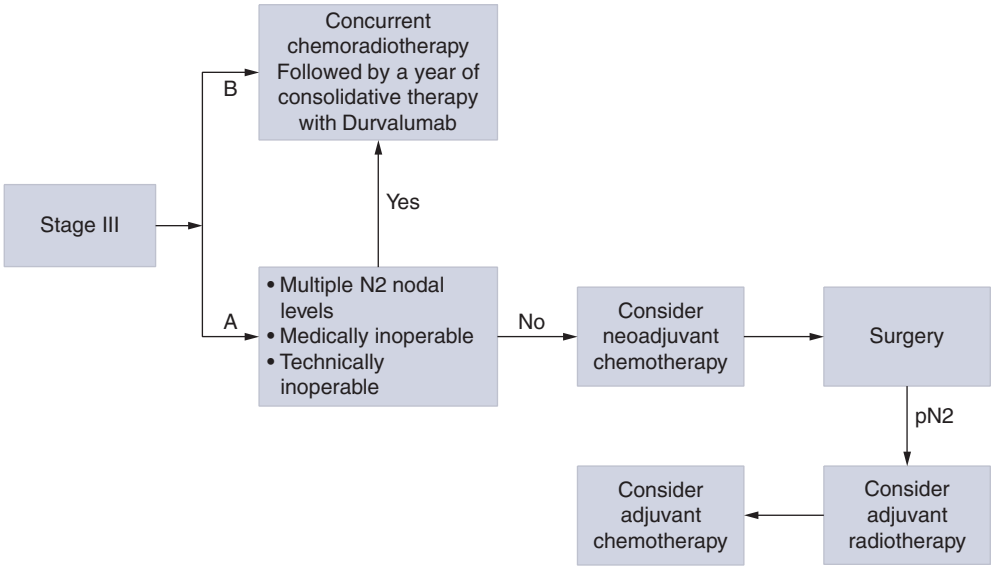


FIGURE 24–11 Treatment algorithm for stage III non–small cell lung cancer. See text for details.

TABLE 24–12 Chemoradiation Regimens for Stage III Non–Small Cell Lung Cancer

Regimen	Histology	Doses	Adjuvant Treatment After the Completion of Chemoradiation
Cisplatin + etoposide	All NSCLC	Cisplatin 50 mg/m^2 days 1, 8, 29,36 Etoposide 50 mg/m^2 days 1–5, 29–33	No
Cisplatin + vinblastine	All NSCLC	Cisplatin 100 mg/m^2 days 1 and 29 Vinblastine 5 mg/m^2 weekly × 5	No
Carboplatin + pemetrexed	Adenocarcinoma	Carboplatin AUC 5 day 1 every 21 days × 4 Pemetrexed 500 mg/m^2 day 1 every 21 days × 4	Yes; continue carboplatin + pemetrexed to a total of four cycles
Cisplatin + pemetrexed	Adenocarcinoma	Cisplatin 75 mg/m^2 day 1 every 21 days × 3 Pemetrexed 500 mg/m^2 day 1 every 21 days × 3	Yes; continue cisplatin + pemetrexed to a total of three cycles
Carboplatin + paclitaxel	All NSCLC	Carboplatin AUC 2 weekly during radiation Paclitaxel 45–50 mg/m^2 weekly during radiation	Yes; two cycles of carboplatin AUC 6 + paclitaxel 200 mg/m^2 every 21 days after the completion of chemoradiation

AUC, area under the curve; NSCLC, non–small cell lung cancer.

6 weeks of completing CRT to receive durvalumab 10 mg/kg intravenously every 2 weeks or placebo for up to 12 months.[68] They were stratified by age younger than 65 years vs 65 years and older), sex, and smoking status (current or former smoker vs never smoker). A total of 473 patients were randomized to durvalumab, and 236 patients were randomized to placebo.[68]

The addition of durvalumab improved progression-free survival (PFS) and OS; 12-, 24- and 36-month OS rates with durvalumab and placebo were 83.1% versus 74.6%, 66.3% versus 55.3%, and 57.0% versus 43.5%, respectively, and therapy was generally tolerated well with without compromising patient-reported outcomes.[69,70]

After radiation therapy to the involved lung, any grade of pneumonitis was observed in nearly one third of patients in the durvalumab arm, with 20% attributed to radiation pneumonitis and about 13% attributed to durvalumab.[71] Pneumonitis was the most common immune-related adverse event leading to treatment discontinuation, and four patients died from pneumonitis. This immune-related adverse event needs to be followed closely in patients undergoing this consolidative approach.

If patients have a contraindication to ICI therapy, such as organ transplant or active autoimmune disease, when the safety of immunotherapy has not been well established, consolidative chemotherapy can be considered. However, no level 1 randomized evidence supports a survival benefit with this treatment.[72,73]

Pancoast Tumors

Tumors in the lung apex invading apical structures, termed pancoast tumors (Figs. 24–12 and 24–13), are challenging. Patients with N0 to N1 tumors should undergo preoperative concurrent chemoradiation followed by resection. For these patients, 5-year disease-free survival rates are 40% to 50%.[74] Patients with N2 to N3 disease should be treated with concurrent chemoradiation followed by durvalumab therapy.

Stage IV Disease

The primary goals of systemic therapy in patients with metastatic NSCLC are to reduce symptom burden from cancer, delay progression of symptoms, and improve survival while maintaining quality of life. Before palliative systemic therapy, a consideration should be made for palliative radiotherapy in patients with symptomatic brain or spinal cord metastases, hemoptysis, postobstructiccmetastases. Early referral to specialized palliative care services has also been shown to improve OS.[75]

Advances in tumor analysis by next-generation sequencing (NGS) and other profiling technologies

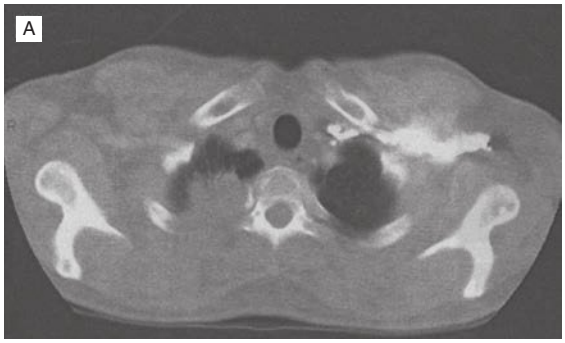


FIGURE 24–12 Pancoast tumor.

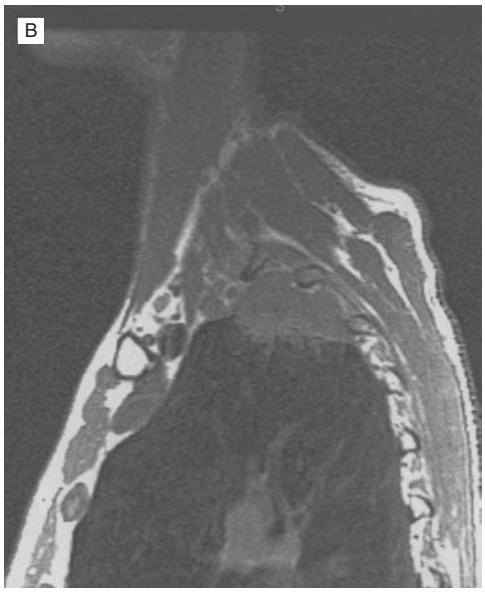


FIGURE 24–13 On magnetic resonance imaging, this non–small cell lung cancer tumor at the right lung apex invades the second right rib and extends apically into the right apical fat, with a loss of the fat plane between the tumor and the T1 nerve. The T2 nerve is also involved by the mass.

provide information on tumor diagnosis and prognosis and provide therapy options for patients. At MDACC, we recommend molecular profiling with NGS for locally advanced, metastatic NSCLC whenever feasible because multiplexed genetic sequencing panels, such as NGS, not only enables the simultaneous assessment of multiple genomic alterations such as *EGFR, ALK, BRAF, RET, ERBB2(HER2)*, and *MET* but also hundreds of other genes that may have potential roles in cancer development and targets for investigational therapies.

It is recommend that all adenocarcinomas, mixed adenosquamous carcinomas, NSCLCs not otherwise specified and all lung cancers occurring in nonsmokers should undergo comprehensive molecular profiling. Because of the importance of molecular testing, attempts should be made to obtain core biopsies rather than fine-needle aspirations to ensure sufficient tissue for profiling.[76] Systemic therapy for NSCLC with actionable molecular alterations is reviewed in Chapter 25, and this chapter focuses on systemic therapy for advanced NSCLC with no actionable mutations.

First-Line Systemic Therapy for Advanced Non–Small Cell Lung Cancer with no Actionable Tumor Mutation

Until 2016, chemotherapy combinations of cisplatin or carboplatin with paclitaxel,[77] docetaxel,[77] pemetrexed[78,79] (nonsquamous only), gemcitabine,[77] or nab-paclitaxel[80] were standard of care first-line therapy option because compared with best supportive care, chemotherapy had been associated with a modest improvement in median OS (1.5 months) and significant gains in symptom control.[81] Multiple platinum-based doublets are effective with response rates from 18% to 35%, PFS of 3 to 6 months, and OS of 8 to 12 months.[77–80,82] A deeper understanding of tumor–immune interactions and development of ICIs have dramatically changed the therapeutic landscape of NSCLC and other malignancies.[83]

Immunotherapy in Advanced Non–Small Cell Lung Cancer

Immune checkpoints are the T-cell regulatory mechanisms of co-stimulatory and inhibitory signals that control the amplitude and quality of immune response. The expression of inhibitory immune checkpoints can be upregulated by tumors and serve as an adaptive immune evasion mechanism.[84] Activation of the programmed cell death 1 (PD-1) receptor by its ligand (PD-L1) has been recognized as a major immune inhibitory mechanism in solid tumors.[85,86] Antibodies that inhibit the PD-1–PD-L1 and cytotoxic T-lymphocyte-associated protein (CTLA-4) pathway produce durable clinical responses in various solid tumors, including NSCLC.[87–90] PD-(L)1 inhibitors improve clinical outcomes compared with traditional chemotherapy and are now standard with or without chemotherapy for NSCLC without oncogenic driver alterations (Table 24–13).

Several factors are taken into consideration when selecting a first-line treatment option for a patient with metastatic NSCLC, including tumor histology, molecular profile, PD-L1 expression levels, preexisting autoimmune diseases, and other comorbid conditions. Next we discuss several of the available first-line options and studies that inform the choice of those options.

Immune Checkpoint Inhibitor Monotherapy

Previous trials focused on cancer vaccines in NSCLC, which were shown to induce tumor-specific immune responses but failed to improve survival.[91] Subsequently, identification and targeting immune checkpoints has renewed the interest in immunotherapy approaches for NSCLC. Clinical studies showed clinical benefit with therapies targeting CTLA-4, PD-1–PD-L1 axis in melanoma, which led to studies in other solid tumors, including metastatic NSCLC.[92] Initial studies in previously treated metastatic NSCLC reported a statistically significant improvement in OS with PD-(L)1 inhibitors compared with docetaxel in patients with platinum-refractory advanced NSCLC and revealed a relationship between higher tumor PD-L1 protein expression and greater efficacies.[93–96] These observations led to clinical trials with PD-(L)1 inhibitors in the

TABLE 24–13 Efficacy of Immune Checkpoint Inhibitor Monotherapy in the First-line Treatment of Patients with Non–Small Cell Lung Cancer

Trial	Patients (*n*)	Patient Population	Treatment Arm(s)	Control Arm	Overall RR	OS (months)	PFS (months)
KEYNOTE 024[98]	305	NSCLC, PD-L1 TPS ≥50%, with no *EGFR* or *ALK* genomic tumor aberrations	Pembrolizumab (P)[a]	Platinum doublet chemotherapy (C)	44.8% (P) vs 27.8% (C)	30 (P) vs 14.2 (C) (HR, 0.60; 95% CI, 0.41–0.89; *P* = .005	10.3 (P) vs 6 (C) (HR, 0.50; 95% CI, 0.37–0.68: *P* <.001)
KEYNOTE 042[100]	1274	NSCLC, PD-L1 TPS ≥1%, with no *EGFR* or *ALK* genomic tumor aberrations	Pembrolizumab (P)[a]	Platinum doublet chemotherapy (C)	27% (P) vs 27% (C)	16.7 (P) vs 12.1 (C) (HR, 0.81; 95% CI, 0.71–0.93; *P* = .0036).	5.4 (P) vs 6.5 (C) (HR, 0.07; 95% CI, 0.94–1.21)
IMpower 110[99]	572 (high PD-L1 subgroup treatment arm (atezolizumab *n* = 107), control arm (chemotherapy, *n* = 98)	NSCLC whose tumors express PD-L1 (TC ≥ 1% or IC ≥ 1%), no *EGFR* or *ALK* genomic tumor aberrations	Atezolizumab (A)[b]	Platinum doublet chemotherapy (C)	For high PD-L1 group[c]: 38.3% (A) vs 28.6% (C)	For high PD-L1 groupc: 20.2(A) vs 13.1 (C) (HR, 0.59; 95% CI, 0.40–0.89; P = .0106)	For high PD-L1 groupc: 8.1(A) vs 5.1 (C) (HR, 0.63; 95% CI, 0.45–0.88)

[a]The recommended pembrolizumab dosage for this indication is 200 mg intravenously every 3 weeks.
[b]The recommended atezolizumab dosage for treatment of patients with non–small cell lung cancer (NSCLC) is 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks
[c]High programmed cell death ligand 1 (PD-L1) expression (PD-L1–stained ≥50% of tumor cells [≥50%] or PD-L1–stained tumor-infiltrating immune cells [ICs] covering ≥10% of the tumor area [IC ≥ 10%]) by the VENTANA PD-L1 (SP142) Assay (Ventana Medical Systems, Inc.).
CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RR, Response rate; TPS, tumor proportion score.

first-line setting with PD-L1 protein expression being a stratification and/or an inclusion criteria.

In the KEYNOTE 024 (NCT02142738) trial, patients with treatment-naïve NSCLC without *EGFR* or *ALK* gene aberrations and PD-L1 tumor proportion score (TPS) of 50% of higher (PD-L1 expression as determined by an IHC assay using the PD-L1 IHC 22C3 pharmDx Kit) were randomized to pembrolizumab 200 mg intravenously every 3 weeks for up to 35 cycles or platinum-based chemotherapy for four to six cycles.[97] The chemotherapy regimens included platinum–pemetrexed for patients with nonsquamous NSCLC and platinum–paclitaxel or gemcitabine for those with squamous NSCLC. Pemetrexed maintenance was allowed after initial platinum-based therapy. Crossover from chemotherapy to pembrolizumab was also allowed in the event of progression. A total of 154 patients were assigned to pembrolizumab, and 151 patients were assigned to chemotherapy, with the most common chemotherapy regimen being carboplatin plus pemetrexed.[97] The median PFS with pembrolizumab in patients with PD-L1 TPS of 50% or greater was 10.3 months versus 6.0 months in the chemotherapy group with an HR of 0.50 (95% CI, 0.37–0.68; P <.001).[97] In an updated analysis, median OSs were 30.0 months (95% CI, 18.3–months to not reached) with pembrolizumab and 14.2 months (95% CI, 9.8–19.0 months) with chemotherapy (HR, 0.63; 95% CI, 0.47–0.86). Eighty-two patients assigned to chemotherapy crossed over on study to receive pembrolizumab. When adjusted for crossover using the two-stage method, the HR for OS for pembrolizumab versus chemotherapy was 0.49 (95% CI, 0.34–0.69). Treatment-related grade 3 to 5 adverse events were less frequent with pembrolizumab compared with chemotherapy and were 31.2% vs 53.3%, respectively.[98] This trial demonstrated that in patients with NSCLC with PD-L1 TPS of 50% or greater, treatment with pembrolizumab monotherapy in the first-line therapy of metastatic NSCLC showed improved PFS,

OS, response rate, duration of response, and safety profile compared with platinum-based chemotherapy, leading to its approval in the first-line setting.

IMpower110 (NCT02409342), was a randomized, open-label trial in patients with therapy-naïve patients with stage IV NSCLC whose tumors expressed PD-L1 (tumor cells [TCs] ≥1% or tumor-infiltrating immune cells (ICs) ≥1% measured by VENTANA PD-L1 [SP142 assay]). Patients were randomized (1:1) to receive atezolizumab 1200 mg every 3 weeks versus platinum-based chemotherapy. Although there was no statistically significant difference in OS between the arms for the lower PD-L1 subgroups (TC ≥5% or IC ≥5% and TC ≥1% or IC ≥1%), in the high PD-L1 subgroup (TC ≥50% or IC ≥10%), the median PFS was 8.1 months in the atezolizumab arm and 5.0 months in the platinum-based chemotherapy arm (HR, 0.63; 95% CI, 0.45–0.88). Median OS was 20.2 months for patients in the atezolizumab arm compared with 13.1 months in the chemotherapy arm (HR, 0.59; 95% CI, 0.40–0.89; $P = .0106$). Confirmed overall response rate (ORR) was 38% versus 29%, and grades 3 to 4 treatment-related adverse events were reported in 12.9% in the atezolizumab arm compared with 44.1% in chemotherapy.[00]

Subsequently efforts focused on investigation of clinical efficacy of immunotherapy in tumors with low or absent PD-L1 expression. The KEYNOTE 042 (NCT02220894) study explored the use of pembrolizumab in the first-line setting by using a PD-L1 TPS 1% or greater as the cutoff. Patients were randomized to receive pembrolizumab 200 mg intravenously every 3 weeks or investigator's choice of a carboplatin-containing regimen with either pemetrexed or paclitaxel for their treatment-naïve locally advanced or metastatic NSCLC.[100] In addition to selection criteria, PD-L1 protein expression was also used for patient stratification (TPS ≥50% vs TPS 1-49%). OS in the TPS 50% or greater NSCLC subgroup, the TPS 20% or greater NSCLC subgroup, and the overall population (TPS ≥1%) were the major efficacy measures.[100] KEYNOTE 042 demonstrated statistically significant OS improvements for those randomized to pembrolizumab compared with chemotherapy in all three populations.[100] Although there was no significant difference in PFS or ORR between therapy arms in the TPS 1% or greater population (overall population), the median OS was improved to 16.7 months in the pembrolizumab arm compared with 12.1 months in chemotherapy arm (HR, 0.81; 95% CI, 0.71–0.93; $P = .0036$). It is important to point out that in this study, OS benefit had been largely driven by tumors that had high PD-l1 IHC TPS score. In the TPS 50% or greater subgroup, the estimated median OSs were 20 months in the pembrolizumab arm and 12.2 months for chemotherapy arm (HR, 0.69; 95% CI, 0.56–0.85; $P = .0006$). In contrast, for patients with PD-L1 TPS of 1% to 49%, there was no significant difference in OS compared with chemotherapy with a median OS of 13.4 versus 12.1 months (HR, 0.92; 95% CI, 0.77–1.11). The grade 3 to 5 drug-related adverse events were less frequent at 18% with pembrolizumab versus 41.0 % for chemotherapy.[100] These findings led to the FDA approval of pembrolizumab monotherapy for tumors with PD-L1 TPS of 1% or higher by a companion diagnostic test using PD-L1 IHC assay in the first-line therapy of patients with metastatic NSCLC.

In a similar trial design, the PD-1 inhibitor nivolumab failed to demonstrate improved OS benefit in the phase 3 CheckMate 026 (NCT02041533) study. This study compared nivolumab with histology-dependent platinum-based doublets in treatment-naïve metastatic NSCLC. PD-L1 expression level of 5% or greater on TCs was selected as a cutoff for eligibility. In this study, nivolumab did not show OS benefit compared with a platinum doublet.[101] When comparing results of KEYNOTE-042 and CheckMate 026, it should be noted that the chemotherapy arm in CheckMate 026 permitted crossover to nivolumab after disease progression, whereas KEYNOTE-042 did not. In CheckMate 026,60% of patients in the chemotherapy arm received subsequent ICI therapy at the time of their progression, but only 20% of patients in the chemotherapy arm received subsequent ICI therapy in the KEYNOTE 042 study, which might have contributed to a difference in OS benefit in these two studies.

Because of relative limited clinical activity in low PD-L1–expressing tumors and generally nonoverlapping toxicity profiles of PD-(L)1 inhibitors and chemotherapy, subsequent efforts shifted to combination therapy strategies, which included chemotherapy, biologic agents, and other ICIs. Multiple therapy combinations have resulted in improved clinical outcomes for first-line therapy of patients with NSCLC compared with platinum doublets and have received FDA approvals (Table 24–14).

Combination Therapies Containing Immune Checkpoint Inhibitors s

KEYNOTE 189 (NCT02578680) was a randomized open-label study of first-line treatment of metastatic nonsquamous NSCLC. Patients were randomized (2:1) to receive pembrolizumab 200 mg given intravenously every 3 weeks (or placebo) in combination with pemetrexed and investigator's choice of either cisplatin or carboplatin every 3 weeks for four cycles followed by pembrolizumab (or placebo) and pemetrexed maintenance. Treatment with pembrolizumab continued until disease progression, unacceptable toxicity, or a maximum of 24 months. The primary efficacy outcome measures were OS and PFS.[101] The trial demonstrated a statistically significant improvement in PFS and OS

TABLE 24–14 Efficacy of Immune Checkpoint + Chemotherapy and/or Combination Immune Checkpoint Therapies in the First-Line Treatment of Patients with Non–Small Cell Lung Cancer

Trial	Patients (*n*)	Patient Population	Treatment Arm(s)	Control Arm	Overall RR	OS (months)	PFS (months)
KEYNOTE 189[103]	616	Nonsquamous cell NSCLC, with no *EGFR* or *ALK* genomic tumor aberrations	Pembrolizumab, cisplatin, or carboplatin, and pembrolizumab (triple [T])	Cisplatin or carboplatin and pemetrexed (C)	47.6% (T) vs 18.9% (C)	22 (T) vs 10.7 (C) (HR, 0.56; 95% CI, 0.45–0.70).	9 (T) vs 4.9 (C) (HR, 0.48; 95% CI, 0.40–0.58)
KEYNOTE 407[104]	559	Squamous cell NSCLC	Pembrolizumab, cisplatin, or carboplatin and paclitaxel or nab-paclitaxel (triple [T])	cisplatin OR carboplatin and paclitaxel or nab-paclitaxel (C)	58% (T) vs 35% (C)	15.9 (T) vs 11.3 (C) (HR, 0.64; 95% CI, 0.49–0.85; *P* = .0017)	6.4 (T) vs 4.8(C) (HR, 0.56; 95% CI, 0.45–0.70; *P* <.0001)
IMpower 130[105]	724	Nonsquamous NSCLC	Atezolizumab, protein-bound paclitaxel, and carboplatin followed by maintenance atezolizumab (A)	Protein-bound paclitaxel and carboplatin followed by maintenance pemetrexed (C)	49.2% 31.9% (OR, 2.07)	18.6 (A) vs 13.9 (C) (HR, 0.80; 95% CI, 0.64–0.99; *P* = .0384)	7.2 (A) vs 6.5 (C) (HR, 0.75; 95% CI, 0.63–0.91; *P* = .0024)
IMpower 150[107]	1202	Nonsquamous NSCLC	Atezolizumab, carboplatin, paclitaxel, and bevacizumab (ABCP); atezolizumab, carboplatin and paclitaxel (ACP)	Carboplatin, paclitaxel, and bevacizumab (C)	55% (ABCP) vs 42% (C)[a]	19.2 (ABCP) vs 14.7 (C)[a] arm (HR, 0.78; 95% CI, 0.64–0.96; *P* = .016)	8.5 (ABCP) vs 7(C)[a] (HR, 0.71; 95% CI 0.59–0.85; *P* = .0002)
CheckMate 227[108]	793	NSCLC, PD-L1 tumor expression ≥1% by PD-L1 IHC 28-8 pharmDx, with no *EGFR* or *ALK* genomic tumor aberrations	Ipilimumab and nivolumab (I + N)[b]	Platinum doublet chemotherapy (C)	36% (I + N) vs 30% (C)	17.1 (I + N) vs 14.9(C) (HR, 0.79; 95% CI, 0.67–0.94; *P* = 0.0066)	5.1 (I + N) vs 5.6 (C) (HR, 0.82; 95% CI, 0.69–0.97)
CheckMate 9LA[110]	719	NSCLC with no *EGFR* or *ALK* genomic tumor aberrations	Nivolumab plus ipilimumab and two cycles of platinum-doublet chemotherapy (four-drug regimen [4DR])[c]	Platinum doublet chemotherapy (C) (four cycles)	38% (4DR) vs 25% (C)	14.1 (4DR) vs 10.7 (C) (HR, 0.69; 96.71% CI, 0.55–0.87)	6.8 (4DR) vs 5 (C) (HR, 0.70; 95% CI, 0.57–0.86)

[a]Comparative analysis for atezolizumab, carboplatin, paclitaxel, and bevacizumab arm versus platinum-based chemotherapy arm among patients with nonsquamous non–small cell lung cancer (NSCLC) without an *EGFR* or *ALK* mutation.
[b]The recommended dosages for metastatic NSCLC are nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks.
[c]The recommended nivolumab dosage for this indication is 360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks and two cycles of platinum-doublet chemotherapy. The nivolumab and ipilimumab is continued until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression.
CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RR, Response rate.

for patients randomized to pembrolizumab plus chemotherapy. Median PFSs were 9.0 (95%CI, 8.1–9.9) months for pembrolizumab plus chemotherapy and 4.9 (95% CI, 4.7–5.5) months for placebo plus chemotherapy (HR, 0.48; 95% CI, 0.40–0.58), and the median OS was 22.0 (95% CI, 19.5–25.2) months versus 10.7 (95% CI, 8.7–13.6) months, respectively (HR, 0.56; 95% CI, 0.45–0.70). OS and PFS benefits with pembrolizumab were observed regardless of PD-L1 expression or presence of liver or brain metastases. The incidence of therapy-related grade 3 to 5 adverse events was similar in the pembrolizumab–chemotherapy (71.9%) and placebo–chemotherapy (66.8%) arms (HR, 0.49; 95% Confidence interval (CI) 0.38-0.64; P <.00001).[103]

KEYNOTE 407 (NCT02775435) had a trial design similar to KEYNOTE 189 but was conducted for metastatic squamous NSCLC, regardless of PD-L1 tumor expression status, as a first-line systemic therapy for metastatic disease. A total of 559 patients were randomized to pembrolizumab 200 mg or placebo in combination with carboplatin and investigator's choice of either paclitaxel every 3 weeks or nab-paclitaxel weekly on a 3-week cycle for four cycles followed by pembrolizumab or placebo. Patients continued pembrolizumab or placebo maintenance until disease progression, unacceptable toxicity, or a maximum of 24 months. The main efficacy outcome measures were OS, PFS, and ORR.[104] The trial demonstrated statistically significant improvements in OS, PFS, and ORR for patients receiving pembrolizumab plus chemotherapy compared with those randomized to placebo plus chemotherapy. The median PFSs were 6.4 and 4.8 months for the pembrolizumab plus chemotherapy and placebo plus chemotherapy arms, respectively (HR, 0.56; 95% CI, 0.45–0.70; P <.0001). The ORRs were 58% and 35%, favoring the pembrolizumab-containing arm (95% CI, 9.9–36.4; P = .0008). The median OSs were 15.9 and 11.3 months for the pembrolizumab plus chemotherapy and placebo plus chemotherapy arms, respectively (HR, 0.64; 95% CI, 0.49–0.85; P = .0017). Treatment-related adverse events of grade 3 or higher occurred in 69.8% of the patients in the pembrolizumab-combination group and in 68.2% of the patients in the placebo-combination group. But discontinuation of treatment because of adverse events was more frequent in the pembrolizumab-combination group than in the placebo-combination group (13.3% vs 6.4%).[104]

IMpower130 (NCT02367781) was a randomized, open-label trial for treatment-naïve stage IV nonsquamous NSCLC. Patients with activating mutations were allowed to receive prior *EGFR* or *ALK* kinase inhibitor if appropriate. The trial randomized 724 patients to receive atezolizumab 1200 mg as an intravenous (IV) infusion every 3 weeks plus protein-bound paclitaxel and carboplatin followed by single-agent atezolizumab maintenance or to receive protein-bound paclitaxel plus carboplatin followed by maintenance pemetrexed at the investigator's discretion (control). The primary efficacy outcome measures were PFS and OS.[105] In the primary analysis population (intention to treat, *EGFR* mutation, *ALK* translocation wild type n = 681), the median PFS was 7.2 months (95% CI, 6.7–8.3) for the atezolizumab arm compared with 6.5 months (95% CI, 5.6–7.4) for the control arm (HR, 0.75; 95% CI, 0.63–0.91; P = .0024). Median OSs were 18.6 months (95% CI, 15.7–21.1) and 13.9 months (95% CI, 12.0–18.7), respectively (HR, 0.80; 95% CI, 0.64–0.99; P = .0384). Treatment-related grade 3 to 4 adverse events were reported in 381 (81%) of 473 patients in the atezolizumab plus chemotherapy arm and 164 (71%) of 232 patients in the control arm.[106]

IMpower150 (NCT02366143), was an open-label, randomized, three-arm study for first-line treatment of patients with metastatic nonsquamous NSCLC and was designed to conduct comparisons between atezolizumab, carboplatin, paclitaxel, and bevacizumab (four-drug regimen); atezolizumab, carboplatin, and paclitaxel three3-drug regimen); or carboplatin, paclitaxel, and bevacizumab (control arm). After completion of four or six cycles of carboplatin and paclitaxel, patients continued to receive bevacizumab in the four-drug arm and the control arm and continued to receive atezolizumab in the two experimental arms until disease progression or unacceptable toxicity. In this study atezolizumab was given at 1200 mg as an IV infusion every 3 weeks. The major efficacy measures were OS and PFS.[107]

Among patients with nonsquamous NSCLC without an *EGFR* or *ALK* mutation, median PFSs were 8.5 months for patients receiving the four-drug regimen and 7 months for those in the control arm (HR, 0.71; 95% CI, 0.59–0.85; P = .0002). Median OSs were 19.2 months for patients receiving the four-drug regimen and 14.7 months for the control arm (HR, 0.78; 95% CI, 0.64–0.96; P = .016). The ORRs were 55% in the four-drug arm and 42% in the control arm. No significant differences in interim OS or final PFS were observed between the three-drug arm and the control arm. The incidence of treatment-related adverse events was reported in 219 (55.7%) of 393 patients in the four-drug arm and 188 (47.7%) of 394 patients in the control arm. The most common adverse reaction resulting in discontinuation of atezolizumab was pneumonitis (1.8%). With this study, the FDA approved the use of atezolizumab in combination with bevacizumab, paclitaxel, and carboplatin for the first-line treatment of patients with metastatic nonsquamous NSCLC with no *EGFR* or *ALK* genomic tumor aberrations. In a preplanned analysis, in patients with *EFGR* mutation (124 *EGFR* mutant, including 91 with sensitizing mutation), PFS was reported to be longer in

the four-drug arm than the control arm (median PFS, 8.3 months vs 6.8 months; stratified HR, 0.61; 95% CI, 0.52–0.72). Although the number is small this subgroup analysis provided evidence to use atezolizumab plus bevacizumab and chemotherapy in patients with *EGFR*-mutant NSCLC who have failed TKIs.[107] However, use of this regimen in patients with *EGFR*-mutant adenocarcinoma is not yet FDA-approved.

Efforts to spare toxicities of chemotherapy also led to exploration of non–chemotherapy-containing ICI combinations. CheckMate-227 (NCT02477826) was a randomized multiarm study in patients with stage IV or recurrent NSCLC.[108] As a part of this study, patients with PD-L1 of 1% or higher (by using PD-L1 IHC 28-8 pharmDx [Agilent Technologies, Inc.] platform) were stratified according to histologic subtype (squamous NSCLC vs nonsquamous NSCLC) and were randomized to nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks, platinum doublet (chemotherapy arm) every 3 weeks for up to four cycles, or nivolumab at a flat dose of 240 mg every 2 weeks. The median PFSs were 5.1 months (95% CI, 4.1 to 6.3) in the nivolumab plus ipilimumab arm and 5.6 months (95% CI, 4.6–5.8) in the chemotherapy arm (HR, 0.82; 95% CI, 0.69–0.97). Median OSs were 17.1 months (95% CI, 15–20.1) versus 14.9 (95% CI, 12.7–16.7) (HR, 0.79; 95% CI, 0.67–0.94; $P = .0066$) favoring nivolumab plus ipilimumab arm over the chemotherapy arm. Confirmed ORRs were 36% (95% CI, 31–41) and 30% (95% CI, 26–35), favoring the nivolumab plus ipilimumab arm. Median response durations were 23.2 months in the nivolumab plus ipilimumab arm and 6.2 months in the chemotherapy arm.[108] Based on this study, the FDA approved the use of ipilimumab and nivolumab combination as first-line treatment for patients with metastatic NSCLC whose tumors express PD-L1 (≥1%), as determined by an FDA-approved test.[109]

Addition of chemotherapy to ICI therapy has been considered particularly because of the early progression and transient higher death rates compared with the chemotherapy arms for patients, particularly with PD-L1 protein expression low or negative tumors (Fig. 24–14). This can be observed not only because

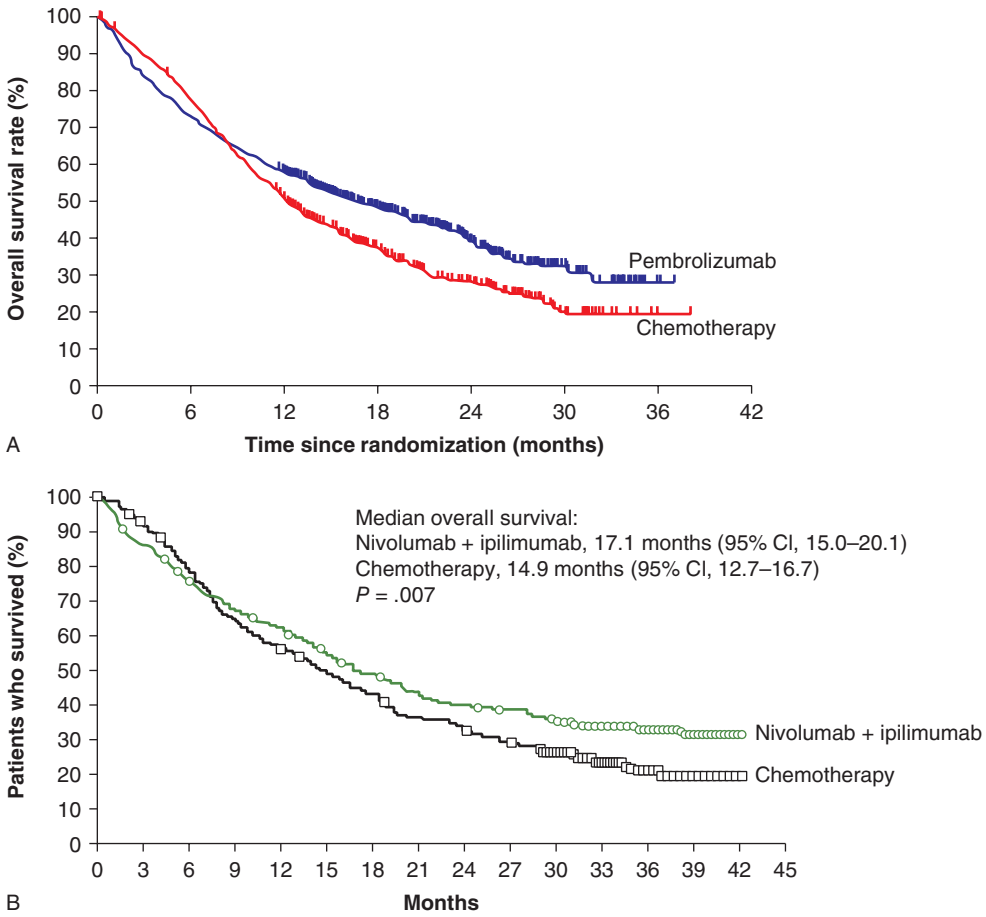


FIGURE 24–14 **Kaplan-Meier estimates of survival. A. KEYNOTE 042 in programmed cell death ligand 1 (PD-L1) tumor proportion score (TPS) 1% or greater population. B. CheckMate 227 in the PD-L1 %1 or greater population. In both studies, there is a crossover in overall survival because of early deaths with immune checkpoint inhibitors. CI, confidence interval.**

of the lack of response to ICI in primary resistance to immunotherapy but also because of delayed responses to ICI. Despite the OS benefit with combined ICI therapy in CheckMate 227, early progression and transient higher death rates compared with the chemotherapy arm led to studies exploring combination ICIs with an abbreviated course of chemotherapy. The aim was to rapidly achieve disease control and prevent early death while limiting the duration of cytotoxic therapy. Efficacy of this strategy was investigated in the CheckMate-9LA (NCT03215706) study, which randomized patients to receive standard platinum doublet vs nivolumab plus ipilimumab and two cycles of platinum-doublet chemotherapy as first-line treatment for patients with metastatic or recurrent NSCLC, unselected for PD-L1 expression and with no *EGFR* or *ALK* aberrations. Although these data are not yet published in final form, early progression and death were not observed on the ICI–chemotherapy arm, which was reflected in improved median PFS of 6.8 months (95% CI, 5.6–7.7) versus 5 months (95% CI, 4.3–5.6) (HR, 0.70; 95% CI, 0.57–0.86). Median OSs were 14.1 months (95% CI, 13.2–16.2) versus 10.7 months (95% CI, 9.5–12.5) (HR, 0.69; 96.71% CI, 0.55–0.87). Similar to other studies with combined ICI and chemotherapy, ORR was increased as well (38% (95% CI, 33–43) versus 25% (95% CI, 21–30), respectively).[110]

At MDACC, for patients with a good performance status and with tumor PD-L1 expression less than 50%, in patients with rapidly progressive disease or high disease burden regardless of the tumor PD-L1 status and in patients for whom tumor PD-L1 status is not readily available, we typically choose combined ICI and chemotherapy based on KEYNOTE 189, KEYNOTE 407, IMpower 130, IMpower 150, and CheckMate 9LA studies. For patients with tumor PD-L1 TPS score of 50% or greater and without high disease burden, we offer anti–PD-(L)1 monotherapy (KEYNOTE 024, IMpower 110). In patients with tumor PD-L1 1% or greater, the nivolumab and ipilimumab combination is an acceptable alternative, particularly for patients who wish to avoid chemotherapy (CheckMate 227). For frail patients with tumor PD-L1 1% or greater, pembrolizumab alone is appropriate (KEYNOTE 042).

Programmed Cell Death Ligand 1 As a Biomarker

In earlier studies with PD-(L)1 inhibitors, PD-L1 protein expression in the surface of the TCs correlated with responses to PD-(L)1 inhibitors. Subsequently, prospective trials validated the predictive utility of PD-L1 IHC. Thus, tumor expression of PD-L1 was approved by the FDA as a companion diagnostic before ICI therapy. There are numerous PD-L1 monoclonal antibodies, and efforts to incorporate stromal cell PD-L1 protein expression are ongoing. Currently, three platforms have been validated in prospective studies for patient selection of first-line NSCLC therapy. In PD-L1 monoclonal antibody clone 22C3 in Dako platform, PD-L1 protein expression is evaluated by means of IHC with PD-L1 scoring system based on tumor PD-L1 expression on TC membranes (TPS). This has been validated in the KEYNOTE 024, KEYNOTE 042, and KEYNOTE 189 studies.[97,100,102] The PD-L1 IHC 28-8 pharmDx platform has been prospectively tested in the CheckMate 227 study and received FDA approval.[111] With the IMPower110 study, the FDA also approved the VENTANA PD-L1 (SP-142) assay (Ventana Medical Systems, Inc.) as a companion diagnostic test for selecting patients with NSCLC for treatment with atezolizumab. It is important to note that the VENTANA platform is different compared with the PD-L1 IHC 22C3 pharmDx Kit and PD-L1 IHC 28-8 pharmDx because PD-L1 expression not only takes into account tumor cells but also tumor-infiltrating ICs.[99]

Different clones, protocol conditions, instruments, and scoring or readout methods may pose challenges in introducing different PD-L1 assays for immunotherapy.[112] Efforts to assess the feasibility of harmonizing the clinical use of independently developed commercial PD-L1 IHC assays led to the development of the Blueprint study, which assessed the comparability of PD-L1 scoring in commercially available PD-L1 IHC platforms. FDA-approved monoclonal anti–PD-L1 antibodies clone, 22C3, 28-8, SP263; their platforms PD-L1 IHC 22C3 pharmDx, PD-L1 IHC 28-8 pharmDx 28-8 and VENTANA PD-L1 (SP263), and their respective protocols showed close similarity and were comparable. In contrast, the VENTANA PD-L1 SP142 assay showed less sensitivity (lower TPS scores).[113] At MDACC, we use the 22C3 pharmDx qualitative IHC assay and TPS scoring because it was the first companion diagnostic test to receive FDA approval for ICI monotherapy in PD-L1–positive tumors. It is important to note that these assays were not compared in the setting of a prospective clinical trial; therefore, none can be deemed "interchangeable" with another.[112]

Therapies in the Setting of Contraindications to Immune Checkpoint Inhibitor Therapy

If ICI therapy is contraindicated owing to the presence of autoimmune or inflammatory diseases or in patients with organ transplants, cisplatin–carboplatin–based combinations with paclitaxel,[77] docetaxel,[77] pemetrexed[78,79] (nonsquamous only) gemcitabine,[77] nab-paclitaxel,[80] or vinorelbine[114] remain standard of care therapy (Table 24–15).

The addition of the vascular endothelial growth factor (VEGF)monoclonal antibody bevacizumab to carboplatin–paclitaxel can be considered in patients with nonsquamous NSCLC based on the phase III Eastern

TABLE 24–15 Summary of Platinum-Based Chemotherapy Trials in Patients with Non–Small Cell Lung Cancer

Pivotal Trial	Histology	Drug	Response Rate (%)	PFS (months)	OS (months)	Trial Interpretation
ECOG 1594 (2002)[77]	All NSCLC	Cisplatin 75 mg/m² day 1 + paclitaxel 135 mg/m² over 24 hours day 2 every 3 weeks	21	3.4	7.8	No significant difference between the four-drug regimens
		Cisplatin 100 mg/m² day 1 + gemcitabine 1000 mg/m² day 1, day 8 every 4 weeks	22	4.2	8.1	
		Cisplatin 75 mg/m² + docetaxel 75 mg/m² every 3 weeks	17	3.7	7.4	
		Carboplatin AUC 6 + paclitaxel 225 mg/m² every 3 weeks	19	3.1	8.1	
Socinski et al (2012)[80]	All NSCLC	Carboplatin AUC 6 day 1 + nab-paclitaxel 100 mg/m² days 1, 8, 15 every 3 weeks	33	6.3	12.1	Similar efficacy; nab-paclitaxel associated with more neutropenia and less neuropathy
		Carboplatin AUC 6 + paclitaxel 200 mg/m² every 3 weeks	25	5.8	11.2	
ECOG 4599 (2006)[82]	Nonsquamous	Carboplatin AUC 6 + paclitaxel 200 mg/m² +bevacizumab 15 mg/kg every 3 weeks × 6; then maintenance bevacizumab every 3 weeks	35	6.2	12.3	Benefit of adding bevacizumab to the induction and maintenance phases; high risk of bleeding in squamous histology
		Carboplatin AUC 6 + paclitaxel 200 mg/m² every 3 weeks × 6	15	4.5	10.3	
Scagliotti et al (2008)[78,79]	Nonsquamous	Cisplatin 75 mg/m² + pemetrexed 500 mg/m² every 3 weeks	29	5.5	12.6	Benefit of pemetrexed in nonsquamous histology
		Cisplatin 75 mg/m² + gemcitabine 1250 mg/m² day1, day 8 every 3 weeks	22	5.0	10.9	
	Squamous	Cisplatin 75 mg/m² + pemetrexed 500 mg/m² every 3 weeks	23	4.4	9.4	Benefit of gemcitabine in squamous NSCLC
		Cisplatin 75 mg/m² + gemcitabine 1250 mg/m² day 1, day 8 every 3 weeks	31	5.5	10.8	

AUC, area under the curve; ECOG, Eastern Cooperative Oncology Group; NSCLC, non–small cell lung cancer; OS, overall survival; PFS, progression-free survival.

Cooperative Oncology Group (ECOG) 4599 trial.[82] Patients were randomized to carboplatin and paclitaxel with or without bevacizumab. The bevacizumab-containing arm a had better response rate of 35% vs 15% (P <.001), better PFS at 6.2 months versus 4.5 months (P <.001), and improved OS at 12.3 months versus 10.3 months (P =.003). However, there were higher rates of adverse events in the bevacizumab-containing arm, including a higher risk of severe bleeding (4.4% vs 0.7%; P <.001). Patients with squamous histology,

hemoptysis, uncontrolled hypertension, and those older than 70 years of age are at a higher risk for bleeding from bevacizumab and are not candidates for bevacizumab.

Bevacizumab was also combined with pemetrexed and carboplatin in the phase III PointBreak study and compared with paclitaxel–carboplatin–bevacizumab (four cycles) followed by maintenance with pemetrexed plus bevacizumab or bevacizumab alone. Although there was a very modest PFS improvement for patients treated with pemetrexed (6 vs 5.6 months; HR, 0.83; 95% CI, 0.71–0.96), there was no improvement in OS.[115] No randomized data exist to substantiate the precise benefit of bevacizumab added to pemetrexed–carboplatin and pemetrexed maintenance.

At MDACC, for ICI-ineligible patients, we favor first-line therapy with pemetrexed–carboplatin followed by pemetrexed maintenance for patients with lung adenocarcinoma and either gemcitabine or taxane with carboplatin for SCC of the lung.

Maintenance Therapy

The triplet combination of carboplatin, pemetrexed, and pembrolizumab has become a standard of care for patients with nonsquamous NSCLC based on the KEYNOTE 189 trial, as detailed earlier. After four to six cycles of the triplet therapy, patients continue both pemetrexed and pembrolizumab as maintenance. Whether both pemetrexed and pembrolizumab need to be continued as maintenance therapy remains unknown, and clinical trials are planned to answer this question. For patients with SCC, pembrolizumab alone is continued as maintenance. Optimal duration of therapy with ICI has not been established. In the CheckMate 153 trial, patients who discontinued nivolumab within 1 year with those who continued treatment until disease progression or severe adverse events were compared as an exploratory endpoint. In preliminary results available from 163 patients, those continuing nivolumab treatment experienced an improvement in PFS (median PFS not reached [NR] vs 10.3 months; HR, 0.42; 95% CI, 0.25–0.71), and there was only a nonsignificant trend toward improvement in OS (NR vs 23.2 months; HR, 0.63; 95% CI, 0.33–1.22).[116] Although some clinical trials allowed therapy until progression or unacceptable toxicity occurs, some studies had 2 years of therapy with ICI; therefore, the optimal treatment duration remains an open question. It remains unclear if longer treatment duration leads to longer survivorship or increased risk of toxicity. At MDACC, we generally continue treatment with ICIs at least 2 years or until progression or unacceptable toxicity occurs. After 2 years of therapy, depending on the patient's tolerance and preferences, a recommendation is made to continue or discontinue therapy.

Before the immunotherapy era, multiple trials studied maintenance chemotherapy—either continuation maintenance (continuing the same nonplatinum drug or drugs) or switch maintenance (initiating a non–cross-resistant nonplatinum drug) (Table 24–16).[115,117–122] Pemetrexed maintenance has been shown to improve PFS and OS in two phase 3 studies in patients with nonsquamous NSCLC.[118,123] For example, in the PARAMOUNT study, 539 patients with an objective response or stable disease after four cycles of cisplatin and pemetrexed therapy were randomized to pemetrexed or placebo. Maintenance pemetrexed resulted in improved PFS (median, 4.1 vs 2.8 months; HR, 0.62; 95% CI, 0.49–0.79), OS (median, 13.9 vs 11.0 months), and 1-year survival rate (58% vs 45%).[123] Maintenance with bevacizumab versus pemetrexed versus the combination pemetrexed plus bevacizumab after therapy with pemetrexed, carboplatin, and bevacizumab was studied in the ECOG 5508 study. Although there was a statistically significant improvement in PFS (HR, 0.67; P <.001) with combined maintenance, there was no improvement in OS (HR, 0.90; P = .28)[124] compared with monotherapy with either pemetrexed or bevacizumab.

TABLE 24-16 Summary of Maintenance Chemotherapy Trials in Patients with Non–Small Cell Lung Cancer

Trial	Histology	Drug	Response Rate (%)	PFS (months)	OS (months)	Trial Interpretation
Fidias et al (2009)[117]	All NSCLC	Maintenance docetaxel 75 mg/m^2 every 3 weeks × 6 after 4 cycles of carboplatin + gemcitabine	41.4	5.7	12.3	Better PFS with switch maintenance; no OS benefit
		No maintenance; docetaxel at time of progression	NA	2.7	9.7	
Ciuleanu et a, (2009)[118]	Nonsquamous	Maintenance pemetrexed 500 mg/m^2 every 3 weeks after four cycles of platinum doublet	58	4.4	15.5	Benefit of switch maintenance with pemetrexed

(Continued)

TABLE 24-16 Summary of Maintenance Chemotherapy Trials in Patients with Non–Small Cell Lung Cancer (*Cont.*)

Trial	Histology	Drug	Response Rate (%)	PFS (months)	OS (months)	Trial Interpretation
		No maintenance	NA	1.8	10.3	
SATURN (2010)[119]	*EGFR* mutant	Erlotinib 150 mg/day maintenance after four cycles of platinum-based chemotherapy	NA	11	NA	Benefit of switch maintenance with erlotinib in *EGFR*-mutant patients
	NSCLC	No maintenance	NA	3	NA	
	EGFR WT	Erlotinib 150 mg/day maintenance after four cycles of platinum-based chemotherapy	11.9	3.07	12	
	NSCLC	No maintenance	5.4	2.7	11	
IFCT-GFPC 0502 (2012)[120]	All NSCLC (mostly *EGFR* WT)	Erlotinib 150 mg/day maintenance after cisplatin–gemcitabine	NA	2.9	11.4	No benefit of switch maintenance with erlotinib or maintenance with gemcitabine in *EGFR* WT patients
		Gemcitabine 1250 mg/m^2 day 1, day 8 maintenance	NA	3.8	12.1	
		No maintenance	NA	1.9	10.8	
PARAMOUNT (2013)[121]	Nonsquamous	Maintenance pemetrexed 500 mg/m^2 every 3 weeks after four cycles of cisplatin + pemetrexed	NA	4.4	13.9	Benefit of continuation maintenance with pemetrexed
		No maintenance	NA	2.8	11	
AVAPERL (2012)[122]	Nonsquamous	Carboplatin AUC 6 + pemetrexed 500 mg/m^2 + bevacizumab 15 mg/kg every 3 weeks × 4; then maintenance pemetrexed 500 mg/m^2 +bevacizumab 15 mg/kg every 3 weeks	NA	7.4	Not reached	PFS benefit of adding pemetrexed to maintenance bevacizumab after cisplatin-pemetrexed induction
		Carboplatin AUC 6 + pemetrexed 500 mg/m^2 + bevacizumab 15 mg/kg every 3 weeks × 4; then bevacizumab 15 mg/kg every 3 weeks	NA	3.7	12.8	
PointBreak, (2013)[115]	Nonsquamous	Carboplatin AUC 6 + pemetrexed 500 mg/m^2 + bevacizumab 15 mg/kg every 3 weeks × 4; then maintenance pemetrexed 500 mg/m^2 + bevacizumab 15 mg/kg every 3 weeks	34	6	12.6	No difference between the two treatment strategies
		Carboplatin AUC 6 + paclitaxel 200 mg/m^2 + bevacizumab 15 mg/kg every 3 weeks × 4; then maintenance bevacizumab 15 mg/kg every 3 weeks	33	5.6	13.4	

(*Continued*)

TABLE 24-16 Summary of Maintenance Chemotherapy Trials in Patients with Non–Small Cell Lung Cancer (*Cont.*)

Trial	Histology	Drug	Response Rate (%)	PFS (months)	OS (months)	Trial Interpretation
Fidias et al (2009)[117]	All NSCLC	Maintenance docetaxel 75 mg/m^2 every 3 weeks × 6 after four cycles of carboplatin + gemcitabine	41.4	5.7	12.3	Better PFS with switch maintenance; no OS benefit
		No maintenance; docetaxel at time of progression	NA	2.7	9.7	
Ciuleanu et a, (2009)[118]	Nonsquamous	Maintenance pemetrexed 500 mg/m^2 every 3 weeks after four cycles of platinum doublet	58	4.4	15.5	Benefit of switch maintenance with pemetrexed
		No maintenance	NA	1.8	10.3	
SATURN (2010)[119]	*EGFR* mutant	Erlotinib 150 mg/day maintenance after four cycles of platinum-based chemotherapy	NA	11	NA	Benefit of switch maintenance with erlotinib in *EGFR*-mutant patients
	NSCLC	No maintenance	NA	3	NA	
	EGFR WT	Erlotinib 150 mg/day maintenance after four cycles of platinum-based chemotherapy	11.9	3.07	12	
	NSCLC	No maintenance	5.4	2.7	11	
IFCT-GFPC 0502 (2012)[120]	All NSCLC (mostly *EGFR* WT)	Erlotinib 150 mg/day maintenance after cisplatin–gemcitabine	NA	2.9	11.4	No benefit of switch maintenance with erlotinib or maintenance with gemcitabine in *EGFR* WT patients
		Gemcitabine 1250 mg/m^2 day 1, day 8 maintenance	NA	3.8	12.1	
		No maintenance	NA	1.9	10.8	
PARAMOUNT (2013)[121]	Nonsquamous	Maintenance pemetrexed 500 mg/m^2 every 3 weeks after four cycles of cisplatin + pemetrexed	NA	4.4	13.9	Benefit of continuation maintenance with pemetrexed
		No maintenance	NA	2.8	11	
AVAPERL (2012)[122]	Nonsquamous	Carboplatin AUC 6 + pemetrexed 500 mg/m^2 + bevacizumab 15 mg/kg every 3 weeks × 4; then maintenance pemetrexed 500 mg/m^2 +bevacizumab 15 mg/kg every 3 weeks	NA	7.4	Not reached	PFS benefit of adding pemetrexed to maintenance bevacizumab after cisplatin-pemetrexed induction
		Carboplatin AUC 6 + pemetrexed 500 mg/m^2 + bevacizumab 15 mg/kg every 3 weeks × 4; then bevacizumab 15 mg/kg every 3 weeks	NA	3.7	12.8	

(Continued)

TABLE 24-16 Summary of Maintenance Chemotherapy Trials in Patients with Non–Small Cell Lung Cancer (*Cont.*)

Trial	Histology	Drug	Response Rate (%)	PFS (months)	OS (months)	Trial Interpretation
PointBreak, (2013)[115]	Nonsquamous	Carboplatin AUC 6 + pemetrexed 500 mg/m^2 + bevacizumab 15 mg/kg every 3 weeks × 4; then maintenance pemetrexed 500 mg/m^2 + bevacizumab 15 mg/kg every 3 weeks	34	6	12.6	No difference between the two treatment strategies
		Carboplatin AUC 6 + paclitaxel 200 mg/m^2 + bevacizumab 15 mg/kg every 3 weeks × 4; then maintenance bevacizumab 15 mg/kg every 3 weeks	33	5.6	13.4	
ECOG 5508[124]	Nonsquamous	Carboplatin (AUC = 6), paclitaxel (200 mg/m^2) and bevacizumab (15 mg/kg) every 3 weeks for up to 4 cycles followed by maintenance therapy with bevacizumab (15 mg/kg)	NR	4.2	14.4	Even though there are statistically significant differences in progression free survival for the combination maintenance versus bevacizumab, there were no statistically significant differences in overall survival; thus, maintenance with either single-agent bevacizumab or single-agent pemetrexed is considered standard, and maintenance with the combination is not necessary
		Carboplatin (AUC = 6), paclitaxel (200 mg/m^2), and bevacizumab (15 mg/kg) every 3 weeks for up to 4 cycles followed by maintenance therapy with pemetrexed (500 mg/m^2)		5.1	15.9	
		Carboplatin (AUC = 6), paclitaxel (200 mg/m) and bevacizumab (15 mg/Kk) every 3 weeks for up to 4 cycles followed by maintenance therapy with bevacizumab (15 mg/kg) and pemetrexed (500 mg/m^2)		7.5	16.4	

AUC, area under the curve; ECOG, Eastern Cooperative Oncology Group; NA, not applicable; NSCLC, non–small cell lung cancer; OS, overall survival; PFS, progression-free survival; WT, wild type.

Thus maintenance therapy with either pemetrexed or bevacizumab is reasonable for nonsquamous NSCLC after bevacizumab-based first-line therapy.

At MDACC, if ICI therapy is contraindicated, we recommend pemetrexed maintenance as monotherapy for patients with nonsquamous NSCLC

Chemotherapy for Patients with Platinum-Refractory Disease

Patients with disease progression on or after first-line therapy who maintain good performance status are candidates for further palliative systemic therapy. The agents that have proven efficacy after progression on a platinum-based doublet include single-agent docetaxel, paclitaxel, nab-paclitaxel, gemcitabine, pemetrexed (in nonsquamous NSCLC only), and ramucirumab in combination with docetaxel[125] (see Table 24–16). If ICIs have not been given in the first line, then pembrolizumab, nivolumab, or atezolizumab can be given as a second-line therapy (Table 24–17).[78,93–95,97,125–133]

Reexposure to platinum in subsequent lines of therapy increases response rates but not PFS or OS, even in patients with long (>6 months) platinum-free intervals,[129] and is not frequently used. Currently, there are no data to support the use of a different PD-(L)1 inhibitor after failing immunotherapy when used either singly or in combination for first-line treatment (eg, the use of atezolizumab as second-line therapy after failing a pembrolizumab-containing combination as first-line therapy). The only combination therapy approved by the FDA in the second-line setting is docetaxel with the anti-VEGF receptor 2 (anti-VEGFR2) monoclonal antibody ramucirumab.[125] In the pivotal Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL) trial comparing docetaxel alone with docetaxel plus ramucirumab in patients with NSCLC of any histology, the combination arm had better PFS (4.5 vs 3 months; $P < .0001$) and OS (10.5 vs 9.1 months; $P = .023$) with no increased risk of severe bleeding. It is important to highlight that only 14% of patients enrolled in the REVEL study had received prior bevacizumab, making it difficult to draw conclusions about this group. Also, unlike the phase III bevacizumab trials

TABLE 24–17 Summary of Second- and Third-Line Chemotherapy and Targeted Therapy Trials in Patients with Non–Small Cell Lung Cancer

Pivotal Trial	Histology	Drug	Response Rate (%)	PFS (months)	OS (months)	Trial Interpretation
***Second* Line**						
TAX 317 (2000)[126]	All NSCLC	Docetaxel 75 mg/m² every 3 weeks	7.1	2.65	7	Benefit of second-line docetaxel
		Best supportive care	0	1.67	4.6	
TAX 320 (2000)[127]	All NSCLC	Docetaxel 75 mg/m² every 3 weeks	6.7	2.1	5.7	Benefit of docetaxel over vinorelbine (less toxicity, same PFS and OS)
		Vinorelbine 30 mg/m² weekly or ifosfamide 2 mg/m²/day, days 1–3 every 3 weeks	0.8	1.9	5.6	
Hanna et al (2004)[128,129]	Nonsquamous	Pemetrexed 500 mg/m² every 3 weeks	12.8	3.5	9	Benefit of pemetrexed over docetaxel in nonsquamous histologies
		Docetaxel 75 mg/m² every 3 weeks	9.9	3.5	9.2	
	Squamous	Pemetrexed 500 mg/m² every 3 weeks	2.8	2.3	6.2	Benefit of docetaxel over pemetrexed in squamous NSCLC
		Docetaxel 75 mg/m² every 3 weeks	8.1	2.7	7.4	

(Continued)

TABLE 24–17 Summary of Second- and Third-Line Chemotherapy and Targeted Therapy Trials in Patients with Non–Small Cell Lung Cancer (*Cont.*)

Pivotal Trial	Histology	Drug	Response Rate (%)	PFS (months)	OS (months)	Trial Interpretation
GOIRC 02 (2006)/ NVALT-7 (2012)[129]	All NSCLC	Carboplatin AUC 5 + pemetrexed 500 mg/m2 every 3 weeks	15	3.6	8.7	No benefit of platinum doublets over nonplatinum single-agent second-line therapy
		Pemetrexed 500 mg/ m^2 every 3 weeks	9	3.5	8.2	
REVEL (2014)[125]	All NSCLC	Docetaxel 75 mg/ m^2+ ramucirumab 10 mg/kg every 3 weeks	23	4.5	10.5	Benefit of ramucirumab when added to docetaxel in second line
		Docetaxel 75 mg/m^2 every 3 weeks	14	3.0	9.1	
TAILOR (2013)[130]	*EGFR* wild-type NSCLC	Erlotinib 150 mg/day	3	2.4	5.4	No benefit of second-line erlotinib in *EGFR* wild-type NSCLC
		Docetaxel 75 mg/m^2 every 3 weeks	15	2.9	8.2	
Third Line						
BR.21 (2005)[131]	All NSCLC (*EGFR* status unknown)	Erlotinib 150 mg/day	8.9	2.2	6.7	Third-line erlotinib can prolong survival in patients with NSCLC and unknown *EGFR* status
		Placebo	<1	1.8	4.7	
DELTA (2014)[132]	*EGFR* wild-type NSCLC	Erlotinib 150 mg/day	17	1.3	9	Docetaxel is superior to erlotinib as second- or third-line therapy in patients with no activating *EGFR* mutations
		Docetaxel 60 mg/m^2 every 3 weeks	17	2.9	10.1	

AUC, area under the curve; AVAPERL, A Study of Avastin (Bevacizumab) With or Without Pemetrexed as Maintenance Therapy After Avastin in First Line in Patients With Non-Squamous Non-Small Cell Lung Cancer; DELTA, Docetaxel and Erlotinib Lung Cancer Trial; GOIRC, Italian Oncology Group for Clinical Research; IFCT-GFPC, Intergroupe Francophone de Cancérologie Thoracique-Groupe Francaus de Pneumo-Carcerologie; NSCLC, non–small cell lung cancer; NVALT, Dutch society of pulmonologists; OS, overall survival; PARAMOUNT, A Phase 3, Double-Blind, Placebo-Controlled Study of Maintenance Pemetrexed plus Best Supportive Care versus Best Supportive Care Immediately Following Induction Treatment with Pemetrexed + Cisplatin for Advanced Non-Squamous Non-Small Cell Lung Cancer; PFS, progression-free survival; REVEL, Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy; SATURN, Sequential Tarceva in Unresectable NSCLC, a phase 3 placebo controlled study; TAILOR, Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours.

that excluded patients with SCC, 25% of patients on this trial had squamous cell histology, and there was no increased risk of bleeding seen in this group. As subsequent lines of therapy, pemetrexed (for nonsquamous NSCLC), docetaxel, and gemcitabine monotherapy can be considered if not used in prior lines of therapy, all of which significantly improve PFS after first-line chemotherapy. Notably, there have been no randomized clinical trials to compare these three agents nor is there evidence of OS benefit in this refractory setting.

TABLE 24–18 Summary of Immunotherapy Trials in the Second-line Treatment of Patients with Non–Small Cell Lung Cancer

Trial	Patients (n)	Patient population	Treatment Arm(s)	Control Arm	Overall RR	OS (months)	PFS (months)
CheckMate 017[94]	272	Previously treated squamous NSCLC	Nivolumab (N)[a]	Docetaxel (D)	20% (N) vs 9% (D)	9.2 (N) vs 6 (D) (HR, 0.59; 95% CI, 0.44–0.79; *P* <.001)	3.5 (N) vs 2.8 (D) (HR, 0.62; 95% CI, 0.47–0.81; *P* <.001)
CheckMate 057[93]	582	Previously treated nonsquamous NSCLC	Nivolumab (N)[a]	Docetaxel (D)	19% (N) vs 12% (D)	12.2 (N) vs 9.4 (D) (HR, 0.73; 96% CI, 0.59–0.89; *P* = .002)	2.3 (N) vs 4.2 (D) (HR, 0.92; (95% CI, 0.77–1.11; P = .39)
KEYNOTE 010[95]	345 (pembrolizumab 2 mg/kg) 346 (pembrolizumab 10 mg/kg) 343 (docetaxel)	Previously treated NSCLC	Pembrolizumab 2 mg/kg (P)	Docetaxel (D)	18 (P) vs 9.3 (D)	10.4 (P) vs 8.5 (D)[b] (HR, 0.71 95% CI, 0.58–0.88; *P* = ·.0008)	3.9 (P) vs 4 (D) (HR, 0.88; 95% CI 0.74–1.05; *P* = .07)
			Pembrolizumab 10 mg/kg (P)	Docetaxel (D)	18.5 (P) vs 9.3 (D)	12.7 (P) vs 8.5 (D)[b] (HR, 0.61; 95% CI, 0.49–0·75; P = .0001)	4 (P) vs 4 (D) (HR, 0.79; 95% CI, 0.66–0.94; P = .004)
OAK[151]	850	Previously treated NSCLC	Atezolizumab (A)	Docetaxel (D)	14% (A) vs 13% (D)	13.8 (A) vs 9.6 (D) (HR, 0.73; 95% CI, 0·62–0·87; *P* =·.0003).	2.8 (A) vs 4 (D) (HR, 0.95; 95% CI, 0·82–1.10; *P* = .49

[a]Nivolumab, at a dosage of 3 mg/kg every 2 weeks.
[b]Among patients with programmed cell death ligand 1 tumor proportion scores ≥50%, overall survival (OS) was 14.9 months (pembrolizumab 2 mg/kg) versus 8.2 months (docetaxel); hazard ratio (HR), 0.54; 95% confidence interval (CI), 0.38–0.77; *P* = .0002. OS was 17.3 months (pembrolizumab 10 mg/kg) versus 8·2 months (docetaxel); HR, 0.50; CI, 0.36–0·70; *P* <.0001).
NSCLC, non–small cell lung cancer; OAK, A Study of Atezolizumab Compared With Docetaxel in Participants With Locally Advanced or Metastatic Non-Small Cell Lung Cancer Who Have Failed Platinum-Containing Therapy (OAK); PFS, progression-free survival; RR: response rate.

Toxicity profile, prior therapies, and patient preferences generally guide this therapy decision.[126,127,134]

Treatment of Stage IV Non–Small Cell Lung Cancer in Older Adults

Treatment of advanced NSCLC in the older adults has been addressed in several prospective studies and retrospective analyses, and the International Society of Geriatric Oncology (SIOG) has issued clear guidelines.[135] The general consensus is that older adult patients (defined as patients 70 years of age or older) with good performance status should receive standard therapy. They derive the same level of clinical benefit as their younger counterparts. However, they may experience a higher level or toxicities secondary to an age-related decline in organ function, so close monitoring for toxicities is required.

Management of Oligometastatic Disease

The term "oligometastatic" was used initially by Hellman and Weichselbaum[136] to describe a restricted locoregional tumor load. It has now become synonymous with a limited number (typically one to five) metastatic lesions. Several retrospective and small prospective trials in the setting of oligometastatic NSCLC demonstrated a potential clinical benefit for patients receiving aggressive therapy.[137–142] In patients with solitary brain metastasis resection or stereotactic radiation of the brain lesion followed by definitive therapy to the primary tumor (resection or radiation), compared

with no treatment for the primary tumor, was associated with significant improvement in median OS (26 months vs 13 months) and 5-year survival rates (34% vs 0%).[143]

In patients with solitary adrenal metastasis, adrenalectomy and definitive therapy to the primary tumor result in good outcomes, with a median OS of 26 months and a 5-year survival rate of 30%, which has been consistent in multiple studies.[144] Patients who develop isolated adrenal metastasis more than 6 months after the resection of the primary tumor are the ones with the most benefit.

Patients with oligometastatic disease (one to five lesions) should undergo complete staging, including PET-CT scan and brain MRI. They can then be classified into three subgroups,[145] and aggressive consolidative therapies can be considered on a case-by-case basis after a multidisciplinary evaluation.

- **Low risk:** development of oligometastatic disease more than 2 months after resection of the primary tumor (5-year OS, 47.8%).
- **Intermediate risk:** synchronous metastases (at presentation or within 2 months of the resection of the primary) and no lymph node involvement (N0) disease (5-year OS, 36.2%)
- **High risk:** synchronous metastases and N1/N2 disease (5-year OS, 13.8%)

The term *local consolidative therapy (LCT)* is used when the primary tumor and isolated sites of metastasis are ablated by local treatment modalities, such as resection or radiation, after systemic therapy. A randomized phase II study comparing the efficacy of LCT versus standard systemic therapy only in oligometastatic NSCLC showed statistically significant improvement in efficacy outcomes in the LCT arm. Both the PFS and OS favored LCT, with PFS at 14.2 months (95% CI, 7.4–23.1 months) in LCT arm versus 4.4 months (95% CI, 2.2–8.3 months) with maintenance therapy or observation (MT/O) (P = .022) and the OS at 37.6 months in LCT arm versus 9.4 months in the MT/O arm.[146,147] Its important to note that early closure of this trial by the Data Safety and Monitoring Board resulted in random assignment of only 49 patients, which limited subgroup analysis in this study. Furthermore, because this trial preceded the integration of immunotherapy in NSCLC, it did not assess the impact of LCT in this context. Local consolidative therapies may work through multiple mechanisms. LCT may reduce the pool of systemic therapy-resistant cells.[146] Additionally, ablative therapies such as radiation afford the benefits of tumor antigen release, T-lymphocyte expansion, and T-lymphocyte receptor diversification that may manifest as enhanced immunosurveillance and antitumor immunity.[138–150]

At MDACC, we consider local consolidative therapy in patients with good systemic control, particularly those with oligometastatic presentation. However, further research is ongoing to help better define the patient population most likely to benefit from this therapeutic approach, especially with integration of ICI therapy.

FUTURE DIRECTIONS

The treatment for patients with NSCLC, especially in the metastatic setting, has witnessed remarkably rapid change over the past 10 years. This change has been driven by the recognition of significant molecular heterogeneity of disease, identification of targetable genetic changes defining the many subgroups, the development of well-tolerated and effective tyrosine kinase inhibitors, and the addition of immunotherapy to the NSCLC therapeutic armamentarium. Both targeted therapy and immunotherapy are being investigated in patients with early-stage NSCLC with the goal of increasing cure rates.

Certainly, the incorporation of immunotherapy has substantially altered the lives of patients with NSCLC, and its full impact is surely not yet fully realized. However, several challenges remain. An optimal biomarker that facilitates rational selection of initial immunotherapy still eludes us as does the identification of second-line immunotherapy effective in those who progress on PD-(L)1 inhibitors with without anti–CTLA-4. Both of these topics are top priorities in ongoing and future research.

MD ANDERSON PRACTICE TIPS

- We consider surgical treatment in patients with stage IIIA disease with good performance status and without multistation or bulky (>2 cm) mediastinal adenopathy. These patients are treated with neoadjuvant chemotherapy followed by consideration of surgery. Adjuvant radiation therapy is given if there is evidence of mediastinal node involvement based on assessment of surgical pathology.
- We recommend molecular profiling with NGS for all patients with metastatic or recurrent NSCLC
- We consider LCT in patients with good systemic disease control, particularly in those with oligometastatic presentation.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70:7-30.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394-424.
3. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136:E359-E386.
4. Edwards BK, Noone AM, Mariotto AB, et al. Annual Report to the Nation on the status of cancer, 1975-2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. *Cancer*. 2014;120:1290-1314.
5. Bach PB, Kattan MW, Thornquist MD, et al. Variations in lung cancer risk among smokers. *J Natl Cancer Inst*. 2003;95:470-478.
6. Centers for Disease Control and Prevention. https://e-cigarettes.surgeongeneral.gov/documents/2016_SGR_Full_Report_non-508.pdf 2016 (accessed on 6/21/2021).
7. Markowitz SB, Levin SM, Miller A, Morabia A. Asbestos, asbestosis, smoking, and lung cancer. New findings from the North American insulator cohort. *Am J Respir Crit Care Med*. 2013;188:90-96.
8. Torres-Durán M, Ruano-Ravina A, Parente-Lamelas I, et al. Lung cancer in never-smokers: a case-control study in a radon-prone area (Galicia, Spain). *Eur Respir J*. 2014;44:994-1001.
9. Alberg AJ, Samet JM. Epidemiology of lung cancer. *Chest*. 2003;123(suppl):21S-49S.
10. Field RW, Withers BL. Occupational and environmental causes of lung cancer. *Clin Chest Med*. 2012;33:681-703.
11. Sellers TA, Chen PL, Potter JD, et al. Segregation analysis of smoking-associated malignancies: evidence for Mendelian inheritance. *Am J Med Genet*. 1994;52:308-314.
12. Wang JJ, Zheng Y, Sun L, et al. CYP1A1 Ile462Val polymorphism and susceptibility to lung cancer: a meta-analysis based on 32 studies. *Eur J Cancer Prev*. 2011;20:445-452.
13. Langevin SM, Ioannidis JP, Vineis P, Taioli E. Assessment of cumulative evidence for the association between glutathione S-transferase polymorphisms and lung cancer: application of the Venice interim guidelines. *Pharmacogenet Genomics*. 2010;20:586-597.
14. Li W, Li K, Zhao L, Zou H. DNA repair pathway genes and lung cancer susceptibility: a meta-analysis. *Gene*. 2014;538:361-365.
15. Brennan P, Hainaut P, Boffetta P. Genetics of lung-cancer susceptibility. *Lancet Oncol*. 2011;12:399-408.
16. Leão R, Apolónio JD, Lee D, et al. Mechanisms of human telomerase reverse transcriptase (hTERT) regulation: clinical impacts in cancer. *J Biomed Sci*. 2018;25:22.
17. National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. The Health Consequences of Smoking –50 Years of Progress: A Report of the Surgeon General. Atlanta (GA): Centers for Disease Control and Prevention (US); 2014." pubmed URL https://pubmed.ncbi.nlm.nih.gov/24455788/ (accessed on 6/21/2021)
18. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365:395-409.
19. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced lung-cancer mortality with volume CT Screening in a randomized trial. *N Engl J Med*. 2020;382:503-513.
20. US Preventive Services Task Force. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/lung-cancer-screening
21. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med*. 1994;330:1029-1035.
22. Omenn GS, Goodman GE, Thornquist MD, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med*. 1996;334:1150-1155.
23. Lippman SM, Lee JJ, Karp DD, et al. Randomized phase III intergroup trial of isotretinoin to prevent second primary tumors in stage I non-small-cell lung cancer. *J Natl Cancer Inst*. 2001;93:605-618.
24. Khuri FR, Lee JJ, Lippman SM, et al. Randomized phase III trial of low-dose isotretinoin for prevention of second primary tumors in stage I and II head and neck cancer patients. *J Natl Cancer Inst*. 2006;98:441-450.
25. Karp DD, Lee SJ, Keller SM, et al. Randomized, double-blind, placebo-controlled, phase III chemoprevention trial of selenium supplementation in patients with resected stage I non-small-cell lung cancer: ECOG 5597. *J Clin Oncol*. 2013;31:4179-4187.
26. Gaziano JM, Glynn RJ, Christen WG, et al. Vitamins E and C in the prevention of prostate and total cancer in men: the Physicians' Health Study II randomized controlled trial. *JAMA*. 2009;301:52-62.
27. Ebbing M, Bønaa KH, Nygård O, et al. Cancer incidence and mortality after treatment with folic acid and vitamin B12. *JAMA*. 2009;302:2119-2126.
28. Travis WD, Brambilla E, Noguchi M, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol*. 2011;6:244-285.
29. Yatabe Y, Dacic S, Borczuk AC, et al. Best practices recommendations for diagnostic immunohistochemistry in lung cancer. *J Thorac Oncol*. 2019;14:377-407.
30. Morgan RL, De Young BR, McGaughy VR, Niemann TH. MOC-31 aids in the differentiation between adenocarcinoma and reactive mesothelial cells. *Cancer*. 1999;87:390-394.
31. Comprehensive genomic characterization of squamous cell lung cancers. *Nature*. 2012;489:519-525.
32. Comprehensive molecular profiling of lung adenocarcinoma. *Nature*. 2014;511:543-550.
33. Dogan S, Shen R, Ang DC, et al. Molecular epidemiology of EGFR and KRAS mutations in 3,026 lung adenocarcinomas: higher susceptibility of women to smoking-related KRAS-mutant cancers. *Clin Cancer Res*. 2012;18:6169-6177.
34. Beau-Faller M, Prim N, Ruppert AM, et al. Rare EGFR exon 18 and exon 20 mutations in non-small-cell lung cancer on 10 117 patients: a multicentre observational study by the French ERMETIC-IFCT network. Ann Oncol. 2014;25:126-131.
35. Arcila ME, Nafa K, Chaft JE, et al. EGFR exon 20 insertion mutations in lung adenocarcinomas: prevalence, molecular heterogeneity, and clinicopathologic characteristics. Mol Cancer Ther. 2013;12:220-229.
36. D'Angelo SP, Pietanza MC, Johnson ML, et al. Incidence of EGFR exon 19 deletions and L858R in tumor specimens from men and cigarette smokers with lung adenocarcinomas. *J Clin Oncol*. 2011;29:2066-2070.
37. Pan Y, Zhang Y, Li Y, et al. ALK, ROS1 and RET fusions in 1139 lung adenocarcinomas: a comprehensive study of common and fusion pattern-specific clinicopathologic, histologic and cytologic features. *Lung Cancer*. 2014;84:121-126.
38. Gainor JF, Varghese AM, Ou SH, et al. ALK rearrangements are mutually exclusive with mutations in EGFR or KRAS: an analysis of 1,683 patients with non-small cell lung cancer. *Clin Cancer Res*. 2013;19:4273-4281.

39. Tsuta K, Kohno T, Yoshida A, et al. RET-rearranged non-small-cell lung carcinoma: a clinicopathological and molecular analysis. *Br J Cancer*. 2014;110:1571-1578.
40. Arcila ME, Chaft JE, Nafa K, et al. Prevalence, clinicopathologic associations, and molecular spectrum of ERBB2 (HER2) tyrosine kinase mutations in lung adenocarcinomas. *Clin Cancer Res*. 2012;18:4910-4918.
41. Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143:e93S-e120S.
42. MacMahon H, Naidich DP, Goo JM, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. *Radiology*. 2017;284:228-243.
43. Wood DE, Kazerooni EA, Baum SL, et al. Lung Cancer Screening, Version 3.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2018;16:412-441.
44. Vial MR, O'Connell OJ, Grosu HB, et al. Diagnostic performance of endobronchial ultrasound-guided mediastinal lymph node sampling in early stage non-small cell lung cancer: a prospective study. *Respirology*. 2018;23:76-81.
45. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM Classification for Lung Cancer. *J Thorac Oncol*. 2016;11:39-51.
46. Landreneau RJ, Normolle DP, Christie NA, et al. Recurrence and survival outcomes after anatomic segmentectomy versus lobectomy for clinical stage I non-small-cell lung cancer: a propensity-matched analysis. J Clin Oncol. 2014;32:2449-2455.
47. Darling GE, Allen MS, Decker PA, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial. J *Thorac Cardiovasc Surg*. 2011;141:662-670.
48. Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: diagnosis and management of lung cancer, 3rd ed: American College of *Chest* Physicians evidence-based clinical practice guidelines. Chest. 2013;143:e166S-e190S.
49. Onishi H, Araki T, Shirato H, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. *Cancer.* 2004;101:1623-1631.
50. Auperin A, Le Pechoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol.* 2010;28:2181-2190.
51. Curran WJ Jr, Paulus R, Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. *J Natl Cancer Inst.* 2011;103:1452-1460.
52. Sause W, Kolesar P, Taylor SI, et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. *Chest.* 2000;117:358-364.
53. O'Rourke N, Roque IFM, Farre Bernado N, Macbeth F. Concurrent chemoradiotherapy in non-small cell lung cancer. *Cochrane Database Syst Rev.* 2010:Cd002140.
54. Arriagada R, Auperin A, Burdett S, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. *Lancet*. 2010;375:1267-1277.
55. Pignon J-P, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol*. 2008;26:3552-3559.
56. Strauss GM, Herndon JE 2nd, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. *J Clin Oncol*. 2008;26:5043-5051.
57. Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med*. 2004;350:351-360.
58. Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. *Lancet Oncol*. 2006;7:719-727.
59. Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *N Engl J Med*. 2005;352:2589-2597.
60. Kreuter M, Vansteenkiste J, Fischer JR, et al. Randomized phase 2 trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed versus cisplatin and vinorelbine: the TREAT study. *Ann Oncol*. 2013;24:986-992.
61. Park SY, Lee JG, Kim J, et al. Efficacy of platinum-based adjuvant chemotherapy in T2aN0 stage IB non-small cell lung cancer. *J Cardiothorac Surg*. 2013;8:151.
62. Lim E, Harris G, Patel A, et al. Preoperative versus postoperative chemotherapy in patients with resectable non-small cell lung cancer: systematic review and indirect comparison meta-analysis of randomized trials. *J Thorac Oncol.* 2009;4:1380-1388.
63. Postoperative radiotherapy for non-small cell lung cancer. *Cochrane Database Syst Rev.* 2005:Cd002142.
64. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet. 2009;374:379-386.
65. Thomas M, Rübe C, Hoffknecht P, et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. *Lancet Oncol*. 2008;9:636-648.
66. Bradley JD, Hu C, Komaki RR, et al. Long-term results of NRG Oncology RTOG 0617: standard- versus high-dose chemoradiotherapy with or without cetuximab for unresectable stage iii non-small-cell lung cancer. *J Clin Oncol*. 2020;38:706-714.
67. Santana-Davila R, Devisetty K, Szabo A, et al. Cisplatin and etoposide versus carboplatin and paclitaxel with concurrent radiotherapy for stage III non-small-cell lung cancer: an analysis of Veterans Health Administration data. *J Clin Oncol*. 2015;33:567-574.
68. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med*. 2017;377:1919-1929.
69. Gray JE, Villegas A, Daniel D, et al. Three-year overall survival with durvalumab after chemoradiotherapy in stage III NSCLC-update from PACIFIC. *J Thorac Oncol*. 2020;15:288-293.
70. Hui R, Ozguroglu M, Villegas A, et al. Patient-reported outcomes with durvalumab after chemoradiotherapy in stage III, unresectable non-small-cell lung cancer (PACIFIC): a randomised, controlled, phase 3 study. *Lancet Oncol*. 2019;20:1670-1680.
71. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N *Engl J Med.* 2018;379:2342-2350.
72. Tsujino K, Kurata T, Yamamoto S, et al. Is consolidation chemotherapy after concurrent chemo-radiotherapy beneficial for patients with locally advanced non-small-cell lung

cancer? A pooled analysis of the literature. *J Thorac Oncol*. 2013;8:1181-1189.
73. Herbst RS, Tsuboi M, John T, et al. Osimertinib as adjuvant therapy in patients (pts) with stage IB–IIIA EGFR mutation positive (EGFRm) NSCLC after complete tumor resection: ADAURA. *J Clin Oncol*. 2020;38:LBA5-LBA.
74. Kunitoh H, Kato H, Tsuboi M, Shibata T, Asamura H, Ichinose Y, Katakami N, Nagai K, Mitsudomi T, Matsumura A, Nakagawa K, Tada H, Saijo N; Japan Clinical Oncology Group. Phase II trial of preoperative chemoradiotherapy followed by surgical resection in patients with superior sulcus non-small-cell lung cancers: report of Japan Clinical Oncology Group trial 9806. J Clin Oncol. 2008 Feb 1;26(4):644-9. doi: 10.1200/JCO.2007.14.1911. Erratum in: J Clin Oncol. 2011 Nov 20;29(33):4472. Ichonose, Yukito [corrected to Ichinose, Yukito]. PMID: 18235125. https://pubmed.ncbi.nlm.nih.gov/18235125/ (accessed on 6/21/2021).
75. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med*. 2010;363:733-742.
76. International Association for the Study of LUng Cancer. Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors. https://www.iaslc.org/Portals/0/cap-iaslc-amp_lung_molec_testing_faq_approved_20180122_0pdf?ver=2020-04-21-235110-130 2020
77. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med*. 2002;346:92-98.
78. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol*. 2008;26:3543-3551.
79. Scagliotti G, Hanna N, Fossella F, et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two phase III studies. Oncologist. 2009;14:253-263.
80. Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. *J Clin Oncol*. 2012;30:2055-2062.
81. Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. *J Clin Oncol*. 2008;26:4617-4625.
82. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*. 2006;355:2542-2550.
83. Remon J, Besse B, Soria JC. Successes and failures: what did we learn from recent first-line treatment immunotherapy trials in non-small cell lung cancer? *BMC Med*. 2017;15:55.
84. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012;12:252-264.
85. Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. *Ann Rev Immunol*. 2008;26:677-704.
86. Sharpe AH, Wherry EJ, Ahmed R, Freeman GJ. The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. *Nat Immunol*. 2007;8:239-245.
87. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med*. 2012;366:2455-2465.
88. Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. *J Clin Oncol*. 2010;28:3167-3175.
89. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 2012;366:2443-2454.
90. Topalian SL, Sznol M, McDermott DF, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *J Clin Oncol*. 2014;32:1020-1030.
91. Vansteenkiste JF, Cho BC, Vanakesa T, et al. Efficacy of the MAGE-A3 cancer immunotherapeutic as adjuvant therapy in patients with resected MAGE-A3-positive non-small-cell lung cancer (MAGRIT): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2016;17:822-835.
92. Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med*. 2013;369:122-133.
93. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015;373:1627-1639.
94. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. 2015;373:123-135.
95. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016;387:1540-1550.
96. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med*. 2015;372:2018-2028.
97. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med*. 2016;375:1823-1833.
98. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Updated analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer With PD-L1 tumor proportion score of 50% or greater. *J Clin Oncol*. 2019;37:537-546.
99. Spigel D, De Marinis F, Giaccone G, et al. IMpower110: interim overall survival (OS) analysis of a phase III study of atezolizumab (Atezo) vs platinum-based chemotherapy (chemo) as first-line (1L) treatment (Tx) in PD-L1–selected NSCLC. *Ann Oncol*. 2019;30(suppl 5):v851-v934.
100. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet*. 2019;393:1819-1830.
101. Carbone DP, Reck M, Paz-Ares L, et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. *N Engl J Med*. 2017;376:2415-2426.
102. Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378:2078-2092.
103. Gadgeel S, Rodríguez-Abreu D, Speranza G, et al. Updated analysis from KEYNOTE-189: pembrolizumab or placebo plus pemetrexed and platinum for previously untreated metastatic nonsquamous non–small-cell lung cancer. *J Clin Oncol*. 2020;38:1505-1517.
104. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med*. 2018;379:2040-2051.
105. West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20:924-937.
106. US Food and Drug Administration. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-atezolizumab-nab-paclitaxel-and-carboplatin-metastatic-nsclc-without-egfralk (accessed on 6/21/2021).

107. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med*. 2018;378:2288-2301.
108. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N Engl J Med*. 2019;381:2020-2031.
109. US Food and Drug Administration. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nivolumab-plus-ipilimumab-first-line-mnsclc-pd-l1-tumor-expression-1 (accessed on 6/21/2021).
110. Reck M, Ciuleanu TE, Dols MC, et al. Nivolumab (NIVO) + ipilimumab (IPI) + 2 cycles of platinum-doublet chemotherapy (chemo) vs 4 cycles chemo as first-line (1L) treatment (tx) for stage IV/recurrent non-small cell lung cancer (NSCLC): CheckMate 9LA. *J Clin Oncol*. 2020;38(15 suppl):9501.
111. Ramalingam SS, Ciuleanu TE, Pluzanski A, et al. Nivolumab + ipilimumab versus platinum-doublet chemotherapy as first-line treatment for advanced non-small cell lung cancer: three-year update from CheckMate 227 Part 1. *J Clin Oncol*. 2020;38(15 suppl):9500.
112. Torlakovic E, Lim HJ, Adam J, et al. "Interchangeability" of PD-L1 immunohistochemistry assays: a meta-analysis of diagnostic accuracy. *Mod Pathol*. 2020;33:4-17.
113. Tsao MS, Kerr KM, Kockx M, et al. PD-L1 Immunohistochemistry comparability study in real-life clinical samples: results of Blueprint phase 2 project. *J Thorac Oncol*. 2018;13:1302-1311.
114. Tan EH, Szczesna A, Krzakowski M, et al. Randomized study of vinorelbine—gemcitabine versus vinorelbine—carboplatin in patients with advanced non-small cell lung cancer. *Lung Cancer*. 2005;49:233-240.
115. Patel JD, Socinski MA, Garon EB, et al. PointBreak: a randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer. *J Clin Oncol*. 2013;31:4349-4357.
116. Spigel DR, McLeod M, Hussein MA, et al. Randomized results of fixed-duration (1-yr) vs continuous nivolumab in patients (pts) with advanced non-small cell lung cancer (NSCLC). *Ann Oncol*. 2017;28(suppl 5):V461.
117. Fidias PM, Dakhil SR, Lyss AP, et al. Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer. *J Clin Oncol*. 2009;27:591-598.
118. Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet*. 2009;374:1432-1440.
119. Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol*. 2010;11:521-529.
120. Pérol M, Chouaid C, Pérol D, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. *J Clin Oncol*. 2012;30:3516-3524.
121. Paz-Ares LG, de Marinis F, Dediu M, et al. PARAMOUNT: final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. *J Clin Oncol*. 2013;31:2895-2902.
122. Barlesi F, Scherpereel A, Rittmeyer A, et al. Randomized phase III trial of maintenance bevacizumab with or without pemetrexed after first-line induction with bevacizumab, cisplatin, and pemetrexed in advanced nonsquamous non-small-cell lung cancer: AVAPERL (MO22089). *J Clin Oncol*. 2013;31:3004-3011.
123. Paz-Ares L, de Marinis F, Dediu M, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. Lancet Oncol. 2012;13:247-255.
124. Ramalingam SS, Dahlberg SE, Belani CP, et al. ECOG-ACRIN 5508: pemetrexed, bevacizumab or the combination as maintenance therapy for advanced non-squamous NSCLC. *J Clin Oncol*. 2019;37:9002.
125. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet*. 2014;384:665-673.
126. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol*. 2000;18:2095-2103.
127. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol*. 2000;18:2354-2362.
128. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol*. 2004;22:1589-1597.
129. Ardizzoni A, Tiseo M, Boni L, et al. Pemetrexed versus pemetrexed and carboplatin as second-line chemotherapy in advanced non-small-cell lung cancer: results of the GOIRC 02-2006 randomized phase II study and pooled analysis with the NVALT7 trial. *J Clin Oncol*. 2012;30:4501-4507.
130. Garassino MC, Martelli O, Broggini M, et al. Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. *Lancet Oncol*. 2013;14:981-988.
131. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med*. 2005;353:123-132.
132. Kawaguchi T, Ando M, Asami K, et al. Randomized phase III trial of erlotinib versus docetaxel as second- or third-line therapy in patients with advanced non-small-cell lung cancer: Docetaxel and Erlotinib Lung Cancer Trial (DELTA). *J Clin Oncol*. 2014;32:1902-1908.
133. Fehrenbacher L, von Pawel J, Park K, et al. Updated efficacy analysis including secondary population results for OAK: a randomized phase III study of atezolizumab versus docetaxel in patients with previously treated advanced non-small cell lung cancer. *J Thorac Oncol*. 2018;13:1156-1170.
134. Anderson H, Hopwood P, Stephens RJ, et al. Gemcitabine plus best supportive care (BSC) vs BSC in inoperable non-small cell lung cancer—a randomized trial with quality of life as the primary outcome. UK NSCLC Gemcitabine Group. Non-Small Cell Lung Cancer. *Br J Cancer*. 2000;83:447-453.
135. Pallis AG, Gridelli C, Wedding U, et al. Management of elderly patients with NSCLC; updated expert's opinion paper: EORTC Elderly Task Force, Lung Cancer Group and International Society for Geriatric Oncology. *Ann Oncol*. 2014;25:1270-1283.
136. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol*. 1995;13:8-10.
137. Khan AJ, Mehta PS, Zusag TW, et al. Long term disease-free survival resulting from combined modality management of

patients presenting with oligometastatic, non-small cell lung carcinoma (NSCLC). *Radiother Oncol*. 2006;81:163-167.
138. Inoue T, Katoh N, Aoyama H, et al. Clinical outcomes of stereotactic brain and/or body radiotherapy for patients with oligometastatic lesions. Japanese *J Clin Oncol*. 2010;40:788-794.
139. Pfannschmidt J, Dienemann H. Surgical treatment of oligometastatic non-small cell lung cancer. *Lung Cancer*. 2010;69: 251-258.
140. Salama JK, Hasselle MD, Chmura SJ, et al. Stereotactic body radiotherapy for multisite extracranial oligometastases: final report of a dose escalation trial in patients with 1 to 5 sites of metastatic disease. *Cancer.* 2012;118:2962-2970.
141. Sheu T, Heymach JV, Swisher SG, et al. Propensity score-matched analysis of comprehensive local therapy for oligometastatic non-small cell lung cancer that did not progress after front-line chemotherapy. *Int J Radiat Oncol Biol Phys.* 2014;90:850-857.
142. Iyengar P, Wardak Z, Gerber DE, et al. Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: a phase 2 randomized clinical trial. *JAMA Oncol.* 2018;4:e173501.
143. Flannery TW, Suntharalingam M, Regine WF, et al. Long-term survival in patients with synchronous, solitary brain metastasis from non-small-cell lung cancer treated with radiosurgery. *Int J Radiat Oncol Biol Phys.* 2008;72:19-23.
144. Moreno P, de la Quintana Basarrate A, Musholt TJ, et al. Adrenalectomy for solid tumor metastases: results of a multicenter European study. *Surgery*. 2013;154:1215-22; discussion 22-3.
145. Ashworth AB, Senan S, Palma DA, et al. An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligometastatic non-small-cell lung cancer. *Clin Lung Cancer*. 2014;15:346-355.
146. Gomez DR, Tang C, Zhang J, et al. Local consolidative therapy vs. maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer: long-term results of a multi-institutional, phase II, randomized study. *J Clin Oncol.* 2019;37:1558-1565.
147. Gomez DR, Blumenschein GR Jr, Lee JJ, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. *Lancet Oncol.* 2016;17:1672-1682.
148. Mitchell KG, Farooqi A, Ludmir EB, et al. Improved overall survival with comprehensive local consolidative therapy in synchronous oligometastatic non-small-cell lung cancer. *Clin Lung Cancer.* 2020;21:37-46.e7.
149. Menon H, Ramapriyan R, Cushman TR, et al. Role of radiation therapy in modulation of the tumor stroma and microenvironment. *Front Immunol*. 2019;10:193.
150. Menon H, Chen D, Ramapriyan R, et al. Influence of low-dose radiation on abscopal responses in patients receiving high-dose radiation and immunotherapy. *J Immunother Cancer*. 2019;7:237.
151. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet.* 2017,389(10066):255-265.

25

Targeted Therapies in Non–Small Cell Lung Cancer

Yasir Y. Elamin
Don L. Gibbons
Marcelo V. Negrao

KEY CONCEPTS

- Non–small cell lung cancer (NSCLC) can be classified based on recurrent genetic alterations in genes encoding proteins essential to cell proliferation and survival. These genetic alterations are transformative, meaning that they play a pivotal role in transforming a noncancerous cell into a cancerous one. NSCLCs that harbor these alterations are called oncogene-addicted. These genetic alterations are typically mutually exclusive and are characterized by impressive sensitivity to small-molecule receptor tyrosine kinase.
- Identifying patients with targetable alterations has important therapeutic and prognostic implications. Molecular profiling of advanced NSCLC using tumor tissue, cell-free DNA (cfDNA), or both is strongly recommended irrespective of tobacco exposure history.
- Oncogene-addicted advanced NSCLC should be treated with targeted agents specific to each genetic alteration. This is based on impressive clinical activity and the tolerability of targeted agents. There are Food and Drug Administration–approved targeted agents for NSCLC that harbor alterations in EGFR (epidermal growth factor receptor), *ALK* (anaplastic lymphoma kinase), ROS proto-oncogene 1 (ROS1), rearrangements, B-Raf proto-oncogene (BRAF), rearranged during transfection (RET), neurotrophic receptor tyrosinekinase gene (NTRK1-3), and MET (mesenchymal-epithelial transition) as well as promising agents for HER2 (human epidermal growth factor receptor 2) and NRG1 (neuregulin 1).
- Targeted treatment based on clinical demographic characteristics alone is not recommended.
- Emergence of resistance targeted therapy is inevitable. Resistance mechanisms can be broadly divided into target dependent or independent. The latter means activation of bypass pathways, leading to clinical resistance. Identifying resistance mechanisms to targeted therapy can determine treatment decisions and; therefore, obtaining a tissue biopsy, cfDNA, or both on progression is generally indicated.
- Treatment of patients with oncogene-addicted NSCLC upon progression on a targeted agent should be individualized. Treatment options include clinical trial enrollment, continuing the same targeted agent with local ablative therapy of progressing lesions, and cytotoxic chemotherapy with or without immunotherapy.

The wide use of molecular profiling techniques combined with a better understanding of signaling pathways in lung cancer and other tumors has led to the identification of mutually exclusive, activating genetic alterations in specific tyrosine kinases that can be targeted using tyrosine kinase inhibitors (TKIs). Matching a specific targeted TKI to the specific driver mutation identified has produced a paradigm shift in the treatment of non–small cell lung cancer (NSCLC), with targeted therapy considered the preferred initial treatment for patients with NSCLC who have such genetic alterations. We now have approved targeted therapies for NSCLC that harbor activating alterations in EGFR (epidermal growth factor receptor), *ALK* (anaplastic lymphoma kinase), ROS proto-oncogene 1 (ROS1), rearrangements, B-Raf proto-oncogene (BRAF), rearranged during transfection (RET), neurotrophic receptor tyrosinekinase gene (NTRK1-3), and MET (mesenchymal-epithelial transition), as well as promising agents for HER2 (human epidermal growth factor receptor 2) and NRG1 (neuregulin 1). Herein, we will discuss each of these genetic alterations.

The National Comprehensive Cancer Network (NCCN) guidelines recommend testing NSCLC for EGRF, *ALK*, ROS1, BRAF and NTRK (https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf).

This is largely consistent with recommendations from the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association of Molecular Pathologists.[1,2] There is not a single standard platform for testing that is typically done on tissue biopsies from the primary or metastatic sites. More recently, there has been increase in the use of cell-free DNA (cfDNA) for genotyping because it provides a less invasive source of tumor DNA. cfDNA is particularly useful in patients with insufficient tumor samples for molecular profiling or when obtaining a biopsy is not feasible. The currently available cfDNA profiling platforms have generally shorter turnaround time compared with tumor tissue sequencing; however, they are less broad in their coverage compared with tumor tissue profiling. The cfDNA specificity ranges between 60% and 95%.[3] A limitation of cfDNA is a false-negative rate of approximately 30%.[4,5] This may reflect limited tumor DNA shedding into blood as a result of limited tumor burden.[6,7] A negative result from cfDNA should not exclude the potential existence of a targetable alteration, especially when there is a strong clinical suspicion. Clinical therapeutic decisions can be made based on positive cfDNA results because clinical studies have shown comparable outcomes to those achieved based on tumor tissue sequencing.[8–12]

Table 25–1 summarizes the key genetic alterations and their testing techniques.

EGFR MUTATIONS

EGFR is a transmembrane protein and a member of the HER family of tyrosine kinase receptors that transduces important intracellular signaling.[13] Activating mutations in the *EGFR* gene lead to activation of downstream signaling, resulting in cell proliferation, survival, and migration independent of extracellular stimuli.[14–16] EGFR mutations are the most common targetable alterations in NSCLC, occurring in approximately 15% of lung adenocarcinoma in the United States.[17] These mutations occur more frequently in nonsmokers, females, and Asian populations. EGFR mutations can be divided into classical mutations, L858R, or exon 19 deletions, comprising most EGFR-mutant NSCLC cases, or atypical mutations spanning exons 18 to 21, including in-frame insertions or point mutations within exon 20.[18]

Classical EGFR Mutations

The most frequent EGFR mutations are in-frame deletions in exon 19 that represent approximately 45% of all EGFR mutations followed by point mutations in exon 21 (L858R), seen in 40%.

In advanced NSCLC, the presence of a classical EGFR mutation (exon 19 deletion or L858R) strongly predicts for sensitivity to EGFR TKIs such as erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib; therefore, EGFR TKIs are standard-of-care first-line treatment for metastatic NSCLC harboring a classical EGFR mutation. Several phase 3 clinical trials showed the superiority of first-generation TKIs (erlotinib and gefitinib) and a second-generation TKI (afatinib) over platinum-based cytotoxic chemotherapy in terms of clinical efficacy and tolerability.[19–25] However, newer data suggest improved outcomes with the third-generation TKI osimertinib in the frontline setting.

In the phase III FLAURA trial, in which patients with treatment-naïve EGFR-mutant NSCLC were randomized to osimertinib or a standard of care EGFR TKI (gefitinib or erlotinib), osimertinib led to improved

TABLE 25-1 Key Genetic Alterations and Related Testing Techniques in Non–Small Cell Lung Cancer

Genetic Alteration	Frequency in Lung Adenocarcinoma (%)	Testing Techniques
EGFR mutations (exon 19 deletions, L858R, exon 20 insertions, others)	15	NGS, RT-PCR, Sanger sequencing
ALK fusions	3–5	FISH break-apart probe, IHC (*ALK* [D5F3] CDx Assay is FDA-approved), NGS, RT-PCR
ROS1 fusions	2	FISH break-apart probe, NGS, RT-PCR
BRAF mutations	4	NGS, RT-PCR, Sanger sequencing
MET exon 14 skipping mutations	2–4	NGS, RT-PCR
HER2 mutations	1.5	NGS, RT-PCR, Sanger sequencing
RET fusions	1–2	FISH break-apart probe, NGS, RT-PCR
NTRK fusions	1	NGS
NRG1 fusions	0.2–0.3	NGS, IHC

ALK, anaplastic lymphoma kinase; BRAF, rearrangements, B-Raf proto-oncogene; EGFR, epidermal growth factor receptor; FISH, fluorescence in situ; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; MET, mesenchymal-epithelial transition; NGS, next-generation sequencing; NRG1, neuregulin 1; NTRK1-3, neurotrophic receptor tyrosinekinase gene; RET, rearranged during transfection; ROS1, ROS proto-oncogene 1; RT-PCR: reverse-transcriptase polymerase chain reaction.

overall survival (OS) compared with standard of care TKI (38.6 months vs 31.8 months).[8] Progression-free survival (PFS) was also longer in patients treated with osimertinib compared with those treated with erlotinib or gefitinib (18.9 months vs 10.2 months). Objective response rates (ORRs) for osimertinib and standard-of-care TKIs were comparable (80% and 76%, respectively). Furthermore, osimertinib was better tolerated than standard-of-care EGFR TKI. Importantly, the PFS in the subset of patients with central nervous system (CNS) metastases receiving osimertinib was 15.2 months compared with 9.6 months in patients receiving a first-generation EGFR TKI. Among patients with brain metastases evaluable for response, the intracranial response rate was 91% with osimertinib compared with 68% with a first-generation EGFR TKI. Based on these data, osimertinib is now approved by the U.S. Food and Drug Administration (FDA) and the preferred EGFR TKI for the first-line treatment of patients with NSCLC that exhibits a classical EGFR mutation.

Dacomitinib is a second-generation TKI that was approved by the FDA in 2018 for the first-line treatment of patients with metastatic NSCLC with EGFR exon 19 deletion or L858R mutation. A phase III trial compared dacomitinib with gefitinib in patients with treatment-naïve EGFR-mutant NSCLC.[26] Dacomitinib demonstrated an improved OS (34 months vs 27 months) as well as improved PFS (14.7 months vs 9.2 months). Treatment-related toxicities were significantly higher in patients treated with dacomitinib, especially diarrhea and skin rash.

Treatment with an EGFR TKI is generally continued until there is disease progression. Upon progression, a biopsy of a progressive lesion is usually indicated to determine the mechanism(s) of EGFR TKI-acquired resistance. Resistance mechanisms that are observed in all TKIs may be broadly divided into EGFR dependent (eg, secondary EGFR mutations or EGFR amplification) and EGFR independent (eg, MET amplification and small cell transformation).[27–31] Mechanisms of acquired resistance to first- and second-generation TKIs include the acquisition of a secondary EGFR mutation. The most common secondary EGFR mutation is T790M, which increases the affinity of the mutant oncoprotein for ATP to near wild-type levels leading to TKI resistance.[29,32–34] In a phase III trial, osimertinib has shown superior outcomes compared with platinum-based chemotherapy in patients with acquired EGFR T790M-positive NSCLC who progressed on prior TKI. Osimertinib demonstrated a PFS of 10.1 months compared with 4.4 months observed with platinum-based chemotherapy.[35] Osimertinib is FDA-approved for EGFR T790M-positive NSCLC patients who progressed on first- or second-line EGFR TKIs.

EGFR TKIs are generally well tolerated. Their side effects are primarily related to inhibition of the wild-type EGFR tyrosine kinase activity. Accordingly, the commonest adverse events of EGFR TKIs include cutaneous reactions and diarrhea.[36] Cutaneous reactions include acneiform rash, xeroderma, pruritus and paronychia.[36,37] Given its selectivity for the mutant protein, osimertinib generally has a better safety profile.[38,39] Other notable rare adverse events, including interstitial lung disease (ILD), electrocardiogram QT prolongation, and cardiomyopathy, are seen in fewer than 1% to 3% of patients treated with EGFR TKIs.[36,40]

There are no approved targeted therapies for patients with disease progression on osimertinib. Therefore, such patients should preferably be treated in a clinical trial. Other treatment options include local ablative therapy with radiation or surgery with osimertinib continuation for patients with oligoprogressive disease and platinum-based chemotherapy. A subset of 111 patients with NSCLC with EGFR mutation or *ALK* fusion were included in the IMpower 150 trial, which investigated the addition of atezolizumab (anti–programmed cell death ligand 1 [PD-L1 antibody]) to the combination of carboplatin, paclitaxel, and bevacizumab, all of whom had progressed on a prior TKI. Patients with EGFR-/*ALK*-positive NSCLC who were randomized to receive atezolizumab had longer PFS (9.7 months vs 6.1 months) and OS (median not reached vs 17.5 months) compared with the control group.[41] As such, the combination of carboplatin, paclitaxel, bevacizumab, and atezolizumab may be considered for patients who progress on an EGFR TKI. A similar regimen is being investigated in KEYNOTE-789, a randomized phase 3 trial evaluating pemetrexed plus platinum chemotherapy (carboplatin or cisplatin) with or without pembrolizumab in patients with TKI-resistant EGFR-mutant metastatic NSCLC (NCT03515837). The trial outcomes are pending.

Atypical EGFR Mutations

Atypical EGFR mutations represent 10% to 15% of all EGFR mutations.[42–44] The most common of these are in-frame insertions within exon 20 of EGFR, which are generally resistant to currently approved EGFR TKIs.[45,46] Historical data for patients with EGFR exon 20 insertion mutations have shown that overall response rates are approximately 3% to 8% to first-line therapy with erlotinib, gefitinib, or afatinib. In silico modeling revealed that insertions in exon 20 of EGFR result in steric hindrance of the drug-binding pocket resulting in TKI resistance.[47] Currently, there are no targeted therapies approved for the treatment of patients with EGFR exon 20 insertion mutations. Clinical trials investigating novel EGFR TKIs, such as TAK-788 (mobocertinib) and poziotinib, are in progress.

Afatinib is approved for the first-line treatment of patients with NSCLC whose tumors contain EGFR

TABLE 25-2 Epidermal Growth Factor Receptor Mutations and Standard Therapies in Non–Small Cell Lung Cancer

EGFR Mutation Type	Frequency of All EGFR Mutations (%)	Approved TKIs
Exon 19 deletion and L858R	80–85	Osimertinib (preferred), erlotinib, gefitinib, afatinib, dacomitinib
Exon 20 insertions	5–10	None approved
Atypical point mutations (S768I, L861Q, and G719X	10–15	Afatinib

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

mutations S768I, L861Q, and G719X. The approval is a based on post-hoc analysis of a single group phase 2 trial (LUX-Lung 2) and randomized phase 3 trials (LUX-Lung 3 and LUX-Lung 6).[48] The analysis included 38 patients with EGFR S768I, L861Q, and G719X alone or in combination with each other. In this subset of patients, afatinib demonstrated an ORR of 71.1% with a duration of response of 11.1 months and PFS of 10.7 months. The KCSG-LU15-09 was a multicenter open-label phase II trial that tested osimertinib in the same population of rare EGFR mutations. ORR was 50% (18 of 36 patients; 95% confidence interval [CI], 33%–67%).[49] The median PFS was 8.2 months, and duration of response was 11.2 months (95% CI, 7.7–14.7 months).

Table 25–2 summarizes the types of EGFR mutations and their standard therapy.

ALK FUSIONS

The *ALK* gene was discovered in 1994 when a chromosomal rearrangement t(2;5), resulting in a nucleophosmin (NPM1)–*ALK* fusion, was described in anaplastic large-cell lymphoma.[50–53] Since then, *ALK* fusions have been discovered in several malignancies, including NSCLC. These fusion oncoproteins are transforming in vitro and in vivo, constitutively activating the *ALK* kinase. *ALK* fusions occur in 3% to 5% of patients with NSCLC and are associated with a history of never or light smoking and younger age.[50,51]

Echinoderm microtubule-associated protein-like 4 (EML4) is the most common *ALK* fusion partner in NSCLC resulting in the EML4-*ALK* fusion oncogene. Other rare *ALK* fusions have been described in NSCLC, including kinesin family member 5B (KIF5B)–*ALK*, kinesin light chain 1 (KLC1)–*ALK*, and protein tyrosine phosphatase nonreceptor type 3 (PTPN3)–*ALK* and striatin (STRN)–*ALK*.[54]

ALK fusions can be detected using fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), or next-generation sequencing (NGS). All these tests are FDA-approved for detecting *ALK* fusion in patients with NSCLC.[55]

Metastatic NSCLC that harbors *ALK* fusions are highly sensitive to *ALK* TKIs, which are the standard-of-care first-line therapy for such patients. A summary of clinically relevant *ALK* TKIs is provided next.

Crizotinib

Crizotinib has demonstrated superiority over platinum-based chemotherapy in the frontline setting and was the first *ALK* TKI to be approved by the FDA.[56] However, crizotinib has now been replaced by next-generation *ALK* TKIs that have improved activity and efficacy.

Ceritinib

Ceritinib is a second-generation *ALK* TKI that, like crizotinib, has demonstrated superior efficacy over platinum-based chemotherapy in the first-line setting in terms of PFS and response rate.[57] It has also shown superior efficacy over single-agent chemotherapy in patients who have progressed on first-line crizotinib.

Alectinib

Alectinib is one of the currently preferred *ALK* TKI for the first-line treatment of patients with *ALK*-positive metastatic NSCLC.[58] In the global phase III study (ALEX), patients were randomly assigned to alectinib or crizotinib. The median PFS was 35 months in the alectinib group versus 11 months in the crizotinib group; OS results are not yet mature. The CNS response rates in the subset of patients with baseline measurable CNS lesions in the alectinib and crizotinib groups were 81% and 50%, respectively.

Brigatinib

Brigatinib was compared with crizotinib in the phase III trial ALTA-1L that enrolled treatment-naïve *ALK*-positive patients with advanced NSCLC.[59] Preliminary data demonstrate a PFS of 24 months with brigatinib versus 11 months with crizotinib. Among those with CNS metastases at baseline, the intracranial response rate was significantly higher with brigatinib (78% vs 26%). These data led to the recent FDA approval of brigatinib.

Emerging data indicate that *ALK* fusion variants may have biologic and clinical implications in *ALK*-positive lung cancer. Among EML4-*ALK* variants identified to date, the most common are variant 1 (v1; exon 13 of EML4 fused to exon 20 of *ALK* [E13;A20]) and v3a/b (exon 6a/b of EML4 fused to exon 20 of *ALK* [E6a/b;A20]).[60–62] Preclinical data suggest differential response to crizotinib based on EML4-*ALK* variant.[63] In an analysis of ALTA-1L phase III trial, patients with variant 3 had shorter PFS than patients with variant 1 in both study arms (brigatinib and crizotinib arms).[64] A similar trend was reported in the ALEX trial.[65]

Even though most patients derive clinical benefit from *ALK* TKIs, acquired resistance universally develops, leading to clinical progression. Parallel to what is seen in EGFR TKIs, resistance mechanisms to *ALK* TKIs include *ALK*-dependent and -independent mechanisms.[66–69] Acquired *ALK* resistance mutations are detected in 53% of patients with progressive disease after treatment with alectinib.[70] The most common *ALK* secondary mutations in patients treated with alectinib are G1202R followed by I1171 mutations (I1171T/N/S). G1202R maps to the solvent-exposed region of *ALK*, where the bulkier, charged side chain is thought to lead to steric hindrance of most *ALK* inhibitors.[70,71] Molecular simulation analysis indicated that the I1171T mutation is predicted to disrupt a hydrogen bond between E1167 and alectinib, thus impairing drug binding. *ALK*-independent resistance mechanisms include MET amplification, EGFR pathway activation via an NRG1–ERBB3 (erb-b2 receptor tyrosine kinase 3)–EGFR axis or a TGFα–EGFR autocrine loop, and epithelial–mesenchymal transition.[68,70–72]

Alectinib and brigatinib are generally better tolerated than crizotinib and ceritinib. Common side effects of crizotinib and ceritinib include nausea, vomiting, and diarrhea. The majority of these gastrointestinal toxicities are mild.[56–59] Visual disturbance is a frequent side effect of crizotinib, reported in 25% to 36% of patients treated with crizotinib in phase III trials.[58,59] All grades of pneumonitis and ILD are seen with crizotinib, ceritinib, alectinib, and brigatinib in 3%, 4%, 0.4%, and 4% to 9%, respectively, of patients treated with these TKIs (https://www.accessdata.fda.gov). Brigatinib-related pneumonitis is unique in its early onset (median time to onset, 2 days).[73] Therefore, current prescribing information recommends starting brigatinib at a leading dose of 90 mg for 1 week followed by escalation to 180 mg.

Lorlatinib is a third-generation reversible, ATP-competitive, macrocyclic TKI of *ALK* and ROS1 that has activity against the majority of the known *ALK* TKIs resistance mutations. In a phase II study that included previously treated patients with *ALK*-positive NSCLC,[74] lorlatinib yielded a response rate of 47% in patients who were previously treated by one or more *ALK* TKIs with a CNS response rate of 63%. In patients who were previously treated with two or more *ALK* TKIs, lorlatinib resulted in a response rate of 38.7%. In an analysis of the subset of patients who previously received a second-generation *ALK* TKI, lorlatinib demonstrated a response rate of 69% in patients with *ALK* secondary mutation, whereas the response rate was 27% in those without a secondary mutation.[74] Lorlatinib has been granted FDA approval for the treatment of patients with *ALK*-positive NSCLC who have progressed on crizotinib and at least one other *ALK* inhibitor, as well as for those who have progressed on either alectinib or ceritinib as frontline *ALK* inhibitor therapy for metastatic disease.

Patients with disease refractory to *ALK* TKIs should be considered for chemotherapy with or without immunotherapy. The aforementioned study, IMpower 150, showed that the combination of carboplatin, paclitaxel, bevacizumab, and atezolizumab results in longer median OS and PFS compared with the same regimen without atezolizumab in the subset of patients with TKI previously treated EGFR-/*ALK*-positive NSCLC.[41] Therefore, this combination may be considered for such patients. Alternatively, platinum-based chemotherapy without immunotherapy can be considered. NSCLCs harboring *ALK* fusions are associated with low ORRs to single-agent programmed cell death protein 1 (PD-1) and PD-L1 inhibitors.[75,76] Therefore, PD-1 and PD-L1 inhibitors should not be offered as single agent to patient with *ALK* fusion–positive lung cancer before exhausting other therapeutic options.

ROS1 FUSIONS

ROS1 is a tyrosine kinase receptor that is part of the insulin receptor family. This gene is located on the long arm of chromosome 6 (6q22) and encodes a transmembrane protein with intracellular C-terminal tyrosine kinase domain.[77,78] It shares marked sequence homology and structural similarities to the *ALK* oncogene.[78] ROS1 is susceptible to chromosomal rearrangements that can alter the protein function and lead to constitutive activation of downstream pathways such as mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)–Ak strain transforming (AKT)–mammalian target of rapamycin (mTOR)to promote carcinogenesis.[78,79]

ROS1 fusions account for approximately 2% of NSCLC cases.[79] Clinical and histologic features that are commonly associated with ROS1-positive NSCLC include adenocarcinoma histology, never smokers, and younger patients.[79] CD74 and SLC34A2 are among the most common ROS1 fusion partners in NSCLC, but others such as SDC4 and EZR have also been described.[77,78,80,81] Although important for detection of ROS1 fusions, fusion partners have not been associated

with differences in clinical outcome.[80–82] ROS1 fusion detection can be performed by FISH or NGS.[82,83] For NGS, RNA-based methods are preferred because of higher sensitivity for detecting genomic rearrangements with multiple fusion partners.[84,85]

Crizotinib was the first approved ROS1 fusion TKI. Two phase II trials for advanced NSCLC harboring ROS1 fusions showed crizotinib 250 mg orally (PO) twice a day (bid) led to an ORR of 72%, median duration of response (DoR) of 20 to 24.7 months, and median progression free survival (mPFS) of 16 to 19.3 months.[80,81,86] Long-term follow-up of the PROFILE 1001 trial (median follow-up, 62.6 month) showed that Median overall survival (mOS) was 51.4 months, and 12-, 24-, 36-, and 48-month OS were 79%, 67%, 53%, and 51%, respectively.[81] The most common side effects reported were visual impairment (87%), nausea (51%), edema (47%), diarrhea (45%), vomiting (38%), elevated liver function test (LFT) results (36%), constipation (34%), fatigue (21%), dysgeusia (19%), and dizziness (19%). A total of 94% of events were G1 to G2. Most common G3 toxicities were hypophosphatemia (15%), neutropenia (9%), vomiting (4%), and elevated LFT results (4%).[81]

Ceritinib was also tested for treatment of advanced NSCLC harboring ROS1 fusion in a Korean phase II trial (n = 32). Patients with stage IV ROS1 fusion NSCLC (6% pretreated with crizotinib and 94% treatment-naïve) received ceritinib 750 mg/day until disease progression. With a median follow-up period of 14 months, ORR was 62%, disease control rate (DCR) was 81%, mPFS was 9.3 months (crizotinib-naïve patients, 19.3 months), median DoR was 21 months, and median OS was 24 months. Intracranial disease control and ORR were 63% and 25%, respectively. Despite its efficacy, ceritinib showed high rates of G1 to G2 adverse events, including diarrhea (78%), nausea (59%), anorexia (56%), vomiting (53%), cough (47%), and muscle pain (41%), and the rate of G3 fatigue was 16%.[87]

The incidence of brain metastases in patients with newly diagnosed ROS1 fusion stage IV NSCLC ranges from 19% to 36%.[88,89] A retrospective analysis showed that CNS progression can be the first and sole site of disease progression in almost half of patients treated with crizotinib (47%).[88] This demonstrates that the blood–brain barrier can hamper crizotinib's intracranial penetration and lead to intracranial disease progression. Other than low intracranial concentration, emergence of resistance solvent-front mutations (SFMs) have been shown to account for approximately 64% of cases of extracranial disease progression to crizotinib,[89] with G2032R, D2033N, and S1986F being the most commonly reported.[89,90] These mutations impede drug binding and promote crizotinib resistance.[89] Because of low intracranial penetration and poor activity of crizotinib for resistance SFM, novel ROS1 fusion inhibitors are under clinical development.

In 2019, entrectinib, a dual ROS1-NTRK inhibitor, was approved for treatment of patients with advanced NSCLC harboring ROS1 fusion based on a pooled analysis of three trials (STARTRK-1, STARTRK-2, and ALKA-372-001).[82] Patients with locally advanced or metastatic TKI-naïve ROS1 fusion NSCLC treated with entrectinib 600 mg/day were included in the efficacy analysis. The majority of patients had adenocarcinoma histology, 43% had brain metastasis, and only 32% were treatment-naïve. At median follow-up period of 15.5 months, ORR was 77%, intracranial ORR was 55%, mPFS was 19 months, and duration of response was 24.6 months. Median PFS for patients with IC disease was 13.6 months, and intracranial duration of response was 12.9 months. Median OS was not reached with 82% of patients alive at 18 months. Almost all patients had tumor shrinkage, and response occurred early, usually on the first scan. The most common on-target side effects were dizziness (32%), weight gain (26%), paresthesias (17%), and cognitive changes (6%), which are a result of the potent anti– Tropomyosin receptor kinases A-C (TRKA-C) activity of entrectinib.[82] Because of a better safety profile and higher intracranial activity, we recommend entrectinib for frontline standard-of-care treatment of patients with ROS1 fusion NSCLC.

Lorlatinib, a potent ROS1-*ALK* inhibitor, was specifically developed for higher intracranial penetration[83] and is currently under clinical testing for treatment of patients with ROS1 fusion NSCLC. In a phase I/II trial, the efficacy of lorlatinib 100 mg/day for treatment of patients with ROS1 fusion advanced NSCLC was dependent on prior TKI exposure. For TKI-naïve and crizotinib-pretreated patients, ORRs were 62% and 35%, intracranial response rates were 64% and 50%, and median DoRs were 25.3 and 13.8 months, respectively. Intracranial DoR was not reached. Of the six patients harboring G2032R resistance SFM, none achieved partial response (PR), one had progressive disease (PD), and five had stable disease (SD) (range of SD duration, 2.9–9.6 months).[83]

Repotrectinib is a TKI targeting ROS1-NTRK-*ALK* that exhibits potent activity for inhibiting ROS1 fusion proteins harboring SFM.[90] Repotrectinib also compares favorably with other ROS1 targeting TKIs, such as entrectinib, lorlatinib, ceritinib, and crizotinib, for targeting ROS1 harboring SFM in cell line models.[90] In a preliminary analysis of the dose-escalation part of the phase I/II TRIDENT-1 trial (NCT03093116), patients with TKI-naïve ROS1 fusion treated with repotrectinib (n = 10) had an ORR of 80% and an intracranial ORR of 100%. TKI pretreated patients (n = 17; majority pretreated with crizotinib) had an ORR of 18% and an intracranial ORR of 25%. Of the four patients harboring ROS1 G2032R SFM, three had SD, and one achieved PR.[91] This trial is ongoing to determine the recommended phase II dose, which will allow a better understanding of the efficacy of this agent.

Non–ROS1-mediated resistance remains poorly understood, and no directed therapies are available in this setting. ROS1 fusion NSCLC has low tumor mutational burden,[92] and although data are limited, small benefit from treatment with single-agent PD-1 and PD-L1 inhibitors has been seen (ORR, 17%; PD within 2 months of starting treatment, 43%).[76] Even in the presence of positive (≥1%) or high-positive (≥50%) PD-L1 expression, we do not recommend treatment with single-agent PD-1/PD-L1 inhibitors. Therefore, after exhaustion of targeted therapies, we recommend combination treatment with a platinum doublet plus a PD-1/PD-L1 inhibitor (triple therapy)[93] with or without bevacizumab (quadruple therapy).[41]

BRAF MUTATIONS

BRAF is a proto-oncogene located on the long arm of chromosome 7. The BRAF gene encodes a serine/threonine protein kinase named BRAF, which is a part of the MAPK pathway and a key driver of cell proliferation and growth.[94] Despite being enriched in melanoma,[95] BRAF mutations occur in approximately 4% of NSCLC cases and are usually found in ever smokers.[96–100] BRAF mutations have been previously classified as V600 and non-V600, but in recent years, a better understanding of the non-V600 mutations has allowed further classification of the BRAF mutations into three classes: 1, 2, and 3.[94] Class 1 mutations correspond to V600 mutations, of which V600E is the most common. Class 1 mutations promote RAS-independent constitutive activity of BRAF in the form of a monomer.[101–104] Class 2 BRAF mutations are also RAS-independent constitutively active kinases, but contrary to class 1 mutations, they promote downstream signaling in the form of BRAF homodimers.[94,101] BRAF class 2 mutations are further subcategorized into three groups: a, b, and c.[101] Class 2a refers to mutations located in the activation segment of BRAF and include the K601, L597, and E586 loci.[101] Class 2b refers to mutations located in the glycine-rich P-loop and generally includes the G464 and G469 loci.[101] Class 2c includes BRAF fusions, where coupling of the C-terminal kinase domain with the N-terminal dimerization domain leads to constitutive dimerization and activation of BRAF.[94] It also includes in-frame deletions that remove about five amino acids near the β3–αC region of the BRAF kinase and switch the α-C helix to an activated conformational state to promote dimerization and downstream signaling.[94] BRAF class 3 mutations are RAS-dependent kinase impaired mutations that promote downstream signaling in the form of heterodimers with wild-type RAF (eg, C-RAF). This commonly co-occurs because of additional RAS signaling either through activating RAS mutations or NF1 loss-of-function alterations.[102,103]

Currently, only BRAF class 1 V600E mutations have FDA-approved targeted therapies in NSCLC. Vemurafenib, an anti-BRAF targeting TKI, showed an ORR of 37% to 42%, mPFS of 6.5 to 7.3 months, and median OS of 15.4 months for treatment of patients with NSCLC harboring BRAF V600E mutations.[105,106] The combination of MAPK/ERK Kinase (MEK) inhibitor trametinib and BRAF inhibitor dabrafenib has shown an ORR of 63% to 64%, mPFS of 9.7 to 10.9 months, and median duration of response (mDoR) of 9.0 to 10.4 months in the frontline and salvage settings for BRAF V600E mutant NSCLC.[107,108] Noteworthy, G1and G2 side effects from this combination include pyrexia (44%–53%), nausea (40%–56%), diarrhea (32%–33%), peripheral edema (23%–36%), and skin rash (19%).[107,108] Other side effects of interest include skin squamous cell carcinoma (4%), decreased left ventricle ejection fraction (G3, 6%) and ocular toxicity, which includes conjunctivitis (2.8%–8.9%), uveitis (4%), retinal vein occlusion (0.2%), and serous retinopathy (3%–26%).[107–112]

Mechanisms of resistance to single-agent BRAF inhibitor are better understood than for BRAF-MEK inhibitor combinations. Resistance to BRAF inhibitors can develop through reactivation of downstream signaling of the MAPK pathway by acquired BRAF V600E splice site alterations,[113] C-RAF mutations,[114] and NRAS/MEK mutations.[115] Because of this, novel treatment strategies for overcoming resistance include additional downstream inhibition of the MAPK pathway, such as with ERK inhibitors (eg, ulixertinib, LTT462). Another approach is novel BRAF inhibitors that have dimer inhibition activity (eg, LXH254, fili-rafenib). These compounds are currently undergoing clinical investigation. Clinical trial enrollment is recommended and warranted for this population.

There are currently no approved targeted therapies for lung cancers harboring BRAF class 2 and 3 mutations. Similar to investigational approaches for targeting resistance in BRAF V600E mutant tumors, BRAF dimer inhibitors, MEK inhibitors, ERK inhibitors, and SHP2 inhibitors are undergoing clinical development either as single agents or as combination regimens. This is based on preclinical or early clinical data suggesting that non-V600 mutations may be sensitive to these agents.[116–120] Therefore, clinical trial enrollment is encouraged and recommended for this population.

Recent retrospective data from our group and others have shown that advanced NSCLC harboring BRAF mutations may be more susceptible to PD-1/PD-L1 checkpoint blockade compared with other oncogene-driven NSCLC, yielding better ORR and mPFS.[121,122] In addition, high ORR and prolonged PFS have been reported for phase I/II trials combining BRAF and MEK inhibitors with PD-1/PD-L1 blockade in metastatic melanomas harboring BRAF V600 mutations. These findings are based on preclinical data suggesting that

BRAF and MEK inhibition can enhance antitumor immunity and have synergistic effect with immune checkpoint inhibitors by promoting immunogenic cell death[123] and increased T-cell infiltration and activation in the tumor microenvironment.[124,125] Phase III trials testing TKI plus immune checkpoint blockade combinations in metastatic melanoma are expected to read out soon. If positive results emerge, it is likely that a similar approach will be studied in NSCLC as well.

For patients with advanced NSCLC whose tumors harbor a BRAF V600E mutation, we recommend frontline treatment with dabrafenib and trametinib as standard of care. Upon progression, our approach is to recommend treatment with a chemotherapy-immunotherapy backbone, such as carboplatin, pemetrexed, and pembrolizumab, or an immunotherapy combination with nivolumab and ipilimumab. For other BRAF mutations, we recommend frontline chemoimmunotherapy or nivolumab–ipilimumab combinations because of a lack of prospective clinical data showing efficacy of MEK+/-BRAF inhibitor in this population. Clinical trial enrollment is encouraged for all patients with NSCLC harboring class 1, 2, and 3 BRAF mutations and for patients with NSCLC harboring BRAF class 1 V600E mutations that have become resistant to BRAF+/-MEK inhibitors.

MET ALTERATIONS

MET is a proto-oncogene that codes for the tyrosine kinase hepatocyte growth factor receptor. It is located in the long arm of chromosome 7 at position 31.2. Two types of genetic alterations are described for MET oncogenesis: exon 14 skipping mutations and amplification.

MET exon 14 skipping mutations are oncogenic drivers in 3% to 4% of NSCLCs and 8% to 32% of sarcomatoid lung carcinomas.[126] These alterations are typically enriched in patients with older age.[127] Exon 14 encodes a juxtamembrane region of the MET protein receptor that harbors a CBL E3 ubiquitin ligase binding site, Y1003, and loss of this site impairs ubiquitin-mediated degradation of the MET receptor. This leads to decreased turnover of MET and increases MET signaling through the MAPK and PI3K pathways to drive oncogenesis.[10,128] Diverse mutational mechanisms such as point mutations, insertion and deletions, and large deletions are involved. They can disrupt distinct splicing sites flanking exon 14 and lead to exclusion of this exonic region at the RNA level[128,129] or promote deleterious alterations in the Y1003 locus within exon 14.[130] Tissue RNA-based NGS assays are preferred for detecting MET exon 14 skipping mutations because of previous reports showing a 36% false-negative rate for DNA-based assays.[131,132] However, caution is warranted because RNA-based assays rely on the quality of the RNA extracted from tumor tissue.[131] NGS blood-based assays for circulating tumor DNA (ctDNA) detection can also be used and represent an important tool for detecting MET exon 14 skipping mutations both for clinical trial enrollment and for standard clinical practice.[10]

The TKI crizotinib has shown activity for treatment of patients with advanced NSCLC harboring MET exon 14 skipping mutations in an expansion cohort of the PROFILE 1001 trial (n = 69 patients). Treatment with crizotinib led to an ORR of 32%, median DoR of 9.1 months, and mPFS of 7.3 months.[129] Although crizotinib is not approved by the FDA, it is supported by the NCCN guidelines, which recommend treatment with crizotinib for patients with advanced NSCLC harboring a MET exon 14 skipping mutation (NCCN.org). This is further supported by retrospective data suggesting that patients with NSCLC harboring MET exon 14 skipping mutation treated with a targeted agent have longer mOS (24.6 months) compared with patients who never received a MET TKI (8.1 months; hazard ratio, 0.1; 95% C,I 0.0–0.9; P = .04).[133]

Currently, three novel MET TKIs are in clinical development: capmatinib, tepotinib, and savolitinib. These three compounds have shown more potent activity in preclinical models compared with crizotinib (half maximal inhibitory concentration (IC50) 0.6–3.0nM vs 22.5 nM).[134] In addition, capmatinib, tepotinib, and savolitinib have shown activity in NSCLC harboring MET exon 14 skipping mutations in treatment-naïve and previously treated patients.[10,126,134–136] Table 25–3 summarizes the current findings for TKIs targeting MET exon 14 skipping mutations. Capmatinib 400 mg PO bid recently received FDA Accelerated Approval and is now standard of care for advanced NSCLC harboring MET exon 14 skipping mutations. Tepotinib 500 mg PO daily has also received U.S. FDA Breakthrough Therapy Designation for this same indication and is currently under evaluation.

The two most common side effects of MET TKIs are peripheral edema (36.6%–63.0%) and nausea (26%–48.8%), but grade 3 to 4 events of these toxicities were reported in 1% to 7.5% of patients. Other common side effects include increased LFT results (7%–31.7%), diarrhea (11.4%–22%), vomiting (6%–31.7%), increased creatinine (18%–19.5%), hypoalbuminemia (16%–19.5%), pyrexia (24.4%), anemia (17.1%), and decreased appetite (8%–17.1%). Upper abdominal pain and fatigue can also occur in approximately 5% and 7% to 13.8% of patients, respectively. Pneumonitis was an uncommon event (1.5%).[10,134,135]

Mechanisms of acquired resistance to MET TKIs remain poorly understood. Preliminary data suggest both on-target (eg, secondary MET mutations, MET

TABLE 25-3 Efficacy Results for Tyrosine Kinase Inhibitors Targeting MET Exon 14 Alterations in Patients with Non–Small Cell Lung Cancer

	Capmatinib		Tepotinib	Savolitinib	Crizotinib
	Treatment-Naïve (*n* = 28)	Previously Treated (*n* = 69)	(*n* = 99)	(*n* = 70)	(*n* = 69)
ORR (%)	67.9	40.6	46.5	42.9	32
DCR (%)	96.4	78.3	65.7	82.9	78
mDoR (mo)	11.1	9.7	11.1	9.6	9.1
mPFS (mo)	9.7	5.4	8.5	6.9	7.3
Intracranial disease (*n*)	13		11	NA	NA
Intracranial ORR (%)	54		55	NA	NA

DCR, disease control rate; mDoR, median duration of response; MET, mesenchymal-epithelial transition; mPFS, median progression free survival; NA, not available; ORR, objective response rate.

amplification) and off-target bypass-pathway mediated resistance (eg, RAS and PI3K pathway activation, EGFR amplification), but in up to 50% of the cases, the mechanism(s) of resistance are unknown.[10,130,137,138]

Upon progression with MET TKIs, treatment options include chemotherapy, immunotherapy, or both. Clinical benefit from single-agent or combination immune checkpoint inhibition is modest for treatment of patients with NSCLC harboring MET exon 14 skipping mutations. In a small retrospective cohort, ORR was 17%, and mPFS 1.9 was months.[139] Therefore, we recommend combination treatment with PD-1/PD-L1 inhibitor plus platinum doublet chemotherapy with or without bevacizumab (triple or quadruple therapy)[41,93] as standard of care for patients with NSCLC harboring MET exon 14 skipping mutations that progress on MET TKI as long as performance status and clinical condition allow for it. Clinical trial enrollment, if feasible, is warranted for further drug development in this space. One example is Sym015, which consists of an antibody mixture targeting two nonoverlapping sites in the MET extracellular domain.[140] Sym015 has shown early signs of activity in NSCLC previously treated with MET targeting agents (*n* = 9), including DCR of 56%, PFS of 5.4 months, and DoR of 6.5 months.[141]

MET amplification occurs in 1% to 4% of NSCLCs[142,143] and is a poor prognosis biomarker.[143] It is important to differentiate amplification (true gene focal copy number gain) from high polysomy. For MET amplification, this has been defined through FISH as an increase in the ratio of MET gene copy number gain relative to centromere 7 (CEP7).[144] Commercially available NGS assays use copy number callers to distinguish high polysomy from true copy number gain amplification. However, it remains unclear what is the optimal definition of NGS copy number gain to predict benefit from targeted therapies. Real-time quantitative polymerase chain reaction (RT-qPCR) is also currently used to select patients for clinical trial enrollment.[141]

Treatment strategies under investigation for patients with MET-amplified or -overexpressing tumors include TKIs, monoclonal antibodies, and antibody–drug conjugates. In part 2 of the A8081001 trial, 14 patients with MET amplification, defined as a MET-to-CEP7 ratio of 1.8 or greater, were treated with crizotinib (TKI). Confirmed ORR with crizotinib was dependent on the level of MET amplification: low (MET-to-CEP7 ratio, 1.8–2.2; ORR, 0%), intermediate (MET-to-CEP7 ratio, 2.3-4.9; ORR, 17%), and high (MET-to-CEP7 ratio, ≥5.0; ORR, 67%).[144] In addition, the GEOMETRY-1 study evaluated capmatinib (TKI) in previously treated (cohort 1a: *n* = 69) and treatment-naïve (cohort 5a: *n* = 15) MET-amplified (defined as gene copy number ≥10) advanced NSCLC. ORRs were 40% and 29%, and DCRs were 66.7% and 71% for treatment-naïve and previously treated cohorts, respectively. Median DoR was 7.5 to 8.3 months, and mPFS was 4.1 to 4.2 months.[145] Other MET TKIs are currently under investigation. In a phase I trial, the antibody drug–conjugate telisotuzumab vedotin (ABBV-399) showed an ORR of 18.8%, mDoR of 4.8 months, and mPFS of 5.7 months for treatment of patients with NSCLC with MET overexpression (*n* = 16) as defined by an IHC H-score of 150 or greater.[146] In a dose-escalation phase I trial, the monoclonal antibody Sym015 also showed activity in MET-amplified (defined as ISH MET-to-CEP7 ratio ≥2.2 or NGS/qPCR >5 copies) treatment-naïve NSCLC (*n* = 7) with an ORR of 40%, DCR of 100%, mPFS of 5.5 months, and mDOR of 18.4 months.[141] Because of these promising novel compounds, clinical trial enrollment, if feasible, is encouraged for patients with MET-amplified NSCLC.

HER2 MUTATIONS

Human epidermal growth factor receptor 2 (HER2/ERBB2) is an HER/ERBB family receptor tyrosine kinase. HER2 mutations occur in approximately 1.5% of lung adenocarcinomas.[147] The most frequent HER2 mutations in lung cancer occur in exon 20 with the Y772dupYVMA mutation involving 34% of all HER2 mutations.[147] Point mutations, such as L755X and V777L, have also been detected in NSCLC. Targeting HER2 mutations remain an unmet clinical need in which TKIs and HER2 monoclonal antibodies are currently being tested.

Trastuzumab deruxtecan (t-DxD) is a novel antibody–drug conjugate that was tested in a phase 2 trial that enrolled 42 patients with HER2-mutant NSCLC. The ORR was 61.9% with a PFS of 14 months.[148] In a smaller study of 18 patients, ado-trastuzumab emtansine (also known as T-DM1), another antibody–drug conjugate, resulted in an ORR of 44%.[149] The combination of trastuzumab and pertuzumab yielded an ORR of 21% when tested in a cohort of 36 patients.[150]

Numerous TKIs are under development in this setting. Pyrotinib resulted in an ORR of 32% with a duration of response of 7 months in patients with HER2 exon 20 mutant NSCLC.[151] Afatinib, dacomitinib, and neratinib have limited clinical activity in this setting.[152–154] Other TKIs in clinical testing include poziotinib[147] and mobocertinib (TAK-788).

RET FUSIONS

The RET receptor tyrosine kinase is oncogenically activated by chromosomal rearrangements producing RET gene fusions in 1% to 2% of patients with NSCLC.[155] Several multikinase inhibitors with some degree of anti-RET activity demonstrated modest activity in RET fusion–positive lung cancer in phase 2 studies.[156–158] In a retrospective registry study of 165 patients with RET-positive NSCLC, the response rates to cabozantinib, vandetanib, and sunitinib were 37%, 18%, and 22%, respectively.[159]

Selpercatinib is a highly potent and specific small-molecule inhibitor of the RET kinase, with minimal inhibition of other kinase and nonkinase targets. In a phase II study that enrolled 105 patients with RET-positive NSCLC with prior treatment with platinum-based chemotherapy, selpercatinib resulted in a response rate of 68%. Median DoR was 18 months, and median PFS was 17 months.[160,161] Selpercatinib has received approval from the U.S. FDA for patients with RET fusion–positive advanced NSCLC. Selpercatinib is generally well tolerated. The most common treatment-related adverse events (TRAEs) were dry mouth (33.3%), increased aspartate aminotransferase (AST; 24.5%, increased alanine aminotransferase (ALT; 23.8%), hypertension (23.2%), diarrhea (19.7%), and fatigue (16.8%). Only 2% (14 of 702) of patients discontinued selpercatinib because of TRAEs.[161]

Pralsetinib (BLU-667) is a highly potent and selective RET inhibitor targeting oncogenic RET alterations, including those that confer resistance to multikinase inhibitors.[11] The Arrow study is a phase 1/2 trial evaluating pralsetinib in RET fusion–positive advanced tumors. The ORRs in previously untreated and platinum-pretreated patients with NSCLC were 61% and 73%, respectively.[162]

Emerging data suggest that both selpercatinib and pralsetinib have potent intracranial activity. In patients with baseline measurable CNS disease (selpercatinib, 22 patients; pralsetinib, nine patients), the intracranial ORRs were 81.8% and 56%, respectively.[162,163]

NTRK FUSIONS

The tropomyosin receptor kinase (TRK) family includes three transmembrane receptor proteins: TRKA, encoded by NTRK1, which is located in the long arm of chromosome 1; TRKB, encoded by NTRK2, which is located in the long arm of chromosome 9; and TRKC, which is located in the long arm of chromosome 15.[164,165] TRK receptors have tyrosine kinase activity and are activated by binding with the neurotrophins nerve growth factor, brain-derived neurotrophic factor, and NT-3/4/5.[164] After activation, these receptors promote downstream signaling through the MAPK and PI3K-AKT pathways to promote increased proliferation, cellular growth, and survival.[164] These receptors are expressed in neuronal tissue and are particularly important for nervous system development during embryogenesis.[165] After birth, these receptors continue to be primarily expressed in neuronal tissue and modulate sensory perception (eg, pain, proprioception), body weight, and memory.[165]

TRK can become an oncogenic driver by intra- or interchromosomal rearrangements. This occurs when the TRK tyrosine kinase domain 3¢ terminal is joined by a 5¢ sequence partner to generate a fusion protein that is constitutively activated or overexpressed[164] and promotes continues downstream signaling. Currently, several fusion partners have been detected for NTRK, such as CD74, TPM3, and ETV6.[164,166] Although NTRK fusions can occur in all three NTRK genes, NTRK1 and NTRK3 are the most commonly affected.[167,168] In NSCLC, NTRK fusions are rare oncogenic drivers and occur in approximately 0.2% of adenocarcinomas.[169]

The test of choice for detecting NTRK fusion is NGS with an RNA-based method.[169] Because of the diversity of fusion partners and the need to cover all three NTRK genes, FISH requires large amounts of tissue to

test all necessary probes. IHC has shown lower sensitivity compared with RNA NGS for detecting NTRK fusions[169] likely because of limitations related to staining intensity and location and the tumors site of origin. Because NTRK are rare drivers, NGS allows for testing of several gene fusions, simultaneously decreasing the need for specific NTRK testing, contrary to IHC and FISH. NGS RNA-based methods are also preferred compared with DNA NGS-based methods because of higher sensitivity[169] due to diversity of fusion partners and inaccuracy for detecting truly activating fusions, which are those that include the entire TRK tyrosine kinase domain.

Currently, two TKIs are approved for treatment of patients with solid tumors, including NSCLC, harboring TRK fusions: larotrectinib and entrectinib. In a pooled analysis of three phase 1/2 trials including 159 patients with solid tumors harboring a NTRK fusion, larotrectinib showed an ORR of 79%, mDOR of 35.2 months, and mPFS of 28.3 months.[170] For patients with NSCLC (n = 12), ORR was 75%, and mDOR was not reached.[170] Three patients had measurable intracranial disease with two achieving intracranial response. Most common G1 to G2 toxicities were fatigue (30%), ALT or AST increase (24%–25%), cough (27%), constipation (27%), diarrhea (23%), nausea or vomiting (24%), and dizziness (25%).[170] Most common G3 to G4 toxicities were anemia (10%) and decreased neutrophil count (5%), and no treatment-related deaths were reported.[170] Similarly, the efficacy of entrectinib for treatment of patients with solid tumors harboring NTRK fusions was also evaluated in a pooled analysis of three phase 1 or 2 trials.[168] For the 54 patients evaluated, ORR was 57%, mDoR was 10 months, and mPFS was 11 months.[168] For the NSCLC population (n = 10), ORR was 70%.[168] Twelve patients had baseline intracranial disease, and of them, intracranial ORR was 50%, and intracranial DCR was 83%. Median time to CNS progression was 17 months.[168] Most common G1 to G2 adverse events included dysgeusia (47%), constipation (28%), fatigue (28%), diarrhea (27%), peripheral edema (24%), and dizziness (24%). Most common G3 and G4 adverse events included anemia (12%), weight increase (10%), and fatigue (7%).[168] Of note, additional reported on-target adverse events included peripheral sensory neuropathy (8%), disturbance in attention (4%), hyperesthesia (3%), ataxia (3%), and diplopia (4%). Congestive heart failure was reported in 2% of patients.[168] In light of these results, we recommend frontline treatment with larotrectinib or entrectinib for patients with NSCLC harboring NTRK fusions.

Resistance to NTRK inhibitors can be on target through NTRK mutations or off target by activation of bypass or downstream pathways. On-target NTRK mutations typically occur in the TRK kinase domain and hamper drug binding. Examples include NTRK1 G595R and G667C, NTRK2 G639R, and NTRK3 G623R and G623E mutations.[90,171,172] Currently, two novel TRK inhibitors are undergoing clinical testing to overcome resistance in the presence of these on-target mutations: LOXO-195 and repotrectinib. Both agents have shown high activity in preclinical models harboring NTRK resistance mutations, and both have shown early signs of clinical activity by inducing responses in patients with tumors harboring NTRK1 G595R, NTRK3 G623E, and NTRK3 G623R mutations.[90,173] Preliminary results of a phase I trial evaluating LOXO-195 (NCT03215511) for treatment of patients whose tumors had progressed or had become intolerant to TRK TKIs showed impressive activity of this compound with ORR ranging from 25% to 50% depending on the location of the acquired NTRK resistance mutation.[174]

Integrated preclinical and clinical work with patient-derived cell lines, mouse xenograft models, and paired blood molecular profiling suggests that activation of bypass pathways, such as MAPK through BRAF and KRAS mutations and MET amplification and overexpression, can drive off-target resistance to TRK TKIs.[175] In addition, targeting these pathways with BRAF/MEK inhibitors or MET inhibitors showed activity for overcoming resistance in these cases.[175]

In the setting of disease progression on entrectinib or larotrectinib, we recommend repeat molecular profiling through either blood or tissue-based assays and enrollment or referral for enrollment in clinical trials designed for NTRK fusion tumors that have developed resistance to TRK targeting TKIs.

NRG1 FUSIONS

Neuregulins (NRGs) are signaling proteins that mediate cell–cell interactions in the nervous system, heart, and breast.[176] NRG-producing cells bind to the extracellular domain of the receptor tyrosine kinases ERBB3 and ERBB4 of the NRG-responsive cells to promote ERBB homo- and heterodimerization.[176–178] This activates intracellular pathways, such as PI3K-AKT and MAPK, which regulate proliferation, apoptosis, migration, differentiation, and adhesion.[176,178]

The *NRG1* gene is located on the short arm of chromosome 8.[176] NRG1 proteins and isoforms have an extracellular EGF-like domain that induces activation of ERBB tyrosine kinase receptors.[178] Most NRG1 isoforms undergo proteolytic cleavage and release of the EGF-like domain, with the exception of type III, which has a membrane-tethered EGF-like domain that restricts signaling to cell–cell interactions.[177,178]

NRG1 fusions promote expression of NRG1 III-β3 on the cancer cell surface. This leads to ERBB3

binding and activation, which in turn dimerizes with other ERBB tyrosine kinase receptors. This promotes autocrine, paracrine, and juxtacrine activation of PI3K-AKT and MAPK pathways and ultimately leads to cell growth and oncogenesis.[85,177,178] NRG1 fusions are present in 0.2% of cancers and 0.3% of NSCLCs, making NSCLC the most common histology for these alterations (61%).[84,179] Currently, 17 fusion partners have been identified for NRG1, but CD74 (47%), SLC3A2 (16%), and SDC4 (7%) are the three most common in NSCLC.[84] NRG1 fusions are enriched in invasive mucinous adenocarcinomas (27%–31% of cases) and are often mutually exclusive from KRAS, another driver known to be enriched in this histologic subtype.[84,85,180] Because the DNA rearrangements that generate NRG1 fusions typically occur in two large intronic regions and because the fusion partners are diverse and incomplete characterized, RNA sequencing is favored compared with DNA sequencing for detecting these alterations.[84,85] FISH for NRG1 and IHC for p-ERBB3 are alternatives for NRG1 fusion detection.[84,177,180]

There are currently no approved therapies for patients with NSCLC harboring NRG1 fusions. Responses have been reported with the pan-HER family inhibitor afatinib (DoR, 6–12 months) and with the anti-ERBB3 monoclonal antibody GSK2849330 (DoR, 19 months).[84,85,181] Several agents capable of inhibiting ERBB3, both TKI and monoclonal antibodies, are under investigation for treatment of patients with NRG1 fusion–positive NSCLC (seribantumab [MM-121]; zenocutuzumab [MCLA-128] [NCT04100694; NCT02912949]; GSK2849330). Therefore, enrollment in clinical trials is recommended for these patients.

CONCLUSION

The past decade has seen remarkable progress in the lung cancer field with novel actionable mutations and development of increasingly more effective targeted therapies. However, the universal development of resistance focuses research efforts in this arena.

There is also excitement in the field for targeting driver oncogenes that were previously untargetable, and we look forward to novel compounds in this regard. One example of this is KRAS with several G12C inhibitors under clinical development. Efforts are also being made toward targeting tumor suppressor genes. Despite a current lack of approved therapies in this setting, novel treatment strategies are under investigation. Examples include STK11, KEAP1, and TP53. Although not as straightforward as targeting oncogene driver alterations, we believe the field is making important progress, and we look forward to results of upcoming clinical trials in this setting.

MD ANDERSON CANCER CENTER PRACTICE TIPS

- Use broad genomic profiling for all NSCLC using tumor tissue and cfDNA irrespective of tobacco exposure history. NSCLC should be tested at least for EGFR, *ALK*, ROS1, RET, MET, BRAF, and NTRK.
- If a patient requires start of systemic therapy before genomic profiling results become available, consider starting cytotoxic chemotherapy only for the first cycle. If the patient's tumor is found to harbor a targetable oncogene alteration, this will prevent overlapping toxicities from targeted therapy and immune checkpoint inhibition, such as pneumonitis and hepatitis, when changing treatment to targeted therapy in the subsequent 2 to 3 weeks.
- Always consider clinical trial enrollment if feasible and safe for the patient.
- In patients with oligometastatic disease, consider local consolidation therapy (LCT) with surgery or radiation at the time of best response. LCT should also be considered for patients with oligoprogressive disease along with continuing targeted therapy.
- Tumor biopsy and cfDNA testing should be obtained to identify acquired resistance mechanisms. Clinical trials of novel targeted agents and rationale combinations should be considered based on molecular profiling results.

REFERENCES

1. Lindeman NI, Cagle PT, Aisner DL, et al. Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors: guideline from the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. *J Mol Diagn*. 2018;20:129-159.
2. Leighl NB, Rekhtman N, Biermann WA, et al. Molecular testing for selection of patients with lung cancer for epidermal growth factor receptor and anaplastic lymphoma kinase tyrosine kinase inhibitors: American Society of Clinical Oncology endorsement of the College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology guideline. *J Clin Oncol*. 2014;32:3673-3679.
3. Revelo AE, Martin A, Velasquez R, et al. Liquid biopsy for lung cancers: an update on recent developments. *Ann Transl Med*. 2019;7:349.
4. Sacher AG, Paweletz C, Dahlberg SE, et al. Prospective validation of rapid plasma genotyping for the detection of EGFR and kras mutations in advanced lung cancer. *JAMA Oncol*. 2016;2:1014-1022.
5. Oxnard GR, Thress KS, Alden RS, et al. Association between plasma genotyping and outcomes of treatment with osimertinib (AZD9291) in advanced non-small-cell lung cancer. *J Clin Oncol*. 2016;34:3375-3382.
6. Jenkins S, Yang JC-H, Ramalingam SS, et al. Plasma ctDNA analysis for detection of the EGFR T790M mutation in patients with advanced non-small cell lung cancer. *J Thorac Oncol*. 2017;12:1061-1070.
7. Newman AM, Bratman SV, To J, et al. An ultrasensitive method for quantitating circulating tumor DNA with broad patient coverage. *Nat Med*. 2014;20:548-554.
8. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med*. 2018;378:113-125.
9. McCoach CE, Blakely CM, Banks KC, et al. Clinical utility of cell-free DNA for the detection of ALK fusions and genomic mechanisms of ALK inhibitor resistance in non-small cell lung cancer. *Clin Cancer Res*. 2018;24:2758-2770.
10. Paik PK, Felip E, Veillon R, et al. Tepotinib in non-small-cell lung cancer with MET exon 14 skipping mutations. *N Engl J Med*. 2020;1-13.
11. Subbiah V, Gainor JF, Rahal R, et al. Precision targeted therapy with BLU-667 for RET-driven cancers. *Cancer Discov*. 2018;8:836-849.
12. Leighl NB, Page RD, Raymond VM, et al. Clinical utility of comprehensive cell-free DNA analysis to identify genomic biomarkers in patients with newly diagnosed metastatic non-small cell lung cancer. *Clin Cancer Res*. 2019;25(15):4691-4700.
13. Cataldo VD, Gibbons DL, Pérez-Soler R, et al. Treatment of non-small-cell lung cancer with erlotinib or gefitinib. *N Engl J Med*. 2011;364:947-955.
14. Wieduwilt MJ, Moasser MM. The epidermal growth factor receptor family: biology driving targeted therapeutics. *Cell Mol Life Sci*. 2008;65:1566-1584.
15. Scaltriti M, Baselga J. The epidermal growth factor receptor pathway: a model for targeted therapy. *Clin Cancer Res*. 2006;12:5268-5272.
16. Wee P, Wang Z. Epidermal growth factor receptor cell proliferation signaling pathways. *Cancers (Basel)*. 2017;9(5):52.
17. Kawaguchi T, Koh Y, Ando M, et al. Prospective analysis of oncogenic driver mutations and environmental factors: Japan Molecular Epidemiology for Lung Cancer Study. *J Clin Oncol*. 2016;34:2247-2257.
18. Leduc C, Merlio JP, Besse B, et al. Clinical and molecular characteristics of non-small-cell lung cancer (NSCLC) harboring EGFR mutation: results of the nationwide French Cooperative Thoracic Intergroup (IFCT) program. *Ann Oncol*. 2017;28:2715-2724.
19. Fukuoka M, Wu YL, Thongprasert S, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). *J Clin Oncol*. 2011;29:2866-2874.
20. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009;361:947-957.
21. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2012;13:239-246.
22. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol*. 2013;31:3327-3334.
23. Wu YL, Zhou C, Liam CK, et al. First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study. *Ann Oncol*. 2015;26:1883-1889.
24. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol*. 2011;12:735-742.
25. Zhou C, Wu YL, Chen G, et al. Final overall survival results from a randomised, phase III study of erlotinib versus chemotherapy as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer (OPTIMAL, CTONG-0802). *Ann Oncol*. 2015;26:1877-1883.
26. Wu YL, Cheng Y, Zhou X, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017;18:1454-1466.
27. Le X, Puri S, Negrao MV, et al. Landscape of EGFR-dependent and -independent resistance mechanisms to osimertinib and continuation therapy beyond progression in EGFR-mutant NSCLC. *Clin Cancer Res*. 2018;24(24):6195-6203.
28. Piotrowska Z, Isozaki H, Lennerz JK, et al. Landscape of acquired resistance to osimertinib in EGFR-mutant NSCLC and clinical validation of combined EGFR and RET inhibition with osimertinib and BLU-667 for acquired RET fusion. *Cancer Discov*. 2018;8:1529-1539.
29. Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med*. 2011;3:75ra26.
30. Taniguchi H, Yamada T, Wang R, et al. AXL confers intrinsic resistance to osimertinib and advances the emergence of tolerant cells. *Nat Commun*. 2019;10:259.
31. Yang Z, Yang N, Ou Q, et al. Investigating novel resistance mechanisms to third-generation EGFR tyrosine kinase inhibitor osimertinib in non-small cell lung cancer patients. *Clin Cancer Res*. 2018;24:3097-3107.
32. Kobayashi S, Boggon TJ, Dayaram T, et al. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2005;352:786-792.
33. Oxnard GR, Arcila ME, Sima CS, et al. Acquired resistance to EGFR tyrosine kinase inhibitors in EGFR-mutant lung cancer: distinct natural history of patients with tumors harboring the T790M mutation. *Clin Cancer Res*. 2011;17:1616-1622.

34. Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res*. 2013;19:2240-2247.
35. Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med*. 2017;376:629-640.
36. Takeda M, Okamoto I, Nakagawa K. Pooled safety analysis of EGFR-TKI treatment for EGFR mutation-positive non-small cell lung cancer. *Lung Cancer*. 2015;88:74-79.
37. Van Doorn R, Kirtschig G, Scheffer E, et al. Follicular and epidermal alterations in patients treated with ZD1839 (Iressa), an inhibitor of the epidermal growth factor receptor. *Br J Dermatol*. 2002;147:598-601.
38. Goss G, Tsai CM, Shepherd FA, et al. Osimertinib for pretreated EGFR Thr790Met-positive advanced non-small-cell lung cancer (AURA2): a multicentre, open-label, single-arm, phase 2 study. *Lancet Oncol*. 2016;17:1643-1652.
39. Cross DAE, Ashton SE, Ghiorghiu S, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. *Cancer Discov*. 2014;4:1046-1061.
40. Greenhalgh J, Dwan K, Boland A, et al. First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous non-small cell lung cancer. *Cochrane Database Syst Rev*. 2016;(5):CD010383.
41. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med*. 2018;378:2288-2301.
42. Kobayashi Y, Togashi Y, Yatabe Y, et al. EGFR Exon 18 mutations in lung cancer: molecular predictors of augmented sensitivity to afatinib or neratinib as compared with first- or third-generation TKIs. *Clin Cancer Res*. 2015;21:5305-5313.
43. Klughammer B, Brugger W, Cappuzzo F, et al. Examining treatment outcomes with erlotinib in patients with advanced non-small cell lung cancer whose tumors harbor uncommon EGFR mutations. *J Thorac Oncol*. 2016;11:545-555.
44. Russo A, Franchina T, Ricciardi G, et al. Heterogeneous responses to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in patients with uncommon egfr mutations: new insights and future perspectives in this complex clinical scenario. *Int J Mol Sci*. 2019;20(6):1431.
45. Arcila ME, Nafa K, Chaft JE, et al. EGFR exon 20 insertion mutations in lung adenocarcinomas: prevalence, molecular heterogeneity, and clinicopathologic characteristics. *Mol Cancer Ther*. 2013;12:220-229.
46. Yasuda H, Kobayashi S, Costa DB. EGFR exon 20 insertion mutations in non-small-cell lung cancer: preclinical data and clinical implications. *Lancet Oncol*. 2012;13:e23-e31.
47. Robichaux JP, Elamin YY, Tan Z, et al. Mechanisms and clinical activity of an EGFR and HER2 exon 20-selective kinase inhibitor in non-small cell lung cancer. *Nat Med*. 2018;24:638-646.
48. Yang JC, Sequist L V, Geater SL, et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. *Lancet Oncol*. 2015;16:830-838.
49. Cho JH, Lim SH, An HJ, et al. Osimertinib for patients with non-small-cell lung cancer harboring uncommon EGFR mutations: a multicenter, open-label, phase II trial (KCSG-LU15-09). *J Clin Oncol*. 2020;38:488-495.
50. Takahashi T, Sonobe M, Kobayashi M, et al. Clinicopathologic features of non-small-cell lung cancer with EML4-ALK fusion gene. *Ann Surg Oncol*. 2010;17:889-897.
51. Wang Y, Wang S, Xu S, et al. Clinicopathologic features of patients with non-small cell lung cancer harboring the EML4-ALK fusion gene: a meta-analysis. *PLoS One*. 2014;9:e110617.
52. Shaw AT, Solomon B. Targeting anaplastic lymphoma kinase in lung cancer. *Clin Cancer Res*. 2011;17:2081-2086.
53. Katayama R, Lovly CM, Shaw AT. Therapeutic targeting of anaplastic lymphoma kinase in lung cancer: a paradigm for precision cancer medicine. *Clin Cancer Res*. 2015;21:2227-2235.
54. Sabir SR, Yeoh S, Jackson G, et al. EML4-ALK variants: biological and molecular properties, and the implications for patients. *Cancers (Basel)*. 2017;9(9):118.
55. Tsao MS, Hirsch FR, Yatabe PY (eds). *IASLC Atlas of ALK and ROS1 Testing in Lung Cancer*. 2nd ed. Editorial Rx Press; 2016.
56. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med*. 2013;368:2385-2394.
57. Soria JC, Tan DSW, Chiari R, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. *Lancet*. 2017;389:917-929.
58. Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med*. 2017;377:829-838.
59. Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. *N Engl J Med*. 2018;379:2027-2039.
60. Choi YL, Takeuchi K, Soda M, et al. Identification of novel isoforms of the EML4-ALK transforming gene in non–small cell lung cancer. *Cancer Res*. 2008;68(13):4971-4976.
61. Koivunen JP, Mermel C, Zejnullahu K, et al. EML4-ALK fusion gene and efficacy of an ALK kinase inhibitor in lung cancer. *Clin Cancer Res*. 2008;14:4275-4283.
62. Sasaki T, Rodig SJ, Chirieac LR, et al. The biology and treatment of EML4-ALK non-small cell lung cancer. *Eur J Cancer*. 2010;46:1773-1780.
63. Heuckmann JM, Balke-Want H, Malchers F, et al. differential protein stability and ALK inhibitor sensitivity of EML4-ALK fusion variants. *Clin Cancer Res*. 2012;18:4682-4690.
64. Camidge DR, Niu H, Kim HR, et al. Correlation of baseline molecular and clinical variables with ALK inhibitor efficacy in ALTA-1L. *J Clin Oncol*. 2020;38:9517.
65. Camidge DR, Dziadziuszko R, Peters S, et al. Updated efficacy and safety data and impact of the EML4-ALK fusion variant on the efficacy of alectinib in untreated ALK-positive advanced non-small cell lung cancer in the Global Phase III ALEX study. *J Thorac Oncol*. 2019;14:1233-1243.
66. Pailler E, Faugeroux V, Oulhen M, et al. Acquired resistance mutations to ALK inhibitors identified by single circulating tumor cell sequencing in ALK-rearranged non-small-cell lung cancer. *Clin Cancer Res*. 2019;25:6671-6682.
67. Shaw AT, Solomon BJ, Besse B, et al. ALK resistance mutations and efficacy of lorlatinib in advanced anaplastic lymphoma kinase-positive non-small-cell lung cancer. *J Clin Oncol*. 2019;37:1370-1379.
68. Recondo G, Mezquita L, Facchinetti F, et al. Diverse resistance mechanisms to the third-generation ALK inhibitor lorlatinib in ALK-rearranged lung cancer. *Clin Cancer Res*. 2020;26:242-255.
69. Lin JJ, Zhu VW, Yoda S, et al. Impact of EML4-ALK variant on resistance mechanisms and clinical outcomes in ALK-positive lung cancer. *J Clin Oncol*. 2018;36:1199-1206.
70. Gainor JF, Dardaei L, Yoda S, et al. Molecular mechanisms of resistance to first- and second-generation ALK inhibitors in ALK-rearranged lung cancer. *Cancer Discov*. 2016;6:1118-1133.
71. Katayama R, Shaw AT, Khan TM, et al. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung cancers. *Sci Transl Med*. 2012;4:120ra17.
72. Skoulidis F, Papadimitrakopoulou VA. personalized medicine tackles clinical resistance: alectinib in ALK-positive non-small cell lung cancer progressing on first-generation ALK inhibitor. *Clin Cancer Res*. 2016;22:5177-5182.

73. Ng TL, Narasimhan N, Gupta N, et al. Early-onset pulmonary events associated with brigatinib use in advanced NSCLC. *J Thorac Oncol*. 2020;15:1190-1199.
74. Solomon BJ, Besse B, Bauer TM, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. *Lancet Oncol*. 2018;19:1654-1667.
75. Gainor JF, Shaw AT, Sequist LV, et al. EGFR mutations and ALK rearrangements are associated with low response rates to PD-1 pathway blockade in non-small cell lung cancer: a retrospective analysis. *Clin Cancer Res*. 2016;22:4585-4593.
76. Mazieres J, Drilon A, Lusque A, et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. *Ann Oncol*. 2019;30:1321-1328.
77. Rimkunas VM, Crosby KE, Li D, et al. Analysis of receptor tyrosine kinase ROS1-positive tumors in non-small cell lung cancer: identification of a FIG-ROS1 fusion. *Clin Cancer Res*. 2012;18:4449-4457.
78. Chin LP, Soo RA, Soong R, et al. Targeting ROS1 with anaplastic lymphoma kinase inhibitors: a promising therapeutic strategy for a newly defined molecular subset of non-small-cell lung cancer. *J Thorac Oncol*. 2012;7:1625-1630.
79. Bergethon K, Shaw AT, Ou SHI, et al. ROS1 rearrangements define a unique molecular class of lung cancers. *J Clin Oncol*. 2012;30:863-870.
80. Shaw AT, Ou SHI, Bang YJ, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med*. 2014;371:1963-1971.
81. Shaw AT, Riely GJ, Bang YJ, et al. Crizotinib in ROS1-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001. *Ann Oncol*. 2019;30:1121-1126.
82. Drilon A, Siena S, Dziadziuszko R, et al. Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1-2 trials. *Lancet Oncol*. 2020;21:261-270.
83. Shaw AT, Solomon BJ, Chiari R, et al. Lorlatinib in advanced ROS1-positive non-small-cell lung cancer: a multicentre, open-label, single-arm, phase 1-2 trial. *Lancet Oncol*. 2019;20:1691-1701.
84. Nagasaka M, Ou SHI. Neuregulin 1 fusion-positive NSCLC. *J Thorac Oncol*. 2019;14:1354-1359.
85. Drilon A, Somwar R, Mangatt BP, et al. Response to ERBB3-directed targeted therapy in NRG1 -rearranged cancers. *Cancer Discov*. 2018;8:686-695.
86. Wu YL, Yang JCH, Kim DW, et al. Phase II study of crizotinib in East Asian patients with ROS1-positive advanced non-small-cell lung cancer. *J Clin Oncol*. 2018;36:1405-1411.
87. Cho BC, Lim SM, Kim HR, et al. Open-label, multicenter, phase II Study of ceritinib in patients with non-small-cell lung cancer harboring ROS1 rearrangement. *J Clin Oncol*. 2017;35:2613-2618.
88. Patil T, Smith DE, Bunn PA, et al. The incidence of brain metastases in stage IV ROS1-rearranged non-small cell lung cancer and rate of central nervous system progression on crizotinib. *J Thorac Oncol*. 2018;13:1717-1726.
89. Gainor JF, Tseng D, Yoda S, et al. Patterns of metastatic spread and mechanisms of resistance to crizotinib in ROS1-positive non-small-cell lung cancer. *JCO Precis Oncol*. 2017;2017:PO.17.00063.
90. Drilon A, Ou SHI, Cho BC, et al. Repotrectinib (Tpx-0005) is a next-generation ros1/trk/alk inhibitor that potently inhibits ros1/trk/alk solvent-front mutations. *Cancer Discov*. 2018;8(10):1227-1236.
91. Ou S, Cho BC, Kim D, et al. OA09 preliminary clinical activity of repotrectinib (TPX-0005) in advanced ROS1 fusion-positive non-small cell lung cancer. *J Thorac Oncol*. 2018;13(suppl):S1047.
92. Singal G, Miller PG, Agarwala V, et al. Association of patient characteristics and tumor genomics with clinical outcomes among patients with non-small cell lung cancer using a clinicogenomic database. *JAMA*. 2019;321:1391-1399.
93. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378:2078-2092.
94. Yaeger R, Corcoran RB. Targeting alterations in the RAF-MEK pathway. *Cancer Discov*. 2019;9:329-341.
95. Akbani R, Akdemir KC, Aksoy BA, et al. Genomic classification of cutaneous melanoma. *Cell*. 2015;161:1681-1696.
96. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. *Nature*. 2002;417:949-954.
97. Tissot C, Couraud S, Tanguy R, et al. Clinical characteristics and outcome of patients with lung cancer harboring BRAF mutations. *Lung Cancer*. 2016;91:23-28.
98. Villaruz LC, Socinski MA, Abberbock S, et al. Clinicopathologic features and outcomes of patients with lung adenocarcinomas harboring BRAF mutations in the Lung Cancer Mutation Consortium. *Cancer*. 2015;121:448-456.
99. Eric AC, Joshua DC, Angela NB, et al. Comprehensive molecular profiling of lung adenocarcinoma. *Nature*. 2014;511:543-550.
100. Paik PK, Arcila ME, Fara M, et al. Clinical characteristics of patients with lung adenocarcinomas harboring BRAF mutations. *J Clin Oncol*. 2011;29:2046-2051.
101. Dankner M, Lajoie M, Moldoveanu D, et al. Dual MAPK inhibition is an effective therapeutic strategy for a subset of class II BRAF mutant melanomas. *Clin Cancer Res*. 2018;24:6483-6494.
102. Yao Z, Torres NM, Tao A, et al. BRAF mutants evade ERK-dependent feedback by different mechanisms that determine their sensitivity to pharmacologic inhibition. *Cancer Cell*. 2015;28:370-383.
103. Yao Z, Yaeger R, Rodrik-Outmezguine VS, et al. Tumours with class 3 BRAF mutants are sensitive to the inhibition of activated RAS. *Nature*. 2017;548:234-238.
104. Heidorn SJ, Milagre C, Whittaker S, et al. Kinase-dead BRAF and oncogenic RAS cooperate to drive tumor progression through CRAF. *Cell*. 2010;140:209-221.
105. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. *N Engl J Med*. 2015;373:726-736.
106. Subbiah V, Gervais R, Riely G, et al. Efficacy of vemurafenib in patients with non-small-cell lung cancer with BRAF V600 mutation: an open-label, single-arm cohort of the histology-independent VE-BASKET study. *JCO Precis Oncol*. 2019;3:PO.18.00266.
107. Planchard D, Besse B, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously treated BRAFV600E-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. *Lancet Oncol*. 2016;17:984-993.
108. Planchard D, Smit EF, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously untreated BRAFV600E-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. *Lancet Oncol*. 2017;18:1307-1316.
109. Choe CH, McArthur GA, Caro I, et al. Ocular toxicity in BRAF mutant cutaneous melanoma patients treated with vemurafenib. *Am J Ophthalmol*. 2014;158:831-837.e2.
110. Dréno B, Ribas A, Larkin J, et al. Incidence, course, and management of toxicities associated with cobimetinib in combination with vemurafenib in the coBRIM study. *Ann Oncol*. 2017;28:1137-1144.
111. Infante JR, Fecher LA, Falchook GS, et al. Safety, pharmacokinetic, pharmacodynamic, and efficacy data for the oral MEK inhibitor trametinib: a phase 1 dose-escalation trial. *Lancet Oncol*. 2012;13:773-781.
112. Guedj M, Quéant A, Funck-Brentano E, et al. Uveitis in patients with late-stage cutaneous melanoma treated with vemurafenib. *JAMA Ophthalmol*. 2014;132:1421-1425.

113. Poulikakos PI, Persaud Y, Janakiraman M, et al. RAF inhibitor resistance is mediated by dimerization of aberrantly spliced BRAF(V600E). *Nature*. 2011;480:387-390.
114. Antony R, Emery CM, Sawyer AM, et al. C-RAF mutations confer resistance to RAF inhibitors. *Cancer Res*. 2013;73:4840-4851.
115. Sosman JA, Pavlick AC, Schuchter LM, et al. Analysis of molecular mechanisms of response and resistance to vemurafenib (vem) in BRAFV600E melanoma. *J Clin Oncol*. 2012;30(15 suppl):8503.
116. Okimoto RA, Lin L, Olivas V, et al. Preclinical efficacy of a RAF inhibitor that evades paradoxical MAPK pathway activation in protein kinase BRAF-mutant lung cancer. *Proc Natl Acad Sci*. 2016;113:13456-13461.
117. Nichols RJ, Haderk F, Stahlhut C, et al. RAS nucleotide cycling underlies the SHP2 phosphatase dependence of mutant BRAF-, NF1- and RAS-driven cancers. *Nat Cell Biol*. 2018;20:1064-1073.
118. Sullivan RJ, Infante JR, Janku F, et al. First-in-class ERK1/2 inhibitor ulixertinib (BVD-523) in patients with MAPK mutant advanced solid tumors: results of a phase I dose-escalation and expansion study. *Cancer Discov*. 2018;8:184-195.
119. Amir N, Philippe G, Sylvia DB, et al. Type II RAF inhibitor causes superior ERK pathway suppression compared to type I RAF inhibitor in cells expressing different BRAF mutant types recurrently found in lung cancer. *Oncotarget*. 2018;9:16110-16123.
120. Negrao MV, Raymond VM, Lanman RB, et al. Molecular biology and treatment strategies for non-V600 BRAF-mutant NSCLC. *J Clin Oncol*. 2019;37:3102.
121. Dudnik E, Peled N, Nechushtan H, et al. BRAF mutant lung cancer: programmed death ligand 1 expression, tumor mutational burden, microsatellite instability status, and response to immune check-point inhibitors. *J Thorac Oncol*. 2018;13:1128-1137.
122. Negrao M, Skoulidis F, Montesion M, et al. MA03.05 BRAF mutations are associated with increased benefit from PD1/PDL1 blockade compared with other oncogenic drivers in non-small cell lung cancer. *J Thorac Oncol*. 2019;14(suppl):S257-S258.
123. Erkes DA, Cai W, Sanchez IM, et al. Mutant BRAF and MEK inhibitors regulate the tumor immune microenvironment via pyroptosis. *Cancer Discov*. 2020;10:254-269.
124. Liu C, Peng W, Xu C, et al. BRAF inhibition increases tumor infiltration by T cells and enhances the antitumor activity of adoptive immunotherapy in mice. *Clin Cancer Res*. 2013;19:393-403.
125. Ebert PJR, Cheung J, Yang Y, et al. MAP kinase inhibition promotes T Cell and anti-tumor activity in combination with PD-L1 checkpoint blockade. *Immunity*. 2016;44:609-621.
126. Paik PK, Veillon R, Cortot AB, et al. Phase II study of tepotinib in NSCLC patients with METex14 mutations. *J Clin Oncol*. 2019;37:9005.
127. Vuong HG, Ho ATN, Altibi AMA, et al. Clinicopathological implications of MET exon 14 mutations in non-small cell lung cancer—a systematic review and meta-analysis. *Lung Cancer*. 2018;123:76-82.
128. Paik PK, Drilon A, Fan PD, et al. Response to MET inhibitors in patients with stage IV lung adenocarcinomas harboring met mutations causing exon 14 skipping. *Cancer Discov*. 2015;5:842-850.
129. Drilon A, Clark JW, Weiss J, et al. Antitumor activity of crizotinib in lung cancers harboring a MET exon 14 alteration. *Nat Med*. 2020;26:47-51.
130. Awad MM, Lee JK, Madison R, et al. Characterization of 1,387 NSCLCs with MET exon 14 (METex14) skipping alterations (SA) and potential acquired resistance (AR) mechanisms. *J Clin Oncol*. 2020;38:9511.
131. Davies KD, Lomboy A, Lawrence CA, et al. DNA-based versus RNA-based detection of MET exon 14 skipping events in lung cancer. *J Thorac Oncol*. 2019;14:737-741.
132. Jurkiewicz M, Saqi A, Mansukhani MM, et al. Efficacy of DNA versus RNA NGS-based methods in MET Exon 14 skipping mutation detection. *J Clin Oncol*. 2020;38:9036.
133. Awad MM, Leonardi GC, Kravets S, et al. Impact of MET inhibitors on survival among patients (pts) with MET exon 14 mutant (METdel14) non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2017;35:8511.
134. Wolf J, Seto T, Han J-Y, et al. Capmatinib (INC280) in MET ex14-mutated advanced non-small cell lung cancer (NSCLC): efficacy data from the phase II GEOMETRY mono-1 study. *J Clin Oncol*. 2019;37:9004.
135. Lu S, Fang J, Cao L, et al. Abstract CT031: Preliminary efficacy and safety results of savolitinib treating patients with pulmonary sarcomatoid carcinoma (PSC) and other types of non-small cell lung cancer (NSCLC) harboring MET exon 14 skipping mutations. Proceedings: AACR Annual Meeting 2019; March 29-April 3, 2019; Atlanta, GA.
136. Lu S, Fang J, Li X, et al. Phase II study of savolitinib in patients (pts) with pulmonary sarcomatoid carcinoma (PSC) and other types of non-small cell lung cancer (NSCLC) harboring MET exon 14 skipping mutations (METex14+). *J Clin Oncol*. 2020;38:9519.
137. Guo R, Offin M, Brannon AR, et al. MET inhibitor resistance in patients with MET exon 14-altered lung cancers. *J Clin Oncol*. 2019;37:9006.
138. Recondo G, Bahcall M, Spurr LF, et al. Molecular mechanisms of acquired resistance to MET tyrosine kinase inhibitors in patients with MET exon 14 mutant NSCLC. *Clin Cancer Res*. 2020;26(11):2615-2625.
139. Sabari JK, Leonardi GC, Shu CA, et al. PD-L1 expression, tumor mutational burden, and response to immunotherapy in patients with MET exon 14 altered lung cancers. *Ann Oncol*. 2018;29:2085-2091.
140. Poulsen TT, Grandal MM, Skartved NJØ, et al. Sym015: a highly efficacious antibody mixture against met-amplified tumors. *Clin Cancer Res*. 2017;23:5923-5935.
141. Camidge DR, Janku F, Martinez-Bueno A, et al. Safety and preliminary clinical activity of the MET antibody mixture, Sym015 in advanced non-small cell lung cancer (NSCLC) patients with MET amplification/exon 14 deletion (METAmp/Ex14Δ). *J Clin Oncol*. 2020;38:9510.
142. Campbell JD, Alexandrov A, Kim J, et al. Distinct patterns of somatic genome alterations in lung adenocarcinomas and squamous cell carcinomas. *Nat Genet*. 2016;48:607-616.
143. Cappuzzo F, Marchetti A, Skokan M, et al. Increased MET gene copy number negatively affects survival of surgically resected non-small-cell lung cancer patients. *J Clin Oncol*. 2009;27:1667-1674.
144. Camidge DR, Ou S-HI, Shapiro G, et al. Efficacy and safety of crizotinib in patients with advanced c-MET-amplified non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2014;32:8001.
145. Wolf J, Overbeck TR, Han J-Y, et al. Capmatinib in patients with high-level MET-amplified advanced non-small cell lung cancer (NSCLC): results from the phase 2 GEOMETRY mono-1 study. *J Clin Oncol*. 2020;38:9509.
146. Strickler JH, Weekes CD, Nemunaitis J, et al. First-in-human phase I, dose-escalation and -expansion study of telisotuzumab vedotin, an antibody-drug conjugate targeting c-Met, in patients with advanced solid tumors. *J Clin Oncol*. 2018;36:3298-3306.
147. Robichaux JP, Elamin YY, Vijayan RSK, et al. Pan-cancer landscape and analysis of ERBB2 mutations identifies poziotinib as a clinically active inhibitor and enhancer of T-DM1 activity. *Cancer Cell*. 2019;36:444-457.e7.
148. Smit EF, Nakagawa K, Nagasaka M, et al. Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with HER2-mutated metastatic non-small cell lung cancer (NSCLC): interim results of DESTINY-Lung01. *J Clin Oncol*. 2020;38:9504.

149. Li BT, Shen R, Buonocore D, et al. Ado-trastuzumab emtansine for patients with HER2-mutant lung cancers: results from a phase II basket trial. *J Clin Oncol*. 2018;36:2532-2537.
150. Hainsworth JD, Meric-Bernstam F, Swanton C, et al. Targeted therapy for advanced solid tumors on the basis of molecular profiles: results from MyPathway, an open-label, phase IIa multiple basket study. *J Clin Oncol*. 2018;36:536-542.
151. Gao G, Li X, Wang Q, et al. Single-arm, phase II study of pyrotinib in advanced non-small cell lung cancer (NSCLC) patients with HER2 exon 20 mutation. *J Clin Oncol*. 2019;37:9089.
152. Dziadziuszko R, Smit EF, Dafni U, et al. Afatinib in NSCLC with HER2 mutations: results of the prospective, open-label phase II NICHE trial of European Thoracic Oncology Platform (ETOP). *J Thorac Oncol*. 2019;14:1086-1094.
153. Hyman DM, Piha-Paul SA, Won H, et al. HER kinase inhibition in patients with HER2-and HER3-mutant cancers. *Nature*. 2018;554:189-194.
154. Kris MG, Camidge DR, Giaccone G, et al. Targeting HER2 aberrations as actionable drivers in lung cancers: phase II trial of the pan-HER tyrosine kinase inhibitor dacomitinib in patients with HER2-mutant or amplified tumors. *Ann Oncol*. 2015;26:1421-1427.
155. Pan Y, Zhang Y, Li Y, et al. ALK, ROS1 and RET fusions in 1139 lung adenocarcinomas: a comprehensive study of common and fusion pattern-specific clinicopathologic, histologic and cytologic features. *Lung Cancer*. 2014;84:121-126.
156. Drilon A, Rekhtman N, Arcila M, et al. Cabozantinib in patients with advanced RET-rearranged non-small-cell lung cancer: an open-label, single-centre, phase 2, single-arm trial. *Lancet Oncol*. 2016;17:1653-1660.
157. Falchook GS, Ordonez NG, Bastida CC, et al. Effect of the RET Inhibitor vandetanib in a patient with RET fusion-positive metastatic non-small-cell lung cancer. *J Clin Oncol*. 2016;34:e141-e144.
158. Gautschi O, Zander T, Keller FA, et al. A patient with lung adenocarcinoma and RET fusion treated with vandetanib. *J Thorac Oncol*. 2013;8:e43-e44.
159. Gautschi O, Milia J, Filleron T, et al. Targeting RET in patients with RET-rearranged lung cancers: results from the global, multicenter RET Registry. *J Clin Oncol*. 2017;35:1403-1410.
160. Gill J, Prasad V. When are randomized controlled trials needed to assess novel anticancer drugs? An illustration based on the development of selpercatinib, a RET inhibitor. *Ann Oncol*. 2020;31:328-330.
161. Goto K, Oxnard GR, Tan DS-W, et al. Selpercatinib (LOXO-292) in patients with RET-fusion+ non-small cell lung cancer. *J Clin Oncol*. 2020;38:3584.
162. Subbiah V, Hu MI-N, Gainor JF, et al. Clinical activity of the RET inhibitor pralsetinib (BLU-667) in patients with RET fusion+ solid tumors. *J Clin Oncol*. 2020;38:109.
163. Subbiah V, Gainor JF, Oxnard GR, et al. Intracranial activity of selpercatinib (LOXO-292) in RET fusion-positive non-small cell lung cancer (NSCLC) patients on the LIBRETTO-001 trial. *J Clin Oncol*. 2020;38:9516.
164. Amatu A, Sartore-Bianchi A, Siena S. NTRK gene fusions as novel targets of cancer therapy across multiple tumour types. *ESMO Open*. 2016;1:1-9.
165. Huang EJ, Reichardt LF. Neurotrophins: roles in neuronal development and function. *Annu Rev Neurosci*. 2001;24:677-736.
166. Vaishnavi A, Le AT, Doebele RC. TRKing down an old oncogene in a new era of targeted therapy. *Cancer Discov*. 2015;5:25-34.
167. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N Engl J Med*. 2018;378:731-739.
168. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. *Lancet Oncol*. 2020;21:271-282.
169. Solomon JP, Linkov I, Rosado A, et al. NTRK fusion detection across multiple assays and 33,997 cases: diagnostic implications and pitfalls. *Mod Pathol*. 2020;33:38-46.
170. Hong DS, DuBois SG, Kummar S, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. *Lancet Oncol*. 2020;41:1-10.
171. Drilon A, Li G, Dogan S, et al. What hides behind the MASC: clinical response and acquired resistance to entrectinib after ETV6-NTRK3 identification in a mammary analogue secretory carcinoma (MASC). *Ann Oncol*. 2016;27:920-926.
172. Russo M, Misale S, Wei G, et al. Acquired resistance to the TRK inhibitor entrectinib in colorectal cancer. *Cancer Discov*. 2016;6:36-44.
173. Drilon A, Nagasubramanian R, Blake JF, et al. A next-generation TRK kinase inhibitor overcomes acquired resistance to prior trk kinase inhibition in patients with TRK fusion-positive solid tumors. *Cancer Discov*. 2017;7:963-972.
174. Hyman D, Kummar S, Farago A, et al. Abstract CT127: phase I and expanded access experience of LOXO-195 (BAY 2731954), a selective next-generation TRK inhibitor (TRKi). *Cancer Res*. 2019;79:CT127-CT127.
175. Cocco E, Schram AM, Kulick A, et al. Resistance to TRK inhibition mediated by convergent MAPK pathway activation. *Nat Med*. 2019;25:1422-1427.
176. Falls DL. Neuregulins: functions, forms, and signaling strategies. *Exp Cell Res*. 2003;284:14-30.
177. Fernandez-Cuesta L, Plenker D, Osada H, et al. CD74-NRG1 fusions in lung adenocarcinoma. *Cancer Discov*. 2014;4:415-422.
178. Fernandez-Cuesta L, Thomas RK. Molecular pathways: targeting nrg1 fusions in lung cancer. *Clin Cancer Res*. 2015;21:1989-1994.
179. Jonna S, Feldman RA, Swensen J, et al. Detection of NRG1 gene fusions in solid tumors. *Clin Cancer Res*. 2019;25:4966-4972.
180. Trombetta D, Graziano P, Scarpa A, et al. Frequent NRG1 fusions in Caucasian pulmonary mucinous adenocarcinoma predicted by Phospho-ErbB3 expression. *Oncotarget*. 2018;9:9661-9671.
181. Jones MR, Lim H, Shen Y, et al. Successful targeting of the NRG1 pathway indicates novel treatment strategy for metastatic cancer. *Ann Oncol*. 2017;28:3092-3097.

This page intentionally left blank

Section V

Head and Neck Cancer

Section Editor: Bonnie S. Glisson

26 Head and Neck Cancer

This page intentionally left blank

26 Head and Neck Cancer

Ruth Sacks
David Boyce-Fappiano
Amy Moreno
Frank Mott

KEY CONCEPTS

- Head and neck cancers are diverse. In this chapter, we focus on the management of squamous cell carcinomas of the head and neck (HNSCC).
- Tobacco and alcohol use are major risk factors, and the human papillomavirus (HPV) is a risk factor for oropharyngeal cancer (OPC).
- All patients should undergo a multidisciplinary evaluation that includes surgical, medical, and radiation oncology specialists.
- For early-stage HNSCC, surgery or definitive radiation provides excellent local control.
- Most patients present with locally advanced disease requiring a multimodality approach focusing on organ preservation, managing metastatic risk, and minimizing acute and chronic toxicities.
- Immune checkpoint inhibitors are now standard in recurrent and/or metastatic HNSCC.

EPIDEMIOLOGY

In the United States, head and neck cancer is estimated to represent approximately 3.6% (65,630) of new cancer cases and 2% (14,500) of cancer deaths as of 2020.[1] However, the disease is more common in many developing countries, with a worldwide annual incidence of more than 800,000 cases.[2] In more than 90% of these tumors, the histology is squamous cell carcinoma (SCC). Squamous cell carcinoma of the head and neck (HNSCC) primarily affects men, and the median age at diagnosis is 60 years old. Established risk factors include tobacco and alcohol use. Although public health efforts have led to a decrease in tobacco use and thus a reduction in smoking-related malignancies, the incidence of oropharyngeal cancer (OPC) has been steadily rising as a result of the impact of human papillomavirus (HPV) infection.[3,4]

GENETIC PREDISPOSITION

The majority of head and neck cancers are multifactorial diseases influenced by the interaction between carcinogens and/or oncogenic viruses and genetic susceptibility. Certain genetic factors, such as metabolic polymorphisms, DNA repair gene polymorphisms, and variations in other pathways may contribute to carcinogenesis.[5–7] Impaired apoptosis (programmed cell death) may increase the risk of malignancy.[8,9] In HPV-related HNSCC, only a small proportion of HPV-infected individuals have cancer, likely because of genetic susceptibility.[8,10–12] Rare germline mutations have been associated with familial atypical multiple-mole melanoma and Fanconi anemia and confer a risk for the development of HNSCC.[13–15]

RISK ASSESSMENT

The risk of developing HNSCC increases with age; most patients are older than age 50 years. Moreover, there is a clear association with HNSCC development and the use of tobacco and alcohol. Smokeless tobacco and betel quid (combination of betel leaf, lime, and areca nut), commonly used in India and areas of Asia, are associated with the development of oral cavity

cancers. Molecular studies provide evidence that carcinogens found in these substances have a causal role. Mutations in the tumor suppressor gene p53 are prominent in cancers of patients with a history of tobacco and alcohol use.[16] Cancers of the oral cavity, larynx, and hypopharynx are uncommon in individuals with no smoking history. Patients with HNSCC with heavy tobacco and alcohol exposures are at high risk of multiple cancers developing, with "field cancerization" throughout the upper aerodigestive tract and bladder.[17]

In the United States, greater than 70% of cancers arising in the oropharynx, particularly in the palatine tonsils and tongue base, are HPV- related.[18–20] The incidence of OPC in the United States is increasing, primarily because of HPV-associated cases in men.[21] HPV-positive OPC represents a distinct clinical and pathologic subgroup of HNSCC, with poorly differentiated basaloid histopathology and marked tumor responsiveness to radiation and chemotherapy.[22] HPV 16 is the most common viral genotype, with other high-risk HPV genotypes such as HPV 18, 31, or 33 being less common.[20]

Oncogenic oral HPV prevalence is higher in men compared with women and increases with the number of lifetime oral sexual partners and tobacco use.[23] In a study investigating patients with HPV-positive OPC and their long-term sexual partners, the prevalence of oral HPV infection in the partners was comparable with that of the general population, suggesting that the majority of long-term partners had cleared any exposure to active oral HPV infection. However, several patients had a previous or current sexual partner with cervical dysplasia or cervical cancer.[24] A retrospective study from the Swedish Family Cancer Database from 1958 to 1996 found that husbands of women with cervical cancer have a twofold increased risk of tonsillar cancer, supporting HPV transmission via oral sex from a partner with an oncogenic genital HPV infection.[25]

MOLECULAR PATHOGENESIS

The progression of HNSCC is thought to involve multiple stepwise alterations of molecular pathways in the squamous epithelium.[26] Aberrations in the p53 and Rb tumor suppressor pathways are the most common molecular events. The epidermal growth factor receptor (*EGFR*) is also overexpressed in invasive HNSCC in a majority of sample tumors.[27] Binding to *EGFR* by its natural ligands, mainly epidermal growth factor or transforming growth factor–α (TGF-α), prompts dimerization of the receptor, resulting in autoactivation of tyrosine kinase from the intracellular domain of the receptor, intracellular signaling, inhibition of apoptosis, activation of cell proliferation and angiogenesis, and increased metastatic potential.[28]

The molecular pathogenesis of HPV-positive tumors differs from that of HPV-negative tumors. The HPV virus contains a double-stranded genome that encodes proteins E1–E7, associated with viral gene regulation and cell transformation, and L1–L2, associated with the formation of structural capsid proteins for the virus. The E6 and E7 proteins promote carcinogenesis through their respective interactions with tumor suppressor p53 and pRb.[29] The E6 oncoprotein leads to ubiquitination and degradation of p53, causing loss of cell-cycle arrest and apoptosis. In addition, E6 can activate cellular telomerase, allowing the infected cell to maintain telomere length, which plays an essential role in cellular immortalization and transformation. The E7 oncoprotein inactivates Rb proteins, resulting in overactivation of E2F transcription factor with upregulation of cell-cycle genes, which leads to increased DNA synthesis and cell proliferation. Inactivation of Rb proteins produces increased levels of p16, an inhibitor of cyclin dependent kinase–4/cyclin D, via a feedback control mechanism, which is the reason p16 expression serves as a surrogate biomarker for HPV infection.[30]

Smoking-related HNSCCs have a mutation rate approximately twice that of HPV-positive HNSCCs. Mutations include *TP53*, *CDKN2A*, *PTEN*, *PIK3CA*, and *HRAS*. Additional mutations in genes that regulate squamous differentiation, such as *NOTCH1*, *IRF6*, and *TP63* have been described as well as mutations in genes regulating apoptosis.[31]

DIAGNOSIS AND STAGING

Optimal treatment outcomes depend on the precise identification of the primary tumor (Fig. 26–1) as well as the local, regional, and distant extent of disease.

Patients with early-stage disease may present with vague symptoms and minimal physical findings. Patients with locally advanced disease may present with signs and symptoms according to the subsite in the head and neck. Sinusitis, unilateral nasal airway obstruction, and epistaxis may be early signs of cancers of the nasal cavity or paranasal sinuses. Recurrent otitis media may be associated with nasopharyngeal cancer (NPC). Chronic otalgia, dysphagia, odynophagia, and throat soreness lasting weeks may be symptoms of OPC or hypopharyngeal cancers. Many patients with HPV-associated OPC present with an otherwise asymptomatic neck mass and may have limited or no smoking history. Persistent hoarseness demands visualization of the larynx. In supraglottic laryngeal neoplasms a neck mass may be the presenting sign. Careful examination of facial, cervical, and supraclavicular lymph nodes is important because the anatomic patterns of

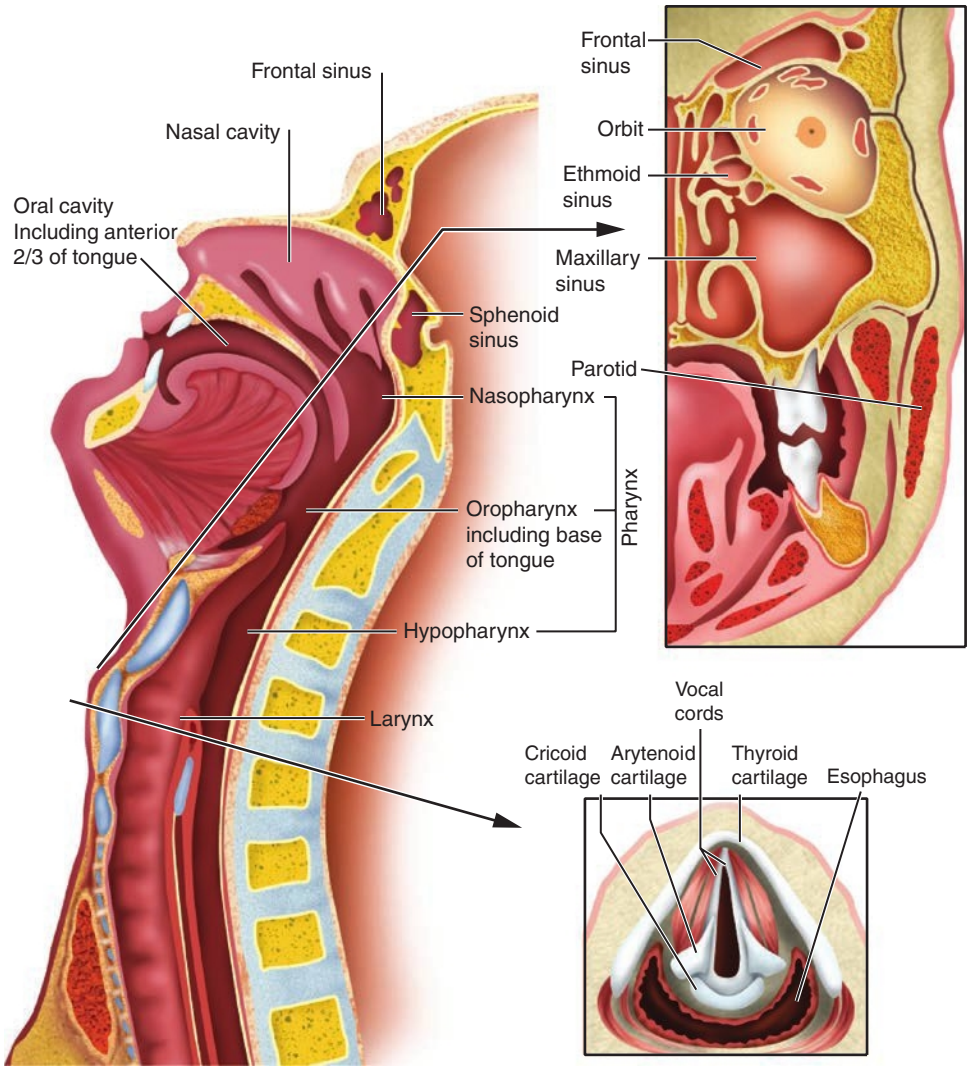


FIGURE 26–1 **Head and neck anatomy.**

lymphatic drainage may reflect the specific subsite of the primary tumor (Fig. 26–2).[32]

Physical examination should include careful inspection of the skin and oral/oropharyngeal mucosal surfaces; palpation of the tongue, floor of the mouth, and oropharynx; systematic palpation of the neck; and an indirect mirror examination of the oropharynx, hypopharynx, and larynx, complemented by fiberoptic endoscopy.[33,34] Leukoplakia (white mucosal patches that cannot be removed by scraping) and higher-risk erythroplakia (red or mixed red-white patches) are the most common premalignant lesions in the head and neck. Any suspicious surface in the oral mucosa should undergo biopsy.

Patients who present with a suspicious neck mass should undergo a systematic examination of the head and neck. If no obvious primary site is found, fine-needle aspiration (FNA) of the mass may establish a diagnosis of cancer. Detection of HPV or Epstein-Barr virus (EBV) DNA in a lymph node suggests a tumor of oropharyngeal or nasopharyngeal origin, respectively. Direct laryngoscopic examination under anesthesia may detect a primary tumor. Suspicious lesions are biopsied, and consideration may be given to tonsillectomy and/or biopsies of the nasopharynx, base of the tongue, and hypopharynx, depending on the pattern of lymphadenopathy. Open biopsy of the neck mass may be performed if FNA and panendoscopy have failed to yield a diagnosis, or in patients suspected of having an alternative process (ie, lymphoma). An experienced head and neck surgeon may be prepared to proceed with selective neck dissection if SCC of unknown head and neck primary origin is determined.

Three-dimensional imaging with computed tomography (CT) from the vertex to clavicles is the preferred local imaging modality for HNSCC.

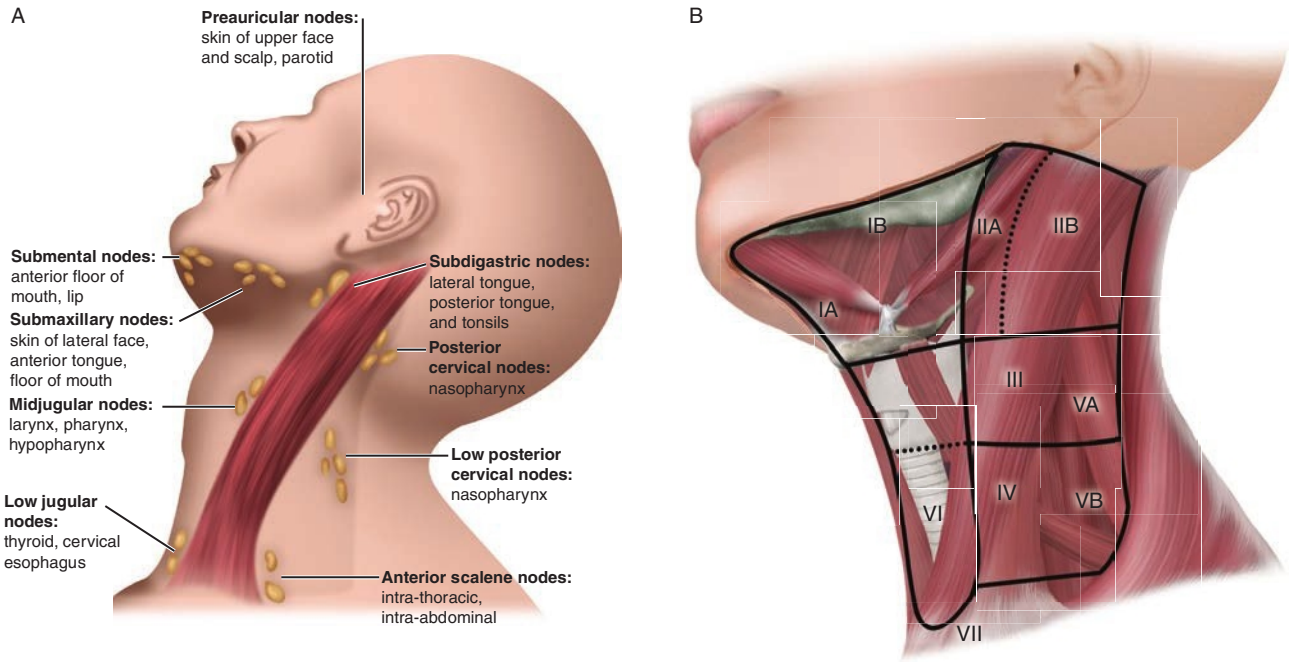


FIGURE 26–2 **A. Nodal drainage. B. Nodal levels in the head and neck. (Reproduced with permission from Hong WK, Bast RB Jr, Hait WN, et al: Cancer Medicine. 8th ed. Shelton, CT: BC Decker—People's Medical Publishing House-USA; 2010: 959-998.)**

Magnetic resonance imaging (MRI) is warranted in specific disease sites such as NPC and skull-base tumors. Because the lungs are the most common site of distant metastases, a chest radiograph or CT for symptomatic or high-risk patients (ie, patients with multiple nodal sites, low neck [level 4] nodes, or supraclavicular metastases) should also be performed. An 18-fluorodeoxyglucose positron emission tomography (FDG-PET) scan is indicated when the primary site is unknown or in the setting of indeterminate findings on cross-sectional imaging. FDG-PET does not replace dedicated imaging with CT and/or MRI of the primary site and neck.

All patients should undergo a thorough multidisciplinary evaluation that includes specialists from surgery, medical oncology, and radiation oncology. Dental, nutrition, and speech/swallow evaluations as well as smoking cessation are recommended. Modified barium swallow tests and baseline audiology examinations should be considered depending on the disease site and expected treatment paradigm.

The American Joint Committee on Cancer (AJCC) TNM staging system classifies tumors according to anatomic site and extent of disease.[35] Head and neck primary tumor (T) staging is complex and varies with the primary subsite. Classifications for lymph nodes (N) are uniform for all sites, with the exception of HPV-positive OPC and NPC.[36] The eighth edition of the AJCC has divided OPC staging based on HPV positivity because of significant differences in prognosis (Table 26–1A, B, C).

NATURAL HISTORY AND IMPLICATIONS FOR THERAPY

For patients with T1/2 disease (stage I/II), surgery or radiotherapy as a single modality is most often applicable and effective. Depending on the primary site and stage, a curative outcome will be achieved in 70% to 95% of cases. Two-thirds of patients with HNSCC will present with stage III or IV disease.[37] In these cases, combined treatment strategies are the standard of care, designed to balance competing goals of tumor eradication and organ preservation.[26,38,39] Despite optimal local therapy, 25% to 50% of patients may develop local or regional recurrence, and nearly 20% to 30% are at risk for development of distant metastases depending on the primary site and staging.[40–42]

Nasopharynx

More than 95% of endemic NPCs are associated with EBV. NPC tends to occur in younger persons and is not associated with tobacco use. NPC is aggressive, with cervical lymph node metastases present in 60% to 90% of patients at diagnosis. Radiotherapy alone to the nasopharynx and bilateral neck is standard of care for clinical T1N0M0 NPC and is associated with high locoregional tumor control rates of more than 90%.[43]

For locally advanced disease, including stage II (T2N0), chemoradiation is preferred.[44] For years, the

Table 26–1A Clinical TNM Staging for Oropharynx (p16–)

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor >2 cm but not >4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced or very advanced local disease
T4a	Moderately advanced local disease Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible[a]
T4b	Very advanced local disease Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional node metastases
N1	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(–)
N2	Metastasis to a single ipsilateral lymph node >3 cm but not >6 cm in greatest dimension and ENE(–); or metastases in multiple ipsilateral lymph nodes none >6 cm in greatest dimension and ENE(–); or in bilateral or contralateral lymph nodes none >6 cm in greatest dimension and ENE(–)
N2a	Metastasis in a single ipsilateral lymph node >3 cm but not >6 cm in greatest dimension and ENE(–)
N2b	Metastasis in multiple ipsilateral lymph nodes but not >6 cm in greatest dimension and ENE(–)
N2c	Metastases in bilateral or contralateral lymph nodes none >6 cm in greatest dimension and ENE(–)
N3	Metastasis in a lymph node >6 cm in greatest dimension and ENE(–); or metastasis in any node(s) and clinically overt ENE(+)
N3a	Metastasis in a lymph node >6 cm in greatest dimension and ENE(–)
N3b	Metastasis in any node(s) and clinically overt ENE(+)
Distant Metastasis (M)	
MX	Presence of distant metastasis cannot be assessed
M0	No evidence of distant metastasis
M1	Distant metastasis

[a]Mucosal extension to the lingual surface of the epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx.
ENE, extranodal extension.
Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging System (2020).

standard of care was concurrent chemoradiotherapy followed by adjuvant chemotherapy based on the Head and Neck Intergroup 0099 trial.[45] As of this writing, induction chemotherapy followed by concurrent chemoradiotherapy is standard for node-positive patients.[46–49] For patients with T1 node-positive tumors, sequential induction followed by radiation can be considered to avoid the toxicity of concurrent chemoradiation. For node-negative patients (T2-4N0) chemoradiation alone is standard.[50,51] Because of the rarity of NPC, patients should be treated at tertiary referral centers when feasible.

The GORTEC 2006-02 trial compared induction docetaxel-cisplatin-5-fluorouracil (TPF) followed by concomitant cisplatin-radiation (RT) versus concomitant therapy alone and showed 3-year progression-free survival (PFS) and overall survival (OS) of 73.9% and 86.3% versus 57.2% and 68.9%, respectively, statistically favoring induction (P = .042 for PFS and P = .05 for OS).[47] In 2019, a phase 3 trial evaluating induction chemotherapy with gemcitabine and cisplatin followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone demonstrated improved 3-year recurrence-free survival (85.3% vs

Table 26–1B Clinical TNM Staging for Oropharynx (p16+)

Primary Tumor (T)	
T0	No primary identified
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor >2 cm but not >4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced local disease Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond[a]
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional node metastases
N1	One or more ipsilateral lymph nodes, <6 cm
N2	Contralateral or bilateral lymph nodes, <6 cm
N3	Lymph node(s) >6 cm
Distant Metastasis (M)	
MX	Presence of distant metastasis cannot be assessed
M0	No evidence of distant metastasis
M1	Distant metastasis

[a]Mucosal extension to the lingual surface of the epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx.
Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging System (2020).

76.5%; hazard ratio [HR] 0.51, 95% CI 0.34–0.77) and OS (94.6% vs 90.3%; HR 0.43, 95% CI 0.24–0.77) in the induction group.[48]

Intensity-modulated radiation therapy (IMRT) improves tumor coverage, quality of life, and reduces xerostomia compared with 3-D conformal techniques.[52–54] Because of protons' unique physical characteristics (Bragg peak, ie, region of maximal dose deposition within tissue followed by a sharp dose falloff and no exit dose) may be advantageous in treating NPC given its proximity to critical organs such as the temporal lobes, brainstem, and optic structures.[55] Two-year locoregional control (LRC) and OS rates of 100% and 89%, respectively, have been demonstrated for proton therapy in NPC.[56] Moreover, reductions in feeding tube placement with intensity-modulated proton therapy (IMPT) versus IMRT is thought to correspond with significant reductions in mean oral cavity doses.[57]

Table 26–1C Clinical Stage Grouping for All Oropharynx

P16 Status	P16–			P16+		
Stage I	T1	N0	M0	T0–T2	N0, N1	M0
Stage II	T2	N0	M0	T0–T2	N2	M0
				T3	N0–N2	M0
Stage III	T3	N0	M0	T0–T3	N3	M0
	T1–T3	N1	M0	T4	N0–N3	M0
Stage IV				Any T	Any N	M1
Stage IVA	T1–T3	N2	M0			
	T4a	N0-N2	M0			
Stage IVB	Any T	N3	M0			
	T4b	Any N	M0			
Stage IVC	Any T	Any N	M1			

Oral Cavity

The majority of oral cavity neoplasms occur in the anterior two-thirds of the tongue (oral tongue) and the floor of the mouth (Fig. 26–3). Additional subsites include the buccal mucosa, lips, hard palate, gingiva, and retromolar trigone. Forty percent of patients present with clinically evident lymph nodes, and bilateral nodal involvement is not uncommon.

Surgical resection is a common and effective local treatment approach.[26,39] Local tumor control rates after surgery for patients with stage I and II tumors can approach 80% to 90% and 50% to 80%, respectively.[58] For deeply invasive T1/2 disease, we favor surgical resection of the primary tumor with simultaneous selective neck dissection.

After surgery, postoperative radiotherapy should be recommended for patients with high-risk factors including pT3 or pT4 disease, pN2 or pN3 disease, low neck (level IV–V) disease, perineural invasion, and lymphovascular invasion, whereas concurrent chemoradiation should be pursued in the presence of positive margins or extranodal extension.[59,60] Refer to "Combined-Modality Therapy" for further details.

Oropharynx

The most common cancers of the oropharynx are of the base of tongue and tonsils, and greater than 80% are HPV-positive and are associated with a better prognosis than HPV-negative disease.[42,61–64] This led to the recent development of separate staging systems for OPC based on HPV status (Table 26–1A, B, C); thus, all patients should undergo tumor HPV DNA testing by in situ hybridization and p16 testing by immunohistochemistry to determine the appropriate prognosis and staging.[61] Ideally, both tests should be performed, but if only one is feasible then p16 is preferred because it reflects HPV-driven carcinogenesis, whereas some tumors may have the HPV virus as a passenger. Despite differences in prognoses, management for HPV-positive and HPV-negative malignancies is similar.[65]

Radiation therapy is used as a single modality for T1 and many T2 tumors, with local control rates of greater than 90%.[66] In most cases, bilateral neck regional lymph nodes are targeted with radiation therapy; however, unilateral neck radiation can be considered for select well-lateralized tonsillar primaries. At MDACC, patients considered ideal candidates for unilateral neck radiotherapy include those with T1–2, N0–N1 tonsillar primary tumors restricted to the tonsillar fossa or anterior pillar, with less than 1 cm of soft palate involvement, and no base of tongue involvement. Five-year OS and disease-free survival rates of 95% and 96% have been reported, with a contralateral nodal recurrence rate of 2%.[67] Unilateral neck radiotherapy for such tonsillar cases is favored because it

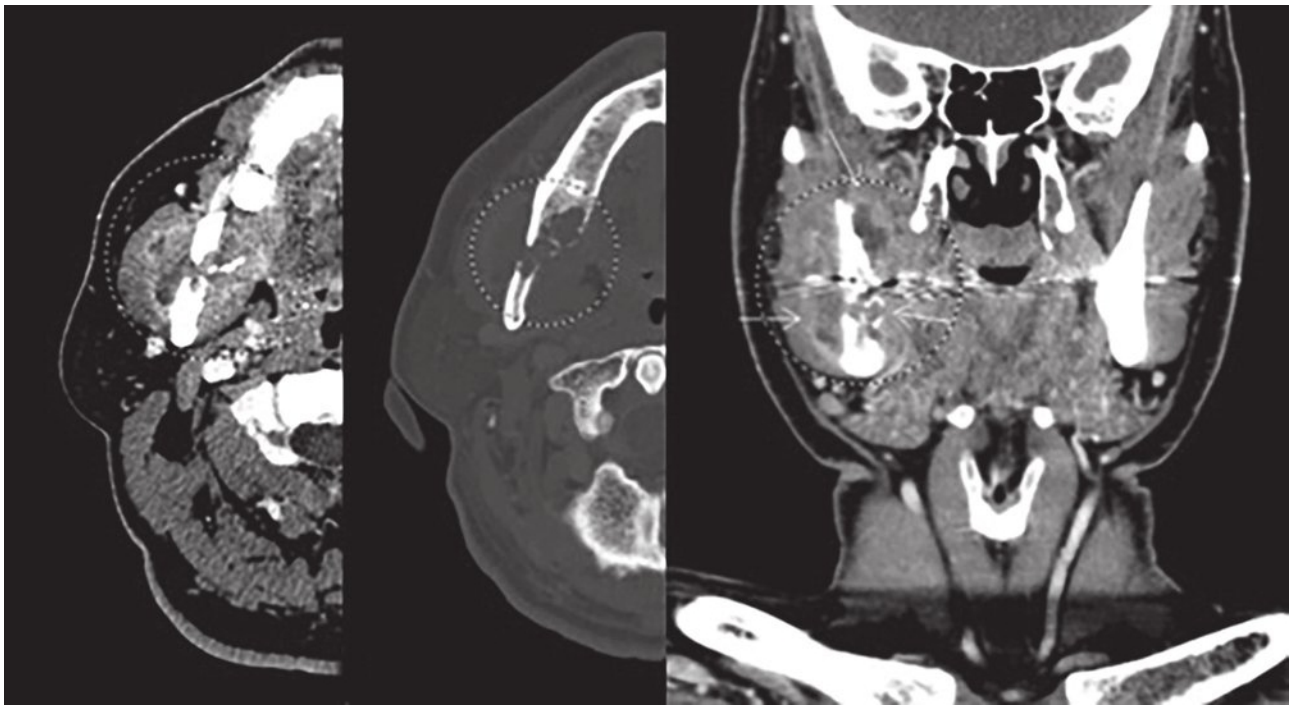


FIGURE 26–3 **Right alveolar ridge cancer with bony destruction and masticator space invasion and bilateral cervical adenopathy, cT4bN2bM0.**

also greatly reduces the radiation doses to the contralateral parotid gland and key swallowing structures.

Surgery with minimally invasive transoral robotic surgery (TORS) approaches is an option for some patients with OPC. The phase 2 ORATOR study compared TORS with definitive radiotherapy. In this study, 71% of patients in the TORS group received postoperative radiotherapy, and 68% of the radiotherapy arm received concurrent chemotherapy for node-positive disease. Survival outcomes were excellent in both groups with data regarding quality-of-life measures seeming to favor definitive radiotherapy.[68]

For locally advanced disease, concomitant chemoradiotherapy is the current standard of care. Because HPV-associated OPC has an improved prognosis, several treatment de-intensification efforts have been studied including systemic therapy de-intensification, radiation dose reduction, and potential toxicity reduction using proton therapy. Proton therapy may be a promising de-intensification option compared with IMRT (Fig. 26–4). MDACC is leading a national multi-institutional phase 2/3 study comparing IMPT versus IMRT for stage III/IV OPC (NCT01893307).

Larynx

Given the critical role of the larynx in communication, swallowing, respiration, and airway protection, organ preservation to maintain functional status and quality of life has been the focus of laryngeal cancer treatment since the 1970s. The most widely used treatment of T1 and T2 tumors is radiotherapy, with control rates greater than 90% for T1 disease and 70% to 80% for T2 tumors.[69] For patients with potentially resectable, locally advanced disease, organ-preserving approaches using chemotherapy and radiation have proven effective and have replaced upfront surgery for many patients.

The Veterans Affairs laryngeal study established induction chemotherapy followed by radiation and surgical salvage, if needed, as an organ-preserving alternative to primary surgery followed by postoperative radiation.[70] The RTOG 91-11 trial established concurrent chemoradiation as an acceptable standard of care.[40] These treatment strategies are discussed in further detail in the "Organ Preservation" section.

Hypopharynx

With 65% to 85% of lesions occurring in the pyriform sinus, carcinoma of the hypopharynx is relatively uncommon but virulent (Fig. 26–5). Treatment is similar to that for the larynx. Small-volume disease may be treated with surgery or radiation, but later-stage disease requires multimodal therapy. At presentation, more than 75% of patients have advanced disease

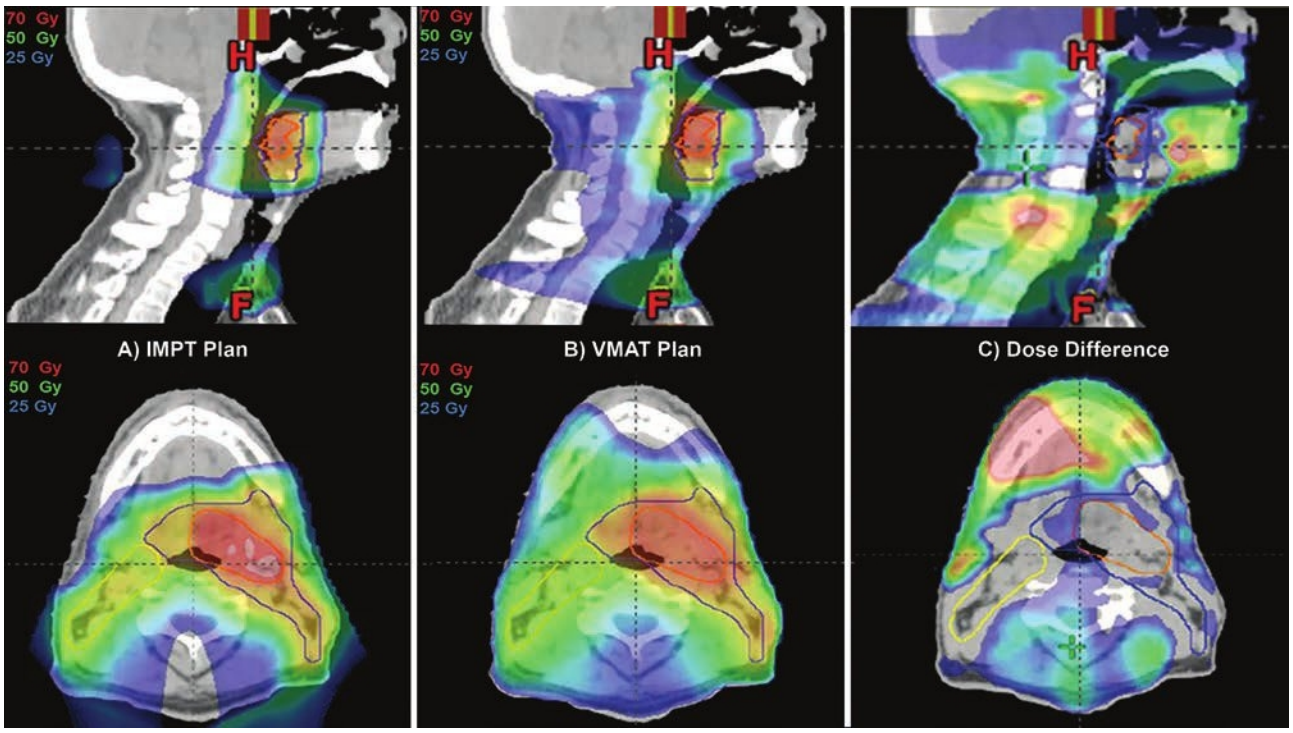


FIGURE 26–4 **Comparative radiation therapy plans for an oropharyngeal case. A. IMPT plan. B. VMAT. C. Dose difference plans. IMPT, intensity-modulated proton therapy; VMAT, volumetric-modulated arc therapy.**

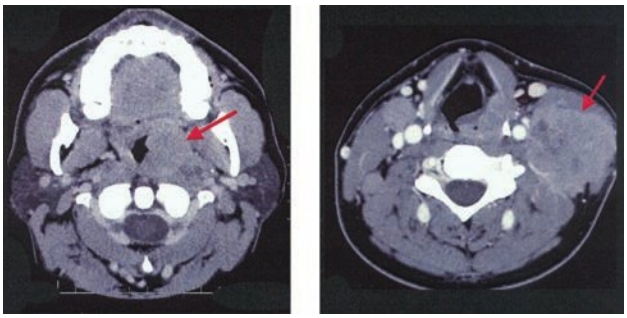


FIGURE 26–5 Axial computed tomography of advanced squamous carcinoma of the pyriform sinus, cT3N3M0.

(T3 or T4). The 5-year OS rate is lower than 30%. For many patients, surgical treatment also requires removal of the larynx. The European Organization for Research and Treatment of Cancer (EORTC), in a phase 3 trial, demonstrated that laryngeal preservation with sequential chemoradiotherapy is a feasible alternative to radical surgery.[71] Refer to the "Organ Preservation" section for further discussion.

COMBINED-MODALITY THERAPY

Induction Chemotherapy

Induction (neoadjuvant) chemotherapy is given before surgery or radiation. It has been investigated as an approach to improve outcomes in terms of OS and tumor control in patients with stage III/IV disease undergoing definitive local therapy. Theoretical advantages to this approach include reducing the risk of distant disease recurrence, enhancing organ preservation, improving response to definitive radiotherapy by reducing tumor bulk, and modification of subsequent local therapy to response. In a 2009 meta-analysis, although concomitant chemoradiation was superior to induction chemotherapy followed by radiation for local control and survival, induction chemotherapy was more effective at decreasing distant failure.[72] This conclusion lent credence to contemporaneous trials investigating induction chemotherapy followed by chemoradiation.

In 2007, two multicenter phase 3 trials, the European TAX 323 and the North American TAX 324, demonstrated the superiority of induction TPF over PF (cisplatin, 5-fluorouracil) (Table 26–2).[73,74] However, these trials did not directly compare induction chemotherapy with definitive chemoradiotherapy. Nevertheless, these trials led to FDA approval of induction TPF for patients with locally advanced HNSCC in 2007. Despite the results of TAX 324, the value of adding induction chemotherapy to chemoradiation remained an unanswered question given the lack of definitive randomized trials comparing this approach with upfront chemoradiation.

Three phase 3 studies compared induction chemotherapy followed by chemoradiation versus chemoradiation alone.[75–77] The Spanish Head and Neck Cancer Group cooperative trial randomly assigned patients with locally advanced SCC of the oral cavity, oropharynx, hypopharynx, and larynx to (1) induction TPF followed by concurrent chemoradiation, (2) induction PF followed by concurrent chemoradiation, or (3) concurrent chemoradiation alone. There were no statistically significant differences between PFS, time-to-treatment failure, and OS in the three groups; however, approximately half of the patients did not complete concurrent chemoradiation.[77]

The PARADIGM trial randomly assigned patients with locally advanced SCC of the oral cavity, oropharynx, hypopharynx, or larynx between induction TPF followed by chemoradiation that was adapted based on induction chemotherapy response versus chemoradiation alone using an accelerated fractionation. Because of slow accrual, the trial closed with 145 patients enrolled, less than half of the planned enrollment. Overall 3-year survival was 73% (95% CI 60%–82%) in the induction TPF followed by chemoradiation group versus 78% in the chemoradiation alone group.[75]

The DeCIDE trial randomized patients with N2/3 M0 disease (based on the AJCC 7th edition staging) between induction TPF followed by chemoradiation or chemoradiation alone.[76] This trial also failed to accrue well, enrolling 280 patients versus the planned 400 patients. There were no statistically significant differences in OS (HR 0.91; 95% CI 0.59–1.41) or relapse-free survival. In competing risk analysis, there was a statistically significant reduction in risk of distant relapse without locoregional recurrence in the induction arm ($P = .043$).

Thus, induction chemotherapy remains investigational, but it is appropriate (1) as a "bridge" to control disease before logistical delays in surgery or radiation, (2) to facilitate locoregional therapy of very advanced disease, and (3) in patients deemed high risk for distant recurrence, such as those with N3 and/or low neck disease. In laryngeal and hypopharyngeal cancer, the induction chemotherapy approach is an effective organ preservation strategy and is further discussed in the "Organ Preservation" section.

Induction chemotherapy is also being studied as a method to select chemosensitive patients to reduce the intensity of subsequent treatment. In a phase 2 ECOG-ACRIN Cancer Research Group trial, response to induction chemotherapy was used to select patients with stage III/IV HPV-associated OPC for reduced radiation dose. Patients who did not achieve a complete

Table 26–2 Induction Chemotherapy Trials

Trial	Phase	Patients	Inclusion Criteria	Treatment	Progression-Free Survival	Overall Survival
European TAX 323	III	358	Stage III/IV, nonmetastatic, untreated SCCHN	TPF followed by RT vs PF followed by RT	Median PFS: 11 vs 8.2 mo (P = .007) 3-y PFS: 17% vs 14%	Median OS: 18.8 vs 14.5 mo (P = .02) 3-y OS: 37% vs 26%
North American TAX 324	III	501	Stage III/IV, nonmetastatic, unresectable or low surgical curability, untreated, SCC of oral cavity, larynx, oropharynx, or hypopharynx	TPF followed by CRT (carboplatin) vs PF followed by CRT (carboplatin)	Median PFS: 38.1 vs 13.2 mo (P = .0114)	Median OS: 70.6 vs 34.8 mo (P = .014) 5-y OS: 52 vs 42%
Spanish Head and Neck Cancer Cooperative Group	III	439	Stage III/IV, nonmetastatic, unresectable, untreated SCC of oral cavity, oropharynx, hypopharynx, or larynx	TPF followed by CRT (cisplatin) vs PF followed by CRT (cisplatin) vs CRT alone (cisplatin)	Median PFS: 20.4 vs 18.1 vs 13.3 mo (P = .083)	Median OS: 35.6 vs 37.1 vs 29.4 mo
PARADIGM	III	145	Stage III/IV, nonmetastatic, unresectable or low surgical curability, untreated SCC of oral cavity, oropharynx, hypopharynx, or larynx	TPF followed by CRT (docetaxel or carboplatin) vs CRT alone (cisplatin)	3-y PFS: 67 vs 69% (P = .82)	3-y OS: 73% vs 78% (P = .77)
DeCIDE	III	280	Nonmetastatic, untreated SCCHN, N2 or N3	TPF followed by CRT (docetaxel, fluorouracil, hydroxyurea) vs CRT (docetaxel, fluorouracil, hydroxyurea)	Not assessed	OS at 3.5 y: 28% vs 31% (P = .69)
GSTCC Italian Study Group	II-III	414	Stage III/IV, nonmetastatic, untreated SCC of oral cavity, oropharynx, hypopharynx	TPF followed by CRT (cetuximab or PF) vs CRT (cetuximab or PF) alone	Median PFS: 30.5 vs 18.5 mo (P = .013) 3-y PFS: 47% vs 38.5%	Median OS: 54.7 vs 37.1 mo (P = .031) 3-y OS: 57.5% vs 46.5%

CRT, concurrent chemoradiation; OS, overall survival; PF, cisplatin/fluorouracil; PFS, progression-free survival; RT, radiation; SCC, squamous cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck; TPF, docetaxel, cisplatin, fluorouracil.

response after induction therapy were given a higher dose of radiation (69.3 Gy in 33 fractions) compared with those who achieved a complete response (54 Gy in 27 fractions). Seventy percent of the total patients achieved a complete clinical response. In patients who received lower-dose radiation with 54 Gy, the 2-year PFS was 80% and OS was 94%, with approximately 3-year median follow-up. There were fewer radiation complications in the lower-dose radiation group such as dysphagia (40% vs 89%; $P = .011$) and nutritional impairment (10% vs 44%; $P = .025$).[78]

Concomitant Radiotherapy and Chemotherapy

Meta-analysis of prospective clinical trials demonstrates enhanced local tumor control and improved survival with combined therapy over radiation alone, establishing chemoradiation as the standard of care in locally advanced nonsurgical disease. The effect of chemotherapy was higher with single-agent platinum than any other types of monotherapies (HR 0.74, 95% CI 0.67–0.82; $P = .006$).[72] Single-agent cisplatin is preferred in this setting.[79–82] For patients with contraindications to cisplatin, cetuximab, an EGFR-targeted monoclonal antibody, is an acceptable alternative. Based on retrospective data, carboplatin was less effective than cisplatin in one randomized trial,[83] although the use of carboplatin in responders, subsequent to induction chemotherapy, is acceptable based on the TAX 324 and PARADIGM trials, especially for cisplatin-ineligible patients.[63,75] Taxanes, potent radiosensitizers, are feasible and effective in weekly low-dose schedules after induction chemotherapy.[63,75,84]

Cetuximab is approved for use in combination with radiation in previously untreated patients. In a landmark study, patients with locoregionally advanced HNSCC were randomly assigned to receive high-dose radiotherapy alone or high-dose radiotherapy plus weekly cetuximab.[85] Locoregional control and OS favored the combination. However, the rates of distant metastases at 1 and 2 years were similar in both groups. Retrospective analysis demonstrated that the main benefit was in patients with OPC.

Cetuximab plus radiotherapy was directly compared with cisplatin plus radiotherapy in 849 patients with locally advanced HPV-associated OPC in a multicenter, noninferiority phase 2 randomized trial (RTOG 1016). In the cetuximab arm, there was inferior PFS (67 vs 78%, HR 1.72, 95% CI 1.29–2.29), decreased OS (78 vs 85%, HR 1.45), and greater locoregional failure (17 vs 10%, HR 2.05, 95% CI 1.35–3.10) at 5 years.[42] In the international trial De-ESCALaTE HPV, 334 patients with locally advanced, low-risk (nonsmoker or <10 pack-year smoking history) HPV-positive OPC were randomly assigned to cetuximab plus radiotherapy versus cisplatin plus radiotherapy. The trial demonstrated decreased OS for cetuximab with radiotherapy with a 2-year rate of 89% versus 98% and increased disease recurrence with a 2-year rate of 16% versus 6%.[86] Given the results of these trials, platinum-based chemoradiation remains standard of care for HPV-positive OPC, with cetuximab-radiotherapy being recommended for patients who are ineligible for cisplatin or patient preference because of concern for cisplatin-related side effects.

The MARCH meta-analysis reported an absolute OS benefit using hyperfractionation over standard fractionation, but survival significantly worsened when adding concomitant chemotherapy.[87] Equivalent outcomes were observed with accelerated radiotherapy and two doses of bolus cisplatin compared with standard fractionation and three doses of bolus cisplatin in the RTOG 0129 trial for patients with stage III/IV HNSCC.[88] Both approaches were feasible and there was less cisplatin-associated toxicity in the accelerated arm.

Adjuvant Chemoradiotherapy

Adjuvant chemoradiotherapy is indicated in patients at high risk of recurrence after surgical resection, generally defined as having positive margins or extracapsular spread.[59,60,89] Two large phase 3 studies, RTOG 9501 and EORTC 22931, tested cisplatin-based concomitant chemoradiotherapy in the adjuvant setting.[59,60]

In RTOG 9501 after a median follow-up of 9.4 years, concomitant chemoradiotherapy significantly improved LRC and disease-free survival with a trend toward improved OS in patients with extracapsular extension and/or positive margins.[90] The incidence of acute grade 3 or greater adverse effects was 34% in the radiotherapy group and 77% in the combined-therapy group ($P < .001$), with no differences in late toxicity. In the EORTC 22931 trial, both the PFS and OS rates were significantly higher in the combined-therapy group than in the radiotherapy group. Severe acute adverse effects were more frequent after combined therapy than in the radiotherapy group. A combined analysis of both adjuvant therapy trials showed significant risk reduction of 48% in locoregional relapse, 30% in disease-free survival, and 28% in OS when using chemoradiation for patients with extracapsular extension and/or positive margins.[91]

RTOG 0234 explored the incorporation of cetuximab into adjuvant chemoradiation.[92,93] This phase 2 trial demonstrated that two biochemoradiotherapy regimens, docetaxel/radiation/cetuximab and cisplatin/radiation/cetuximab, outperformed the historical control of high-dose cisplatin-based chemoradiotherapy from RTOG 9501. Although these results are

promising, comparison with historical controls is problematic, and adding cetuximab to adjuvant chemoradiation is not currently standard.

ORGAN PRESERVATION

Many HNSCCs are diagnosed at a late stage. Stages III and IV tumors often necessitate extensive or radical surgery, which may alter organ function. Problems with radical surgery include loss of speech, loss of swallowing function, or disfigurement without a concomitant improvement in survival time. Therefore, preservation of function is a major challenge.

The Veterans Affairs laryngeal study randomly assigned patients with stage III/IV SCC of the larynx to induction platinum-5FU (PF) followed by definitive radiotherapy or surgery with postoperative radiotherapy.[70] In the chemotherapy group, patients who had no tumor response after two cycles underwent salvage laryngectomy, whereas those with a complete clinical or partial response received a third cycle of chemotherapy followed by radiotherapy. Two-year OS was 68% for both arms, and larynx preservation was achieved for 64% of patients treated with chemotherapy. However, salvage laryngectomy was required for 56% of patients with T4 tumors. Patterns of failure differed with decreased local failures favoring surgery (2% vs 12%; $P < .01$) but decreased distant metastasis favoring sequential therapy (11% vs 17%; $P < .001$). Lefebvre et al later reported that sequential chemotherapy and radiation could also be effective in selected patients with cancers of the hypopharynx.[71]

The RTOG 99-11 study randomly assigned patients with larynx cancer to induction chemotherapy PF followed by radiotherapy versus concomitant cisplatin-radiotherapy versus radiotherapy alone.[94] Surgical salvage was reserved for patients with persistent or locally recurrent disease. Both chemotherapy groups demonstrated improved laryngectomy-free survival, the primary end point of the trial, compared with radiotherapy alone. Crude larynx preservation rates, at 10 years, regardless of survival, were higher with concurrent treatment: 82% compared with 68% and 64% in the sequential chemotherapy/radiation and radiation alone arms. Locoregional control was significantly improved with concomitant chemoradiotherapy (HR 0.58; 95% CI 0.37–0.89; $P = .005$), whereas the induction chemotherapy group showed a nonsignificant trend toward improved OS (HR 1.25; 95% CI, 0.98–1.61; $P = .08$).[95] There were late increased noncancer-related deaths observed with chemoradiation (Table 26–3).[40]

The GORTEC 2000-01 trial compared induction cisplatin/5FU with and without docetaxel followed by radiation therapy in partial responders with both larynx and hypopharynx cancers. The 5-year larynx preservation rate was 60% in the docetaxel arm (vs 39%), at least in part because of the higher response rate with that combination. Survival was the same in both arms. Thus, the TPF regimen, if feasible, is preferred in this setting.[96]

These trials indicate that, for patients with intermediate-stage SCC of the larynx, a combined treatment program with the objectives of tumor eradication and laryngeal preservation is appropriate. It is also important to recognize that patients with locally advanced, destructive primary laryngeal cancers (ie, T4 tumors) were not included in the RTOG 91-11. These patients require total laryngectomy for optimal tumor control.

It should be noted that nonsurgical treatment also carries a risk of morbidity and functional impact. Radiation produces tissue changes that can result in immediate and long-term alterations in speech and swallowing. The adverse impact of radiation may equal or exceed that associated with surgery, depending on the treatment dose and volume, and the sequelae of treatment may manifest or increase in severity years after the completion of treatment. Fibrosis may reduce the range of motion of the tongue and jaw and diminish pharyngeal wall motion.

Historically, 20% to 40% of patients receiving chemoradiotherapy for SCC of the oropharynx and hypopharynx may require long-term gastrostomy tube feedings. However, the long-term gastrostomy rate for patients with OPC treated with modern radiation therapy is less than 10%.[97] Radiation to the larynx often results in swallowing problems related to pharyngeal transport. To counteract the deleterious effects of radiation and chemoradiotherapy, there are rehabilitative options that are best administered by a qualified speech pathologist.

RECURRENT OR METASTATIC DISEASE

Prognosis for recurrent or metastatic HNSCC is generally poor, with median survival ranging from 6 to 15 months. Locoregional recurrence remains the most common pattern of failure, occurring in approximately 20% to 30% of patients.[98] As a result, local therapy is often clinically indicated and most commonly involves radiation therapy with or without surgical resection whenever feasible. Considering that a majority of these patients have received prior radiation therapy for their initial disease, there are concerns regarding the increased risks of toxicities with reirradiation.

Earlier reirradiation studies report 2-year LRC rates of 30% to 50% using 3-D conformal radiotherapy or IMRT but with significant costs in grade 4 and 5

Table 26–3 Laryngeal/Hypopharyngeal—Organ Preservation Trials

Trial	Phase	Patients	Inclusion Criteria	Treatment	Larynx Preservation	OS
VA study	3	332	Untreated stage III/IV SCC of larynx	a) TL followed by RT b) PF × 3 followed by RT	2 y: 66% 3 y: 62%	2 y, 3 y, 5 y: a) 68%, 56%, 45% b) 68%, 53%, 42%
RTOG 91-11	3		Untreated stage III/IV SCC of supraglottic or glottic larynx	a) PF × 3 followed by RT b) RT + P c) RT	5 y, 10 y: a) 71%, 68% b) 84%, 82% c) 66%, 64%	5 y, 10 y: a) 58%, 39% b) 55%, 28% c) 54%, 32%
EORTC 24954-22950	3	450	Stage III/IV SCC of the larynx or hypopharynx	a) PF × 4 followed by RT b) PF alternating + RT	3 y: a) 40% b) 45%	3 y: a) 62.2% b) 64.8%
GORTEC 2000-01	3	213	Untreated stage III/IV SCC of the larynx or hypopharynx	a) PF × 3 followed by RT b) TPF × 3 followed by RT	3 y: a) 57.5% b) 70.3%	3 y: a) 60% b) 60%
EORTC 24981	3	202	SCC of the pyriform sinus or the hypopharyngeal aspect of the aryepiglottic fold	a) TLP followed by RT b) PF × 3 followed by RT	3 y: a) NA b) 42% 10 y: a) NA b) 27%	3 y: a) 43% b) 57% 10 y: a) 14% b) 13%

EORTC, European Organization for Research and Treatment of Cancer; GORTEC, Groupe Oncologie Radiotherapies de la Tête et du Cou; P, cisplatin; PF, cisplatin/fluorouracil; RT, radiation; RTOG: Radiation Therapy Oncology Group; SCC: squamous cell carcinoma; TL, total laryngectomy; TLP, total laryngectomy with partial pharyngectomy; TPF, docetaxel, cisplatin, fluorouracil.

toxicity (Table 26–4).[99–111] Proper patient selection and the use of newer radiation techniques such as stereotactic body radiation therapy (SBRT) are showing promising results. SBRT is a highly conformal therapy that uses advanced image guidance and noncoplanar beam arrangement to deliver highly ablative doses of radiation with millimeter precision in three to five treatments. Preliminary findings of a prospective registry study conducted at MDACC comparing SBRT, proton therapy, and IMRT reported equivalent OS and LRC between modalities, with a significantly lower rate of acute grade 3 and 4 toxicities using SBRT.[99]

Systemic therapy options are determined based on prior therapies, patient comorbidities, performance status, distribution of disease, and programmed death ligand 1 (PD-L1) expression status. It is essential for providers to obtain adequate core biopsies rather than FNAs to perform a PD-L1 combined positive score (CPS), a test mandated by the FDA, on tumor specimens in the setting of first-line metastatic disease. CPS is the number of PD-L1 staining cells (tumor cells and immune cells) divided by the total number of viable tumor cells multiplied by 100.

The randomized phase 3 study KEYNOTE-048 established pembrolizumab (PD-1 monoclonal antibody) with chemotherapy as a first-line regimen in patients with cisplatin-sensitive (no prior cisplatin or >6 months after the completion of chemotherapy as part of curative-intent treatment) metastatic or recurrent HNSCC.[112] Eight-hundred fifty-four patients were stratified based on PD-L1 CPS, p16 status, and ECOG PS and randomly assigned to receive pembrolizumab alone, pembrolizumab plus platinum/5-FU, or cetuximab plus platinum/5-FU.

Pembrolizumab plus chemotherapy compared with cetuximab plus chemotherapy improved OS in the total population (HR 0.65, 95% CI 0.63–0.93; $P < .0001$) along with CPS greater than or equal to 1 and greater than or equal to 20 populations.[112] Single-agent pembrolizumab improved OS compared with cetuximab plus chemotherapy in patients with CPS greater than or equal to 1 (HR 0.78, 95% CI 0.64–0.96; $P = .0086$) and CPS greater than or equal to 20 (HR 0.61, 95% CI 0.45–0.83; $P = .0007$). Notably, in the total population, pembrolizumab alone was not inferior to platinum/5-FU and cetuximab (Table 26–5).

Based on the findings from this trial, patients with PD-L1–positive disease qualify for treatment with pembrolizumab alone; however, we recommend using the CPS as a guide to determine the optimal treatment approach. For patients with CPS 20 or higher, consider pembrolizumab alone. For patients with CPS 1 or higher and lower than 20, consider pembrolizumab with or without chemotherapy depending on ECOG

Table 26–4 Reirradiation Trials and Studies

Study	Patients	Cohort Details	RT Technique	Outcomes	Toxicity
Lee et al 2007 MSK[101]	105	86% SCC (34% surgery, 71% CRT)	IMRT (70%) and 3DRT	2-y LRC: 42% 2-y OS: 37%	G3–4: 15% Brain necrosis: 4%
Langer et al 2007 RTOG 99-11[100]	105	>77% SCC	IMRT and 3DRT, with chemotherapy	2-y LRC: 30% 2-y OS: 26%	G4–5: 28% (8 deaths) ORN: 18% Carotid rupture: 5%
Heron et al 2011[110]	70	100% SCC (SBRT vs. SBRT+ cetuximab)	SBRT	2-y LC: 34% (SBRT), 49% (SBRT+cetux) 2-y OS: 21% (SBRT), 53% (SBRT+cetux)	Acute G3–5: 57% (SBRT), 63% (SBRT+cextux) Late G3–5: 23% (SBRT), 23% (SBRT+cetux)
Phan et al 2015 MDA[104]	60	67% SCC (58% surgery, 73% CRT)	Proton	2-y LRC: 73% (62% SCC) 2-y OS: 70% (60% SCC)	G3: 20% G5: 3% Feeding tube: 10% Higher toxicity with CTV1 ≥50 cm^3
Takiar et al 2015 MDA[102]	207	84% SCC (51% surgery, 67% CRT)	IMRT	2-y LRC: 65% (59% SCC) 2-y OS: 57% (51% SCC)	G3–5 at: 2-y: 32% 5-y: 48% Higher toxicity with CTV1 >50 cm^3
Ward et al 2016 MIRI Collaborative[103]	412	96% SCC (100% RT, 45% surgery, 44% CRT)	IMRT	2-y LRC: 40% (surgery), 66% (definitive RT) 2-y OS: 40%	G3: 19% G4: 4.4% G5: 1.2% Feeding tube: 11%
Yamazaki et al 2016[111]	107	43% surgery	SBRT	2-y LRC: 64% 2-y OS: 35%	Late G3–5: 21% Carotid rupture: 10% (9 deaths; ulceration predictive of carotid rupture)
Romesser et al 2016 MSK[105]	92	57% SCC (39% surgery, 39% CRT)	Proton	1-y LRC: 75% 1-y OS: 65%	Acute G3: 31% Late G3–5: 19% -Skin: 9% -Carotid rupture: 3%
McDonald et al 2016[106]	61	53% SCC (48% surgery, 28% CRT)	Proton	2-y LRC: 80% 2-y OS: 33%	Acute G3–5: 15% Late G3–5: 25% -Necrosis: 15%
Vargo et al 2018[108]	414	99% SCC (70% CRT)	IMRT (52%) and SBRT (48%)	2-y LRF: 57% (IMRT), 45% (SBRT) 2-y OS: 35% (IMRT), 16% (SBRT)	Acute G3–5: 17% (IMRT), 12% (SBRT) Acute G4–5: 5% (IMRT), 0.5% (SBRT) Late G3–5: 12.4% (IMRT), 11.6% (SBRT)
Gogineni et al 2019[109]	60	74% SCC (53% surgery, 57% CRT)	SBRT	2-y LC: 79% 2-y RC: 70% 2-y OS: 45%	Late G3: 3% (aerodigestive tract), 1% (skull base) Late G4–5: None

3DRT, 3D conformal radiation therapy; CRT, chemoradiation; CTV1, clinical target volume 1; ECE, extracapsular extension; G, grade; IMRT, intensity-modulated radiation therapy; LC, local control: LRC, locoregional control; LRF, locoregional failure; ORN, osteoradionecrosis; RC, regional control; RT, radiation; SABR, stereotactic ablative radiotherapy; SBRT, stereotactic body radiation therapy; SCC, squamous cell carcinoma.

Table 26–5 Immunotherapy Trials for Metastatic and Recurrent Head and Neck Cancer

Trial	Phase	Patients	Inclusion Criteria	Treatment	Outcome
KEYNOTE-048	3	882	Treatment naïve, metastatic or recurrent SCC of the oropharynx, oral cavity, hypopharynx, or larynx	Pembrolizumab + platinum + 5-FU vs cetuximab + platinum + 5-FU Pembrolizumab vs cetuximab + platinum + 5- FU	**Median OS:** Total study population: 13 vs 10.7 mo PD-L1 CPS ≥20: 14.7 vs 11 mo PD-L1 CPS ≥1: 13.6 vs 10.4 mo **2 yr OS:** PD-L1 CPS ≥20: 35 vs 19% PD-L1 CPS ≥1: 31 vs 17% **Median OS:** Total study population: 29 vs 19% PD-L1 CPS ≥20: 14.9 vs 10.7 mo PD-L1 CPS ≥1: 12.3 vs 10.3 mo **2 yr OS:** PD-L1 CPS ≥20: 38 vs 22% PD-L1 CPS ≥1: 30 vs 18%
KEYNOTE-040	3	495	Recurrent or metastatic SCCHN of oral cavity, oropharynx, hypopharynx, larynx; failed platinum therapy	Pembrolizumab vs investigator choice therapy	**Median OS:** Total population: 8.4 vs 6.9 mo PD-L1 CPS ≥ 50%: 11.6 vs 6.6 mo PD-L1 CPS <50%: 6.5 vs. 7.1 mo PD-L1 CPS ≥ 1%: 8.7 vs 7.1 mo PD-L1 CPS < 1%: 6.3 vs 7 mo **12 mo OS:** Total population: 37 vs 26.5% PD-L1 CPS ≥ 50%: 47 vs 25% PD-L1 CPS ≥ 1%: 40% vs 26%
KEYNOTE-012	1b	192	Recurrent or metastatic SCCHN	Initial cohort: Pembrolizumab 10 mg/kg q2wk Expansion cohort: Pembrolizumab 200 mg q3wk	**Median OS:** Total population: 8 mo PD-L1 CPS ≥ 1%: 10 mo PD-L1 CPS < 1%: 5 mo **OS 12 mo:** Total population: 38%
KEYNOTE-055	2	171	Recurrent or metastatic SCCHN of oral cavity, oropharynx, hypopharynx, or larynx resistant to both platinum and cetuximab	Pembrolizumab 200 mg q3wk	**Median OS:** 8 mo **OS 6 mo:** Total population: 59% HPV(+): 72%, HPV(–): 55% PD-L1 CPS >1%: 59% PDL-1 CPS <1%: 56%
Checkmate-141	3	361	Recurrent or metastatic SCCHN of oral cavity, pharynx, or larynx; platinum refractory	Nivolumab 3 mg/kg q2wk vs single-agent investigator's choice therapy	**Median OS:** Total population: 7.5 vs 5.1 mo PD-L1 CPS ≥1%: 8.7 vs 4.6 mo PD-L1 CPS <1%: 5.7 vs 5.8 mo **OS 1 y:** Total population: 36 vs 16.6%
NCT02369874	3	736	Recurrent or metastatic SCCHN; platinum refractory	Durvalumab alone vs Durvalumab + tremelimumab	Completed accrual, results pending

5-FU, 5-fluorouracil; CPS, combined positive score; HPV, human papillomavirus; ORR, overall response rate; PD-L1, programmed death-ligand 1; SCC, squamous cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck.

PS. For patients with CPS of 0 or score unavailable, consider chemotherapy with or without pembrolizumab. In the setting of aggressive disease, to avoid early progression, the combination of pembrolizumab with chemotherapy should be considered independent of CPS.

The KEYNOTE 048 trial led to the FDA approval in June 2019 of PF as the designated chemotherapy regimen in combination with pembrolizumab. Although the trial utilized PF as the chemotherapy regimen, our preference at MDACC is a taxane (docetaxel or paclitaxel) in place of infusional 5-FU. This is supported by trials comparing platinum-taxane doublets with PF showing no difference in survival.[113,114] Infusional 5-FU requires a central line and administration via an ambulatory pump over 96 hours with a required second return to the treatment center for pump removal and line flush. It is frequently complicated by diarrhea, mucositis, hand-foot syndrome, and a rare but life-threatening potential for coronary vasospasm and arrhythmias. Hospital admissions to manage these toxicities are not uncommon, and thus the cost of this regimen both in physical toxicity and in monetary resources is high. Docetaxel, on the other hand, is easily administered through a peripheral vein over an hour. It is generally well tolerated, with cosmetic alopecia and neutropenia as its most common side effects. Prophylactic granulocyte–colony-stimulating factor is frequently given to prevent febrile neutropenia. Cumulative neuropathy may occur after several cycles, but therapy is typically limited to 4 to 6 cycles.

For immunotherapy-ineligible patients, frontline platinum doublets and cetuximab are recommended. The phase 3 EXTREME trial demonstrated that the addition of cetuximab to cisplatin/5-FU significantly increased OS, PFS, and response rates compared with cisplatin/5-FU alone.[92] The phase 2 GORTEC 2008-03 trial of the TPEx regimen (docetaxel, platinum, cetuximab) showed a favorable median survival of 14 months.[115] This regimen was subsequently compared against the EXTREME trial regimen (5-FU, platinum, cetuximab), thus substituting docetaxel for 5-FU. Patients with metastatic HNSCC were randomly assigned between EXTREME and TPEx as first-line treatment. After a median follow-up of 30 months, the median OS was 14.5 months for TPEx and 13.4 months for EXTREME (HR 0.87; P = .15). More significantly, the grade 4/5 adverse events were only 34% in the TPEx regimen versus 50% in the EXTREME regimen. Thus, substituting a taxane (specifically docetaxel) for 5-FU results in similar efficacy and reduced toxicity.[116] For patients not considered to be candidates for immunotherapy and/or combination chemotherapy, single agents can be given depending on predicted tolerance and previous exposure. Active single agents include platinums, 5-FU, taxanes, methotrexate, and cetuximab.[117–119]

Second-line therapy is primarily dictated by treatment eligibility and prior exposure to platinum and immunotherapy agents. Subsequent therapy for platinum-refractory disease (<6 months from prior platinum therapy) in immunotherapy-eligible patients includes pembrolizumab or nivolumab, monoclonal antibodies directed against programmed death-1 protein (PD-1). Two large nonrandomized studies, KEYNOTE-012 and KEYNOTE-055, and one phase 3 trial KEYNOTE-040 demonstrated the clinical benefit of pembrolizumab in this setting.[120–122] KEYNOTE-040 randomly assigned 495 patients that failed platinum therapy to pembrolizumab versus the investigator's choice of therapy (methotrexate, docetaxel, or cetuximab).[123] Although the differences in response rates were not statistically significant (15% vs 10%), the duration of response was longer in the pembrolizumab arm (18 months vs 5 months). Overall survival in the total population was 37% versus 27% at 12 months, and median OS was 8.4 versus 6.9 months (HR 0.8 95% CI 0.65–0.98). Exploratory analysis demonstrated that patients with PD-L1 expression of 50% or higher demonstrated a statistically significant survival benefit compared with those with PD-L1 expression lower than 50%.

Nivolumab has shown clinical activity and benefit in the phase 3 trial CHECKMATE-141.[124,125] Three-hundred sixty-one patients were randomly assigned to receive nivolumab versus single-agent physician's choice (methotrexate, docetaxel, or cetuximab). The study demonstrated superior OS (median 7.5 months vs 5.1 months; 97.73% CI 0.51–0.96, HR 0.70; P = .01) and response rates (13.3% vs 5.8%) in the nivolumab arm regardless of PD-L1 expression and p16 status (Table 26–5). A more significant survival benefit was seen in patients with HPV-positive disease (HR 0.56; 95% CI 0.3–0.99) and patients with PD-L1 expression 1% or greater (HR 0.55; 95% CI 0.36–0.83).

For patients with progression of disease after platinum-based therapy and who are immunotherapy ineligible or refractory, subsequent lines of treatment include cetuximab or single-agent chemotherapy. Phase 2 trials have demonstrated the benefit of cetuximab in the platinum-refractory setting and objective response rates are approximately 10%.[126,127]

RISK REDUCTION AND PREVENTION

Tobacco and alcohol use are major risk factors for the development of head and neck cancer; thus, tobacco and alcohol counseling are essential components of prevention and risk reduction. It is important for clinicians to stress the importance of tobacco cessation because of the risk of development of secondary malignancies and the impact on clinical outcomes in patients who continue to smoke during active treatment.

As the incidence of HPV-related head and neck cancer continues to rise, preventive strategies targeting this infectious agent are being explored. HPV vaccination is being used to prevent cervical and HNSCC cancer. Although the HPV vaccine has been shown to reduce the prevalence of oral HPV infections, its impact on the incidence of HNSCC is yet to be determined.[128] As of this writing, there are no chemoprevention strategies that have been shown to decrease the incidence of HNSCC, despite multiple trials with a variety of agents including vitamin A, vitamin E, beta carotene, and retinoid.[129–135]

MD ANDERSON PRACTICE TIPS

- Multidisciplinary discussion and management are necessary to determine the optimal treatment course and to address cancer as well as therapy-related symptoms.
- Early-stage disease is typically treated with curative intent and single-modality treatment, either surgery or radiation.
- Higher-volume stage III (T3N0–1) and stage IV disease without distant metastases should be approached with curative intent, multimodality therapy such as surgery and radiation, or concurrent chemoradiation.
- There are no definitive data that the incorporation of induction therapy before chemoradiation leads to improved survival except in the setting of node-positive nasopharyngeal cancer. Its use with sequential radiation as a larynx preservation strategy is a standard treatment option.
- Chemoradiation with cisplatin is the standard of care for locally advanced disease. However, cetuximab and other agents along with alternative approaches such as induction therapy, followed by carboplatin with radiation, are used in patients with contraindications to cisplatin.
- PD-L1 CPS, performance status, and prior therapies should play an integral role in determining the appropriate treatment in the recurrent or metastatic setting to balance potential therapy benefit with toxicity, especially in the palliative setting. Anti–PD-1 antibodies should be given to all patients with recurrent disease, unless contraindications exist.
- It is likely that immunotherapy will become a standard of care in curative-intent treatment in the near future.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin.* 2020;70:7-30.
2. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
3. National Program of Cancer Registries SEER Stat Database: U.S. Cancer Statistics Incidence Analytic file 1998–2016. United States Department of Health and Human Services, Centers for Disease Control and Prevention Released June 2019, based on the November 2018 submission.
4. Public Health Statement for Creosote. Agency for Toxic Substances and Disease Registry (ATSDR). 2002.
5. Lacko M, Braakhuis BJ, Sturgis EM, et al. Genetic susceptibility to head and neck squamous cell carcinoma. *Int J Radiat Oncol Biol Phys.* 2014;89:38-48.
6. McKay JD, Truong T, Gaborieau V, et al. A genome-wide association study of upper aerodigestive tract cancers conducted within the INHANCE consortium. *PLoS Genet.* 2011;7:e1001333.
7. Flores-Obando RE, Gollin SM, Ragin CC. Polymorphisms in DNA damage response genes and head and neck cancer risk. *Biomarkers*. 2010;15:379-399.
8. Zhou Z, Sturgis EM, Liu Z, et al. Genetic variants of a BH3-only pro-apoptotic gene, PUMA, and risk of HPV16-associated squamous cell carcinoma of the head and neck. *Mol Carcinog.* 2012;5(suppl 1):E54-E64.
9. Ma F, Zhang H, Zhai Y, et al. Functional polymorphism-31C/G in the promoter of BIRC5 gene and risk of nasopharyngeal carcinoma among chinese. *PLoS One.* 2011;6.
10. Guan X, Sturgis EM, Lei D, et al. Association of TGF-beta1 genetic variants with HPV16-positive oropharyngeal cancer. *Clin Cancer Res.* 2010;16:1416-1422.
11. Yu H, Sturgis EM, Liu Z, et al. Modifying effect of MDM4 variants on risk of HPV16-associated squamous cell carcinoma of oropharynx. *Cancer.* 2012;118:1684-1692.
12. Lu M, Liu Z, Yu H, et al. Combined effects of E2F1 and E2F2 polymorphisms on risk and early onset of squamous cell carcinoma of the head and neck. *Mol Carcinog.* 2012;5(suppl 1): E132-E141.
13. Levitus M, Joenje H, de Winter JP. The Fanconi anemia pathway of genomic maintenance. Cell Oncol 2006;28:3-29.
14. Yu KK, Zanation AM, Moss JR, Yarbrough WG. Familial head and neck cancer: molecular analysis of a new clinical entity. *Laryngoscope.* 2002;112:1587-1593.
15. Cabanillas R, Astudillo A, Valle M, et al. Novel germline CDKN2A mutation associated with head and neck squamous cell carcinomas and melanomas. *Head Neck.* 2013;35: E80-E84.
16. Brennan JA, Boyle JO, Koch WM, et al. Association between cigarette smoking and mutation of the p53 gene in squamous-cell carcinoma of the head and neck. *N Engl J Med.* 1995;332:712-717.
17. Yamamoto E, Shibuya H, Yoshimura R, Miura M. Site specific dependency of second primary cancer in early stage head and neck squamous cell carcinoma. *Cancer.* 2002;94:2007-2014.
18. Viens LJ HS, Watson M,, et al. . Human-papillomavirus-associated cancers—United States, 2008-2012. *MMWR Morb Mortal Wkly Rep.* 2016;65:661-666.
19. Gillison ML, Koch WM, Capone RB, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. *J Natl Cancer Inst.* 2000;92:709-720.
20. Vokes EE, Agrawal N, Seiwert TY. HPV-associated head and neck cancer. *J Natl Cancer Inst.* 2015;107:djv344.
21. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol.* 2011;29:4294-4301.
22. Gillison ML. Human papillomavirus-associated head and neck cancer is a distinct epidemiologic, clinical, and molecular entity. *Semin Oncol.* 2004;31:744-754.
23. D'Souza G, McNeel TS, Fakhry C. Understanding personal risk of oropharyngeal cancer: risk-groups for oncogenic oral HPV infection and oropharyngeal cancer. *Ann Oncol.* 2017;28:3065-3069.
24. D'Souza G, Gross ND, Pai SI, et al. Oral human papillomavirus (HPV) infection in HPV-positive patients with oropharyngeal cancer and their partners. *J Clin Oncol.* 2014;32:2408-2415.
25. Hemminki K, Dong C, Frisch M. Tonsillar and other upper aerodigestive tract cancers among cervical cancer patients and their husbands. *Eur J Cancer Prev.* 2000;9:433-437.
26. Haddad RI, Shin DM. Recent advances in head and neck cancer. *N Engl J Med.* 2008;359:1143-1154.
27. Grandis JR, Tweardy DJ. Elevated levels of transforming growth factor alpha and epidermal growth factor receptor messenger RNA are early markers of carcinogenesis in head and neck cancer. *Cancer Res.* 1993;53:3579-3584.
28. Roskoski R, Jr. The ErbB/HER receptor protein-tyrosine kinases and cancer. *Biochem Biophys Res Commun.* 2004;319:1-11.
29. Miller DL, Puricelli MD, Stack MS. Virology and molecular pathogenesis of HPV (human papillomavirus)-associated oropharyngeal squamous cell carcinoma. *Biochem J.* 2012;443:339-353.
30. Liu C, Mann D, Sinha UK, Kokot NC. The molecular mechanisms of increased radiosensitivity of HPV-positive oropharyngeal squamous cell carcinoma (OPSCC): an extensive review. *J Otolaryngol Head Neck Surg*. 2018;47:59.
31. Stransky N, Egloff AM, Tward AD, et al. The mutational landscape of head and neck squamous cell carcinoma. *Science.* 2011;333:1157-1160.
32. Kupferman ME, Sturgis EM, Schwartz DL, et al. Neoplasms of the head and neck. In: *Holland-Frei Cancer Medicine*. 8th ed. People's Medical Publishing House-USA; 2010:59-998.
33. Holsinger FC, Kies MS, Weinstock YE, et al. Videos in clinical medicine. Examination of the larynx and pharynx. *N Engl J Med.* 2008;358:e2.
34. Laurie SA, Licitra L. Systemic therapy in the palliative management of advanced salivary gland cancers. *J Clin Oncol.* 2006;24:2673-2678.
35. Greene FL, Sobin LH. A worldwide approach to the TNM staging system: collaborative efforts of the AJCC and UICC. *J Surg Oncol.* 2009;99:269-272.
36. Brierley J GM, Whittekind C, UICC (International Union Against Cancer). *TNM-Classification of Malignant Tumours*. Wiley-Blackwell; 2017.
37. Howlader N, Noone AM, Krapcho M, et al. *SEER Cancer Statistics Review, 1975-2016*. National Cancer Institute; 2018.
38. Vokes EE, Weichselbaum RR, Lippman SM, Hong WK. Head and neck cancer. *N Engl J Med.* 1993;328:184-194.
39. Forastiere A, Koch W, Trotti A, Sidransky D. Head and neck cancer. *N Engl J Med.* 2001;345:1890-1900.
40. Forastiere AA, Zhang Q, Weber RS, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *J Clin Oncol.* 2013;31:845-852.
41. Quinlan-Davidson SR, Mohamed ASR, Myers JN, et al. Outcomes of oral cavity cancer patients treated with surgery followed by postoperative intensity modulated radiation therapy. Oral Oncol 2017;72:90-97.
42. Gillison ML, Trotti AM, Harris J, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive

oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. *Lancet.* 2019;393:40-50.
43. Lee AW, Sze WM, Au JS, et al. Treatment results for nasopharyngeal carcinoma in the modern era: the Hong Kong experience. *Int J Radiat Oncol Biol Phys.* 2005;61:1107-1116.
44. Chen QY, Wen YF, Guo L, et al. Concurrent chemoradiotherapy vs radiotherapy alone in stage II nasopharyngeal carcinoma: phase III randomized trial. *J Natl Cancer Inst.* 2011;103:1761-1770.
45. Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *J Clin Oncol.* 1998;16:1310-1317.
46. Sun Y, Li WF, Chen NY, et al. Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial. *Lancet Oncol.* 2016;17:1509-1520.
47. Frikha M, Auperin A, Tao Y, et al. A randomized trial of induction docetaxel-cisplatin-5FU followed by concomitant cisplatin-RT versus concomitant cisplatin-RT in nasopharyngeal carcinoma (GORTEC 2006-02). *Ann Oncol.* 2018;29:731-736.
48. Zhang Y, Chen L, Hu G-Q, et al. Gemcitabine and Cisplatin Induction Chemotherapy in Nasopharyngeal Carcinoma. *N Engl J Med.* 2019;381:1124-1135.
49. Yang Q, Cao SM, Guo L, et al. Induction chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: long-term results of a phase III multicentre randomised controlled trial. *Eur J Cancer.* 2019;119:87-96.
50. Li XY, Chen QY, Sun XS, et al. Ten-year outcomes of survival and toxicity for a phase III randomised trial of concurrent chemoradiotherapy versus radiotherapy alone in stage II nasopharyngeal carcinoma. *Eur J Cancer.* 2019;110:24-31.
51. Chan AT, Grégoire V, Lefebvre JL, et al. Nasopharyngeal cancer: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2012;23(suppl 7):vii83-85.
52. Pow EH, Kwong DL, McMillan AS, et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. *Int J Radiat Oncol Biol Phys.* 2006;66:981-991.
53. Hu K, Chan A, Costantino P, Harrison LB. Cancer of the nasopharynx. In: Harrison LB, Sessions RB, Hong WK, eds. *Head and Neck Cancer: A Multidisciplinary Approach*. 4th ed. Wolters Kluwer/Lippincott Williams & Wilkins; 2014.
54. Lee N, Harris J, Garden AS, et al. Intensity-modulated radiation therapy with or without chemotherapy for nasopharyngeal carcinoma: radiation therapy oncology group phase II trial 0225. *J Clin Oncol.* 2009;27:3684-3690.
55. Moreno AC, Frank SJ, Garden AS, et al. Intensity modulated proton therapy (IMPT)—The future of IMRT for head and neck cancer. *Oral Oncol*. 2019;88:66-74.
56. Lewis GD, Holliday EB, Kocak-Uzel E, et al. Intensity-modulated proton therapy for nasopharyngeal carcinoma: decreased radiation dose to normal structures and encouraging clinical outcomes. *Head Neck.* 2016;38(suppl 1):E1886-E1895.
57. Holliday EB, Garden AS, Rosenthal DI, et al. Proton therapy reduces treatment-related toxicities for patients with nasopharyngeal cancer: a case-match control study of intensity-modulated proton therapy and intensity-modulated photon therapy. *Int J Part Ther*. 2015;2:19-28.
58. Koch WA, Starfford E, Bajaj G. Cancer of the oral cavity: general principles and management. In: Harrison LB, Sessions RB, Hong WK, eds. *Head and neck cancer: a multidisciplinary approach*. 3rd ed. J B Lippincott; 2009:265-277.
59. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2004;350:1937-1944.
60. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med.* 2004;350:1945-1952.
61. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med.* 2010;363:24-35.
62. O'Sullivan B, Huang SH, Su J, et al. Development and validation of a staging system for HPV-related oropharyngeal cancer by the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S): a multicentre cohort study. *Lancet Oncol.* 2016;17:440-451.
63. Posner MR, Lorch JH, Goloubeva O, et al. Survival and human papillomavirus in oropharynx cancer in TAX 324: a subset analysis from an international phase III trial. *Ann Oncol.* 2011;22:1071-1077.
64. Gillison ML, D'Souza G, Westra W, et al. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. *J Natl Cancer Inst.* 2008;100:407-420.
65. Garden AS, Fuller CD, Rosenthal DI, et al. Radiation therapy (with or without neck surgery) for phenotypic human papillomavirus-associated oropharyngeal cancer. *Cancer.* 2016;122:1702-1707.
66. Garden AS, Asper JA, Morrison WH, et al. Is concurrent chemoradiation the treatment of choice for all patients with Stage III or IV head and neck carcinoma? *Cancer.* 2004;100:1171-1178.
67. Chronowski GM, Garden AS, Morrison WH, et al. Unilateral radiotherapy for the treatment of tonsil cancer. *Int J Radiat Oncol Biol Phys.* 2012;83:204-209.
68. Nichols AC, Theurer J, Prisman E, et al. Radiotherapy versus transoral robotic surgery and neck dissection for oropharyngeal squamous cell carcinoma (ORATOR): an open-label, phase 2, randomised trial. *Lancet Oncol.* 2019;20:1349-1359.
69. Mendenhall WM, Werning JW. Cancer of the larynx. In: Harrison LB, Sessions RB, Hong WK, eds. *Head and Neck Cancer: A Multidisciplinary Approach.* 4th ed. Lippincott Williams & Wilkins; 2014.
70. Wolf GT, Fisher SG, Hong WK, et al. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl J Med.* 1991;324:1685-1690.
71. Lefebvre JL, Chevalier D, Luboinski B, et al. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. *J Natl Cancer Inst.* 1996;88:890-899.
72. Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol*. 2009;92:4-14.
73. Vermorken JB, Remenar E, van Herpen C, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. *N Engl J Med.* 2007;357:1695-1704.
74. Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med.* 2007;357:1705-1715.
75. Haddad R, O'Neill A, Rabinowits G, et al. Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial. *Lancet Oncol.* 2013;14:257-264.

76. Cohen EE, Karrison TG, Kocherginsky M, et al. Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer. *J Clin Oncol.* 2014;32:2735-2743.
77. Hitt R, Grau JJ, Lopez-Pousa A, et al. A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer. *Ann Oncol.* 2014;25:216-225.
78. Marur S, Li S, Cmelak AJ, et al. E1308: phase II trial of induction chemotherapy followed by reduced-dose radiation and weekly cetuximab in patients with HPV-associated resectable squamous cell carcinoma of the oropharynx—ECOG-ACRIN Cancer Research Group. *J Clin Oncol.* 2017;35:490-497.
79. Szturz P, Wouters K, Kiyota N, et al. Weekly low-dose versus three-weekly high-dose cisplatin for concurrent chemoradiation in locoregionally advanced non-nasopharyngeal head and neck cancer: a systematic review and meta-analysis of aggregate data. *Oncologist.* 2017;22:1056-1066.
80. Oliva M, Huang SH, Xu W, et al. Impact of cisplatin dose and smoking pack-years in human papillomavirus-positive oropharyngeal squamous cell carcinoma treated with chemoradiotherapy. *Eur J Cancer.* 2019;118:112-120.
81. Al-Sarraf M, Pajak TF, Marcial VA, et al. Concurrent radiotherapy and chemotherapy with cisplatin in inoperable squamous cell carcinoma of the head and neck. An RTOG Study. *Cancer.* 1987;59:259-265.
82. Kies MS, Bennett CL, Vokes EE. Locally advanced head and neck cancer. *Curr Treat Options Oncol*. 2001;2:7-13.
83. Fountzilas G, Ciuleanu E, Dafni U, et al. Concomitant radiochemotherapy vs radiotherapy alone in patients with head and neck cancer: a Hellenic Cooperative Oncology Group Phase III Study. *Med Oncol.* 2004;21:95-107.
84. Fakhry C, Westra WH, Li S, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. *J Natl Cancer Inst.* 2008;100:261-269.
85. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2006;354:567-578.
86. Mehanna H, Robinson M, Hartley A, et al. Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial. *Lancet.* 2019;393:51-60.
87. Lacas B, Bourhis J, Overgaard J, et al. Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis. *Lancet Oncol.* 2017;18:1221-1237.
88. Nguyen-Tan PF, Zhang Q, Ang KK, et al. Randomized phase III trial to test accelerated versus standard fractionation in combination with concurrent cisplatin for head and neck carcinomas in the Radiation Therapy Oncology Group 0129 trial: long-term report of efficacy and toxicity. *J Clin Oncol.* 2014;32:3858-3866.
89. Bachaud JM, Cohen-Jonathan E, Alzieu C, et al. Combined postoperative radiotherapy and weekly cisplatin infusion for locally advanced head and neck carcinoma: final report of a randomized trial. *Int J Radiat Oncol Biol Phys.* 1996;36:999-1004.
90. Cooper JS, Zhang Q, Pajak TF, et al. Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys.* 2012;84:1198-1205.
91. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). *Head Neck.* 2005;27:843-850.
92. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med.* 2008;359:1116-1127.
93. Harari PM, Harris J, Kies MS, et al. Postoperative chemoradiotherapy and cetuximab for high-risk squamous cell carcinoma of the head and neck: Radiation Therapy Oncology Group RTOG-0234. *J Clin Oncol.* 2014;32:2486-2495.
94. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med.* 2003;349:2091-2098.
95. Forastiere AA, Adelstein DJ, Manola J. Induction chemotherapy meta-analysis in head and neck cancer: right answer, wrong question. *J Clin Oncol.* 2013;31:2844-2846.
96. Pointreau Y, Garaud P, Chapet S, et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. *J Natl Cancer Inst.* 2009;101:498-506.
97. Setton J, Lee NY, Riaz N, et al. A multi-institution pooled analysis of gastrostomy tube dependence in patients with oropharyngeal cancer treated with definitive intensity-modulated radiotherapy. *Cancer.* 2015;121:294-301.
98. Taneja C, Allen H, Koness RJ, et al. Changing patterns of failure of head and neck cancer. *Arch Otolaryngol Head Neck Surg.* 2002;128:324-327.
99. Mesko S, Nguyen TP, Pollard C 3rd, et al. Head and neck reirradiation with proton therapy (PBT), IMRT, or stereotactic radiotherapy (SABR): clinical outcomes of a prospective registry. *Int J Radiat Oncol Biol Phys*. 2019;105:E378-E379.
100. CJ, Harris J, Horwitz EM, et al. Phase II study of low-dose paclitaxel and cisplatin in combination with split-course concomitant twice-daily reirradiation in recurrent squamous cell carcinoma of the head and neck: results of Radiation Therapy Oncology Group Protocol 9911. *J Clin Oncol.* 2007;25:4800-4805.
101. Lee N, Chan K, Bekelman JE, et al. Salvage re-irradiation for recurrent head and neck cancer. *Int J Radiat Oncol Biol Phys.* 2007;68:731-740.
102. Takiar V, Garden AS, Ma D, et al. Reirradiation of head and neck cancers with intensity modulated radiation therapy: outcomes and analyses. *Int J Radiat Oncol Biol Phys.* 2016;95:1117-1131.
103. Ward MC, Riaz N, Caudell JJ, et al. Refining patient selection for reirradiation of head and neck squamous carcinoma in the IMRT era: a multi-institution cohort study by the MIRI Collaborative. *Int J Radiat Oncol Biol Phys.* 2018;100:586-594.
104. Phan J, Sio TT, Nguyen TP, et al. Reirradiation of head and neck cancers with proton therapy: outcomes and analyses. *Int J Radiat Oncol Biol Phys.* 2016;96:30-41.
105. Romesser PB, Cahlon O, Scher ED, et al. Proton beam reirradiation for recurrent head and neck cancer: multi-institutional report on feasibility and early outcomes. *Int J Radiat Oncol Biol Phys.* 2016;95:386-395.
106. McDonald MW, Zolali-Meybodi O, Lehnert SJ, et al. Reirradiation of recurrent and second primary head and neck cancer with proton therapy. *Int J Radiat Oncol Biol Phys.* 2016;96:808-819.
107. Gao J, Hu J, Guan X, et al. Salvage carbon-ion radiation therapy for locoregionally recurrent head and neck malignancies. *Sci Rep.* 2019;9:4259.
108. Vargo JA, Ward MC, Caudell JJ, et al. A multi-institutional comparison of SBRT and IMRT for definitive reirradiation of recurrent or second primary head and neck cancer. *Int J Radiat Oncol Biol Phys.* 2018;100:595-605.
109. Gogineni E, Zhang I, Rana Z, et al. Quality of life outcomes following organ-sparing SBRT in previously irradiated recurrent head and neck cancer. *Front Oncol*. 2019;9:836.
110. Heron DE, Rwigema J-CM, Gibson MK, et al. Concurrent cetuximab with stereotactic body radiotherapy for recurrent squamous cell carcinoma of the head and neck: a single institution matched case-control study. *Am J Clin Oncol.* 2011;34:165-172.

111. Yamazaki H, Ogita M, Himei K, et al. Reirradiation using robotic image-guided stereotactic radiotherapy of recurrent head and neck cancer. *J Radiat Res.* 2016;57:288-293.
112. Burtness B, Harrington KJ, Greil R, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *Lancet.* 2019;394:1915-1928.
113. Gibson MK, Li Y, Murphy B, et al. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an intergroup trial of the Eastern Cooperative Oncology Group. *J Clin Oncol.* 2005;23:3562-3567.
114. Peyrade F, Cupissol D, Geoffrois L, et al. Systemic treatment and medical management of metastatic squamous cell carcinoma of the head and neck: review of the literature and proposal for management changes. *Oral Oncol*. 2013;49:482-491.
115. Guigay J, Fayette J, Dillies AF, et al. Cetuximab, docetaxel, and cisplatin as first-line treatment in patients with recurrent or metastatic head and neck squamous cell carcinoma: a multicenter, phase II GORTEC study. *Ann Oncol.* 2015;26:1941-1947.
116. Guigay J, Fayette J, Mesia R, et al. TPExtreme randomized trial: TPEx versus Extreme regimen in 1st line recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). *J Clin Oncol.* 2019;37:6002-6002.
117. Forastiere AA, Metch B, Schuller DE, et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: a Southwest Oncology Group study. *J Clin Oncol.* 1992;10:1245-1251.
118. Jacobs C, Lyman G, Velez-García E, et al. A phase III randomized study comparing cisplatin and fluorouracil as single agents and in combination for advanced squamous cell carcinoma of the head and neck. *J Clin Oncol.* 1992;10:257-263.
119. Clavel M, Vermorken JB, Cognetti F, et al. Randomized comparison of cisplatin, methotrexate, bleomycin and vincristine (CABO) versus cisplatin and 5-fluorouracil (CF) versus cisplatin (C) in recurrent or metastatic squamous cell carcinoma of the head and neck. A phase III study of the EORTC Head and Neck Cancer Cooperative Group. *Ann Oncol.* 1994;5:521-526.
120. Mehra R, Seiwert TY, Gupta S, et al. Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma: pooled analyses after long-term follow-up in KEYNOTE-012. *Br J Cancer.* 2018;119:153-159.
121. Seiwert TY, Burtness B, Mehra R, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. *Lancet Oncol.* 2016;17:956-965.
122. Bauml J, Seiwert TY, Pfister DG, et al. Pembrolizumab for platinum- and cetuximab-refractory head and neck cancer: results from a single-arm, phase II study. *J Clin Oncol.* 2017;35:1542-1549.
123. Cohen EEW, Soulieres D, Le Tourneau C, et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. *Lancet.* 2019;393:156-167.
124. Ferris RL, Blumenschein G, Jr., Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2016;375:1856-1867.
125. Gillison ML, Blumenschein G Jr, Fayette J, et al. CheckMate 141: 1-year update and subgroup analysis of nivolumab as first-line therapy in patients with recurrent/metastatic head and neck cancer. *Oncologist.* 2018;23:1079-1082.
126. Vermorken JB, Trigo J, Hitt R, et al. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. *J Clin Oncol.* 2007;25:2171-2177.
127. Fury MG, Sherman E, Lisa D, et al. A randomized phase II study of cetuximab every 2 weeks at either 500 or 750 mg/m2 for patients with recurrent or metastatic head and neck squamous cell cancer. *J Natl Compr Canc Netw*. 2012;10:1391-1398.
128. Herrero R, Quint W, Hildesheim A, et al. Reduced prevalence of oral human papillomavirus (HPV) 4 years after bivalent HPV vaccination in a randomized clinical trial in Costa Rica. *PLoS One.* 2013;8:e68329.
129. Bolla M, Lefur R, Ton Van J, et al. Prevention of second primary tumours with etretinate in squamous cell carcinoma of the oral cavity and oropharynx. Results of a multicentric double-blind randomised study. *Eur J Cancer.* 1994;30a:767-772.
130. van Zandwijk N, Dalesio O, Pastorino U, et al. EUROSCAN, a randomized trial of vitamin A and N-acetylcysteine in patients with head and neck cancer or lung cancer. For the EUropean Organization for Research and Treatment of Cancer Head and Neck and Lung Cancer Cooperative Groups. *J Natl Cancer Inst.* 2000;92:977-986.
131. Mayne ST, Cartmel B, Baum M, et al. Randomized trial of supplemental beta-carotene to prevent second head and neck cancer. *Cancer Res.* 2001;61:1457-1463.
132. Bairati I, Meyer F, Gelinas M, et al. A randomized trial of antioxidant vitamins to prevent second primary cancers in head and neck cancer patients. *J Natl Cancer Inst.* 2005;97:481-488.
133. Benner SE, Pajak TF, Lippman SM, et al. Prevention of second primary tumors with isotretinoin in patients with squamous cell carcinoma of the head and neck: long-term follow-up. *J Natl Cancer Inst.* 1994;86:140-141.
134. Hong WK, Lippman SM, Itri LM, et al. Prevention of second primary tumors with isotretinoin in squamous-cell carcinoma of the head and neck. *N Engl J Med.* 1990;323:795-801.
135. Dannenberg AJ, Lippman SM, Mann JR, et al. Cyclooxygenase-2 and epidermal growth factor receptor: pharmacologic targets for chemoprevention. *J Clin Oncol.* 2005;23:254-266.

This page intentionally left blank

Section VI

Gastrointestinal Cancer

Section Editor: Robert A. Wolff

27 Gastric, Gastroesophageal Junction, and Esophageal Cancers

28 Pancreatic Cancer

29 Biliary Tract Cancer

30 Hepatocellular Carcinoma

31 Small Bowel Cancer and Appendiceal Tumors

32 Colorectal Cancer

33 Anal Cancer

34 Neuroendocrine Tumors

This page intentionally left blank

27 Gastric, Gastroesophageal Junction, and Esophageal Cancers

Mariela Blum Murphy
Elena Elimova
Ahmed Abdelhakeem
Jaffer Ajani

KEY CONCEPTS

- Gastric cancer remains the third most common cause of cancer-related death worldwide.
- Two different pathogeneses of gastric cancer have been proposed, correlating to two histologic types: intestinal and diffuse.
- Gastrectomy is the recommended treatment in relatively early localized gastric cancer (T1b); however, in more advanced gastric cancers (T2N0, T1aN+, or T1b-T3N+), adjunctive therapy in addition to gastrectomy is recommended.
- The results of INT-0116 study (adjuvant chemoradiation) and Medical Research Council ST02/MAGIC and the FLOT study (perioperative chemotherapy) have shaped the current practice of resectable gastric cancer treatment in Western countries.
- In Asia, postoperative chemotherapy has been considered standard after gastrectomy with D2 dissection. In addition to the ACTS-GC trial and CLASSIC trial (S-1 for 1 year and CAPOX for 6 months, respectively), two new regimens (DS and SOX for 6 months) are established standards of care for stage II and/r LN-positive gastric cancer.
- Only 30% to 40% of patients with esophageal cancer have potentially resectable disease at presentation, and in many series, only 5% to 20% of those undergoing surgery alone for clinically localized disease are alive at 3 to 5 years.
- Endoscopic therapy is most effective when used to treat small (<2 cm diameter), solitary, flat lesions that are confined to mucosa (T1a).
- Surgery remains the best chance for durable survival for patients with locally advanced esophageal and gastroesophageal junction (GEJ) cancers.
- Results of the CROSS trial also emphasized the beneficial role of chemoradiotherapy before surgery, which led to a significant increase in overall survival (OS) irrespective of tumor histology.
- More than 60% of patients who present with newly diagnosed gastric, GEJ, and esophageal cancers will have advanced unresectable or metastatic disease. Although a cure is not possible, systemic therapy can prolong survival compared with best supportive care.
- As of this writing, patients in the United States are likely to undergo frontline therapy with platinum-, fluoropyrimidine-, or taxane-based chemotherapy regimens, with the addition of trastuzumab in patients with HER2-positive disease.
- Based on positive results from the RAINBOW trial, paclitaxel and ramucirumab (vascular endothelial growth factor receptor–2 targeted drug) is considered to be a standard for second-line treatment. Ramucirumab monotherapy is also considered a second-line option in advanced gastric cancer.
- Pembrolizumab is currently approved for the treatment of metastatic squamous cell carcinoma (SCC) of the esophagus as second-line treatment for tumors with combined positive score (CPS) more than 10 and programmed cell death protein 1 (PD-L1)–positive advanced gastric cancer as third-line treatment in the US. Nivolumab is also approved in the US for metastatic SCC of the esophagus regardless of PD-L1 expression, and in Japan, South Korea, and Taiwan for the treatment of gastric cancer.
- The Cancer Genome Atlas analysis has uncovered four genotypes of gastric cancer; however, it is not sufficient to change our treatment strategies, and additional work is needed.
- A multimodality approach to therapy will be the cornerstone to screening, diagnosing, staging, treating, and supporting patients with upper gastrointestinal cancers.

GASTRIC CANCER

Epidemiologic Characteristics

The incidence of gastric cancer varies widely worldwide. The highest incidence (>20 per 100,000 in men) is seen in Japan, China, Eastern Europe, and South America, whereas the lowest incidence (<10 per 100,000 in men) is seen in Northern America, parts of Africa, and Northern Europe.[1] In the United States, 27,600 new cases of gastric cancer were estimated in 2020, with 11,010 deaths.[2] Gastric cancers occur at a median age of 69 years for men and 73 years for women.[3] African Americans, Hispanic Americans, and Native Americans are 1.5 to 2.5 times more likely to develop gastric cancer than are Whites.[3] In the United States, there are changing epidemiologic patterns regarding the anatomic location of esophagogastric cancers, with a trend of decreased occurrence of distal or noncardia gastric cancers.[4] The reason for the decline is not known but may be related to change in dietary habits and food preservation. However, an increase in the incidence of gastric cardia cancers has been observed, from 2.4 cases per 100,000 individuals (1977–1981) to 2.9 cases per 100,000 individuals (2001–2006) in the White population.[4] Similarly, the Surveillance, Epidemiology, and End Results (SEER) cancer registry program in the United States shows an approximate 2.5-fold increase in the incidence of gastroesophageal junction (GEJ) adenocarcinomas from 1973 to 1992, from 1.22 cases per 100,000 individuals (1973–1978) to 2.00 cases per 100,000 individuals (1985–1990), with rates stabilizing in the last two decades, with an incidence of 1.94 cases per 100,000 individuals (2003–2008).[3,5]

Population studies suggest that proximal cancers have a different pathogenesis than distal cancers.[6] Potential causes of distal gastric cancers include *Helicobacter pylori* infection or E-cadherin expression loss, whereas proximal gastric cancers may behave similarly to distal esophageal and GEJ cancers, which progress from Barrett metaplasia to dysplasia to invasive adenocarcinoma. Only 26% of newly diagnosed gastric cancers are localized. The 5-year overall survival (OS) rate is 28.3%, which has not changed significantly over the past 30 to 40 years.[1] Surgery is still the only chance for cure, and survival can be improved with multimodality therapy. The 5-year OS rate of patients with advanced disease remains dismal, at less than 5%. Thus, despite decreasing incidence, gastric cancer remains a public health concern in the United States because of its high fatality rate.

Histologic Classification and Risk Factors

The most frequent type of gastric cancer is gastric adenocarcinoma (GAC). The WHO classifies GAC into tubular, papillary, mixed, and poorly cohesive carcinomas, whereas the Lauren classification divides GACs into intestinal, diffuse, and mixed types.[7] Intestinal-type GAC likely begins with an *H pylori* infection that leads to multistep progression (chronic active nonatrophic gastritis, multifocal atrophic gastritis, intestinal metaplasia, dysplasia, and invasive adenocarcinoma).[8] More than 40% to 50% of distal GACs are associated with *H pylori* infection.[6] Other environmental risk factors and inflammatory cytokines may influence and contribute to this multistep progression.

Population studies have identified certain environmental risk factors associated with gastric cancer. Low consumption of fruits and vegetables, high intake of N-nitroso compounds in salted and preserved foods, and occupational exposure in coal mining and nickel, rubber, and timber processing are commonly described risk factors. Additional notable risk factors include meat consumption,[9] smoking,[10] gastric surgery,[11] and reproductive hormones.[12]

Overall, the pathogenesis of intestinal-type GACs involves a series of events. This sequence of events—increased cell proliferation caused by the promotional effects of hypergastrinemia or bile reflux, increased luminal levels of mutagens (eg, N-nitroso compounds and free radicals), and decreased luminal levels of protective factors (eg, vitamin C)—provides an ideal milieu for carcinogenesis in susceptible hosts.[8]

In contrast to intestinal-type gastric cancer, diffuse-type GAC results from defective intracellular adhesion molecules, which is the consequence of loss of E-cadherin protein expression, which is encoded by the cadherin 1 (*CDH1*) gene. This can occur through germline or somatic mutation, loss of heterozygosity, or epigenetic silencing of gene transcription through aberrant methylation of the *CDH1* promoter. A study by Zheng et al showed a positive rate of E-cadherin promoter methylation in dysplasia, early cancer, and advanced cancer.[13] Furthermore, 30% of families with hereditary diffuse gastric cancer show *CDH1* germline mutations, whereas the rest remain genetically unexplained.[14] Currently, many families with hereditary diffuse gastric cancer have *CDH1* germline mutations. Inheritance is dominant. The lifetime cumulative risk for advanced gastric cancer has been estimated to be 40% to 67% in men and 60% to 83% in women.[15] Women in affected families are also at high risk for developing lobular breast cancer, with a cumulative risk of 52%.[15] A germline mutation in *TP53* is associated with familial gastric cancer,[14] which includes Li-Fraumeni syndrome. Another familial cancer syndrome associated with gastric cancer is hereditary nonpolyposis colorectal cancer, resulting from defects of DNA mismatch repair genes (*hMLH1* and *hMSH2*, more frequently) (Table 27–1).[16]

Epstein-Barr virus–associated gastric cancers have distinct clinicopathologic characteristics, including

Table 27–1 Summary of Selected Recurrent Cytogenetic Abnormalities and Frequent Molecular Changes Associated with Gastric Cancer

Conventional Cytogenetics	Simple Karyotypes	Complex Karyotypes
	+X, +8, +9, +19, del(7q), i(8q)	1, 3, 6, 7, 8, 11, 13, 17, 19
Molecular Cytogenetics	**Gains**	**Loss**
	3q, 7p, 7q, 8q, 13q, 17q, 20p, 20q	4q, 9p, 17p, 18q
Genes	**Abnormalities**	**Clinical Association**
c-met	Amplification	Tumor invasion, lymph node metastasis, poor prognosis
K-sam	Amplification	Advanced tumor stage/poor prognosis
c-erbB2	Amplification	Advanced tumor stage, lymph node and liver metastases, poor prognosis
c-myc	Amplification	Poor clinical course/predictor of aggressiveness
TP53	Loss of heterozygosity	Proliferative rate/lymph node metastasis/shortened survival
	Mutation	
	Hypermethylation	
BCL-2	Loss of heterozygosity	Depth of invasion, lymph node metastasis and survival
RUNX3	Deletion	Metastasis
	Hypermethylation	
	Loss of expression	
PTEN	Loss of heterozygosity	Advanced tumor stage/metastasis
	Mutation	
E-cadherin (*CDH1*)	Loss of heterozygosity	Tumor metastatic ability and poor prognosis
	Mutation	
	Hypermethylation	
	Reduced expression	
Cyclin E	Amplification	Disease aggressiveness/lymph node metastasis
p27	Reduced expression	Advanced tumor stage/depth of invasion/lymph node metastasis
p16	Reduced expression	Tumor invasion/metastasis
DNA repair genes/ microsatellite instability	Mutation	Age/low prevalence of lymph node metastasis/ prolonged survival
	Hypermethylation	
	Reduced expression	
Syndecan-1	Reduce expression	Tumor differentiation
β-catenin	Amplification	Lymph node metastasis
CD44s and *CD44v6*	Amplification	Lymph node metastasis
Sp1	Amplification	Cancer angiogenic potential, poor prognosis

male predominance, preferential location in the gastric cardia or postsurgical gastric stump, lymphocytic infiltration, and a more favorable prognosis.[17,18]

Despite recent progress, the precise etiologic characteristics of gastric cancer and the relationship between the environment and host are unknown. Ongoing research promises to better elucidate the tumorigenesis of gastric cancer.

Prevention

Results from a number of population studies have demonstrated an increased likelihood of *H pylori* infection in patients with gastric cancer, particularly cancer of the distal stomach.[19,20] However, gastric cancer does not occur in most patients infected with *H pylori*. Although the role of *H pylori* in gastric cancer

pathogenesis is well defined, currently there is no definitive evidence showing that mass eradication could reduce the incidence of gastric cancer.[21] A large Chinese study of 1630 patients showed no benefit in the prevention of gastric cancer with the eradication of *H pylori*.[22] However, in a subgroup of patients with no precancerous lesions on presentation, gastric cancer did not develop in any patient during a follow-up of 7.5 years after *H pylori* eradication treatment compared with six patients who received placebo ($P = .02$).[22] In another large study, short-term treatment with amoxicillin and omeprazole statistically significantly reduced gastric cancer incidence by 39% during the period extending 14.7 years after *H pylori* treatment.[23] A meta-analysis suggested that eradication could reduce the risk of gastric cancer; however, this meta-analysis was criticized for methodologic issues.[24] As of this writing, the treatment of this infection is strongly recommended for patients with peptic ulcer disease, patients with mucosa-associated lymphoid tissue lymphoma, and after endoscopic resection for esophagogastric cancer; a role for a broad prevention strategy has yet to be defined.

Clinical Presentation

At presentation, the majority of patients with symptoms will have advanced disease. Symptoms can be constitutional, such as night sweats and unintentional weight loss, or they can be vague, such as early satiety, abdominal pain, and nausea. Dysphagia is more common in patients with cancer originating in the gastric cardia or GEJ. Occult gastrointestinal (GI) bleeding is also common, whereas overt bleeding is observed in only 20% of cases.

Pathologic and Molecular Characteristics

More than 95% of gastric cancers are adenocarcinoma. The remaining 5% include neuroendocrine tumor, lymphoma, SCC, and sarcoma.

The Cancer Genome Atlas Research Network has classified gastric cancer into four subtypes based on the molecular characterization of 295 primary adenocarcinomas in a way that can ultimately guide patient therapy.[25] They clearly converged on four major genomic subtypes of gastric cancer with distinct features and classes of molecular alterations:

1. Tumors containing Epstein-Barr virus, along with recurrent mutations in the *PIK3CA* gene pathway, extreme DNA hypermethylation, amplification of Janus kinase 2 (*JAK2*), and extra copies of programmed death ligand 1 (*PD-L1*) and *PD-L2* genes, which are suppressors of immune response. This group made up about 10% of the cancers, with nearly 80% harboring a protein-changing alteration in *PIK3CA*.
2. Tumors showing microsatellite instability, in which malfunctioning DNA repair mechanisms cause a high rate of mutations, including mutations of genes encoding targetable oncogenic signaling proteins. About 20% of tumors fell into this subtype.
3. The largest category of tumors, making up about half of the cancer specimens, was termed *chromosomally unstable*. These contained a jumble of extra or missing pieces of genes and chromosomes (aneuploidy) and have a striking number of genomic amplifications of key receptor tyrosine kinases. This subtype of tumor is frequently found in the junction between the stomach and the esophagus, a type of gastric cancer that has been increasing dramatically in the United States.
4. The fourth group was termed *genomically stable* because they lacked the molecular features of the other three types. These tumors, making up 20% of the specimens, were largely those of a specific class of gastric cancer enriched for the diffuse-type histologic variant, with approximately 30% of these tumors having genomic alterations in the Ras homolog gene family, member A (*RHOA*) signaling pathway. These tumors were characterized by the lack of high levels of aneuploidy and high metastatic potential.

This classification may serve as a valuable adjunct to histopathology and provides patient stratification as a guide to targeted agents.

Staging and Prognosis

Upper GI series with barium swallow and upper esophagogastroduodenoscopy (EGD) are mainstays for diagnosing gastric cancer and provide complementary diagnostic information. EGD is more sensitive and specific to obtain tissue diagnosis. A single biopsy has 70% sensitivity for diagnosing gastric cancer; performing seven biopsies from the ulcer margin and base increases the sensitivity to more than 98%.[26] In contrast, barium swallow with upper GI series can identify both malignant gastric ulcers and infiltrating lesions, including some early gastric cancers. However, the false-negative rate with barium swallow can be as high as 50%[27] and may be even higher for early gastric cancer, and sensitivity can be as low as 14%.[27]

Cancer staging is critical prior treatment, the staging system by the American Joint Committee on Cancer (AJCC) 8th edition (2017) is the most current used (Table 27–2)[28] and includes gastric carcinoma, gastric neuroendocrine carcinoma, GEJ carcinoma with an

epicenter more than 2 cm into the stomach, and cardia carcinoma.

In this newest version, three staging guidelines by the TNM (tumor, node, metastasis) classification of malignant tumors are available: clinical stage (c stage) based on databases from United States and Japan; pathologic stage (p stage) determined after primary surgery of localized GAC; and post-neoadjuvant therapy pathology classification (yp stage), after the use of neoadjuvant therapy before surgery. According to the AJCC 8th edition, Siewert-Stein type II tumors are staged according to the esophageal cancer system, and type III tumors are staged according to the gastric system.

Because of its noninvasive nature, computed tomography (CT) has become the cornerstone of gastric cancer staging, although it is not sensitive at detecting the tumor invasion depth and local and regional lymph node involvement. Contrast-enhanced CT scans of the chest, abdomen, and pelvis can assess the locale(s) of distant extension of GAC. Currently, CT is used in conjunction with endoscopic ultrasonography (EUS) of the primary site, which provides the most accurate data for depth of tumor invasion and locoregional lymph node involvement. Endoscopic ultrasonography has an accuracy of 77% (vs 40%–50% with CT) for staging depth and 69% for staging nodes.[29] The availability of EUS-guided biopsy of suspicious local and regional lymph nodes has circumvented its limitations (Figs. 27–1 and 27–2). Laparoscopy with peritoneal washings is more invasive than CT or EUS, but it has the advantage of directly visualizing the liver surface, peritoneum, and local lymph nodes. It is

Table 27–2 A. American Joint Cancer Committee TNM Staging System for Gastric Cancer

Primary Tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial tumor with invasion of the lamina propria, high-grade dysplasia
T1	Tumor invades the lamina propria, muscularis propria, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria[a]
T3	Tumor penetrates the subserosal connective tissue without invasion of visceral peritoneum or adjacent structures[b,c]
T4	Tumor invades serosa (visceral peritoneum) or adjacent structures[b,c]
T4a	Tumor invades serosa (visceral peritoneum)
T4b	Tumor invades adjacent structures/organs
Regional Lymph Nodes (N)	
Nx	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3	Metastasis in ≥7 regional lymph nodes
N3a	Metastasis in 7–15 regional lymph nodes
N3b	Metastasis in ≥16 regional lymph nodes
Distant Metastases (M)	
Mx	Distant metastasis cannot be assessed
M0	No distant metastases
M1	Distant metastases, microscopically confirmed

[a]A tumor may penetrate the muscularis propria with extension into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures. In this case, the tumor is classified as T3. If there is perforation of the visceral peritoneum covering the gastric ligaments or the omentum, the tumor should be classified as T4.
[b]The adjacent structures of the stomach include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.
[c]Intramural extension to the duodenum or esophagus is not considered invasion of an adjacent structure but is classified using the depth of the greatest invasion in any of these sites.

AJCC Prognostic Stage Groups: B. Clinical (cTNM) 27-2B

When T is ...	And N is ...	And M is ...	Then the stage group is ...
Tis	N0	M0	0
T1	N0	M0	I
T2	N0	M0	I
T1	N1, N2, or N3	M0	IIA
T2	N1, N2, or N3	M0	IIA
T3	N0	M0	IIB
T4a	N0	M0	IIB
T3	N1, N2, or N3	M0	III
T4a	N1, N2, or N3	M0	III
T4b	Any N	M0	IVA
Any T	Any N	M1	IVB

C. Pathological (pTNM)

When T is ...	And N is ...	And M is ...	Then the stage group is ...
Tis	N0	M0	0
T1	N0	M0	IA
T1	N1	M0	IB
T2	N0	M0	IB
T1	N2	M0	IIA
T2	N1	M0	IIA
T1	N3a	M0	IIB
T2	N2	M0	IIB
T3	N1	M0	IIB
T4a	N0	M0	IIB
T2	N3a	M0	IIIA
T3	N2	M0	IIIA
T4a	N1	M0	IIIA
T4a	N2	M0	IIIA
T4b	N0	M0	IIIA
T1	N3b	M0	IIIB
T2	N3b	M0	IIIB
T3	N3a	M0	IIIB
T4a	N3a	M0	IIIB
T4b	N1	M0	IIIB
T4b	N2	M0	IIIB
T3	N3b	M0	IIIC
T4a	N3b	M0	IIIC
T4b	N3a	M0	IIIC
T4b	N3b	M0	IIIC
Any T	Any N	M1	IV

D. Post-Neoadjuvant Therapy (ypTNM) 27-2D

When T is ...	And N is ...	And M is ...	Then the stage group is ...
T1	N0	N0	I
T2	N0	M0	I
T1	N1	M0	I
T3	N0	M0	II
T2	N1	M0	II
T1	N2	M0	II
T4a	N0	M0	II
T3	N1	M0	II
T2	N2	M0	III
T1	N3	M0	II
T4a	N1	M0	III
T3	N2	M0	III
T2	N3	M0	III
T4b	N0	M0	III
T4b	N1	M0	III
T4a	N2	M0	III
T3	N3	M0	III
T4b	N2	M0	III
T4b	N3	M0	III
T4a	N3	M0	III
Any T	Any N	M1	IV

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging System (2020).

sensitive at diagnosing liver metastases and peritoneal carcinomatosis in up to 23% of patients in whom no such involvement was seen on CT[30] and up to 13% of patients with positive cytology only.[31] Diagnostic laparoscopy is usually performed when all noninvasive studies (CT and EUS) demonstrate localized or potentially resectable disease in patients with higher than T1b disease on EUS. Positive peritoneal cytology represents stage IV disease according to the AJCC system.

The effectiveness of fluorodeoxyglucose (FDG) positron emission tomography (PET) at diagnosing gastric cancer is uncertain because as many as 50% of primary tumors are FDG negative, particularly early gastric cancers.[32] Insufficient FDG uptake is mostly associated with diffuse-type gastric cancer with signet ring cells and mucinous content.[33] Currently, FDG-PET has no role in the primary detection of gastric cancer because of its low sensitivity. On the other hand, FDG-PET shows better results in the evaluation of lymph node metastases in gastric cancer compared with CT and could thus have a role in preoperative staging. For patients with FDG-positive disease, FDG-PET can be used to predict histologic response and survival outcomes,[34–36] similar to results seen among patients with distal esophageal and GEJ adenocarcinoma.[37] The addition of FDG-PET to CT increases diagnostic accuracy for recurrent gastric cancer because PET/CT is as sensitive and specific as contrast CT at detecting recurrent disease, except peritoneal seeding.[38]

Among patients with gastric cancer who had surgery, factors affecting gastric cancer prognosis include nodal involvement, tumor location, histologic grade, and lymphovascular invasion.[39] Patients with proximal gastric cancer have a poorer prognosis than those with distal gastric cancer, at 28.5 versus 58.6 months ($P < .02$).[40] Although associations have been found between molecular genetic changes and pathologic features and biologic behavior and prognosis, the clinical significance of these genetic changes has not yet been established. In other words, these genetic parameters have been unable to translate into meaningful clinical diagnostic, predictive, or prognostic biomarkers. Therefore, the putative biomarker screening method for gastric cancer also remains elusive. However, with better appreciation of the complex interplay between environment and host factors leading to gastric tumorigenesis, researchers hope to produce more effective screening methods for high-risk patients, better prognostic and predictive biomarkers, and superior therapeutic indices of cancer drugs.

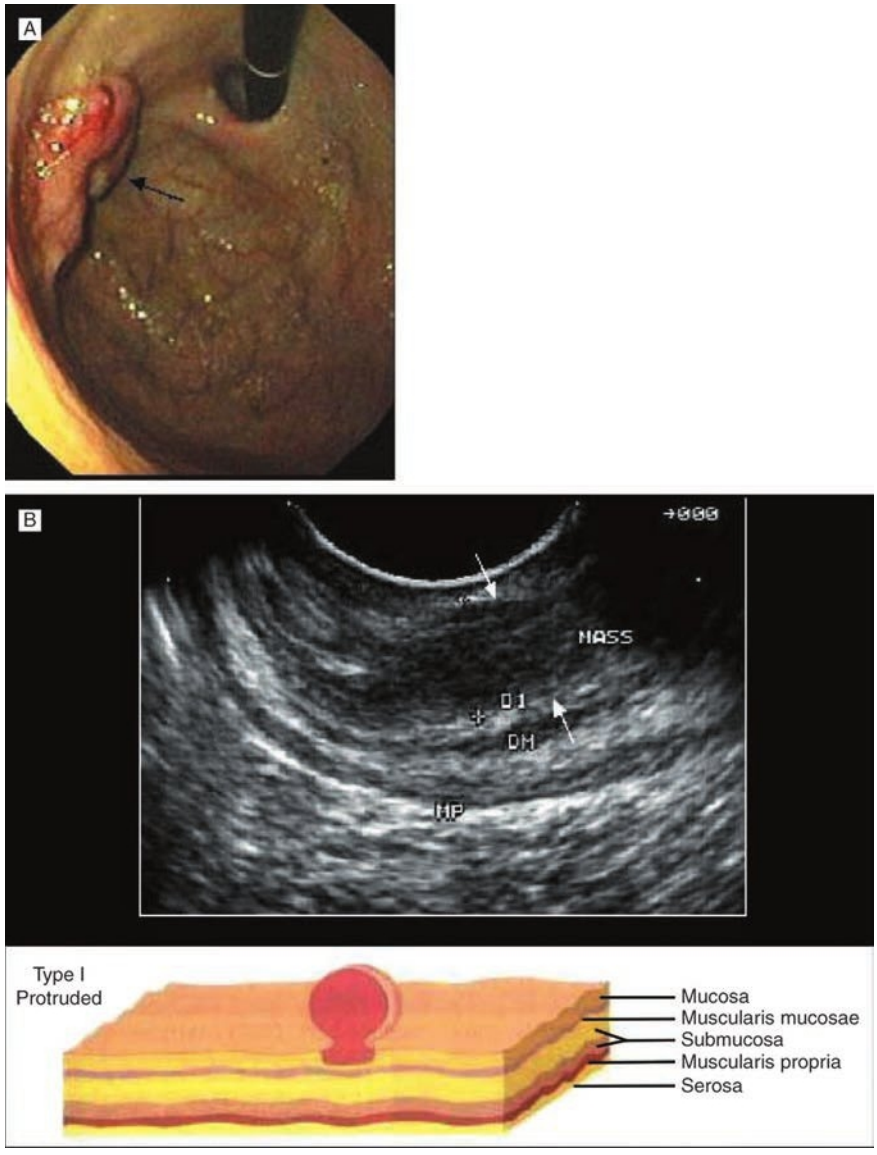


FIGURE 27–1 Gastric cancer: T1 lesion. **A.** Endoscopic view. **B.** Endoscopic ultrasound view. (Reproduced with permission from http://www.massgeneral.org/gastro/endo_homepage.htm)\

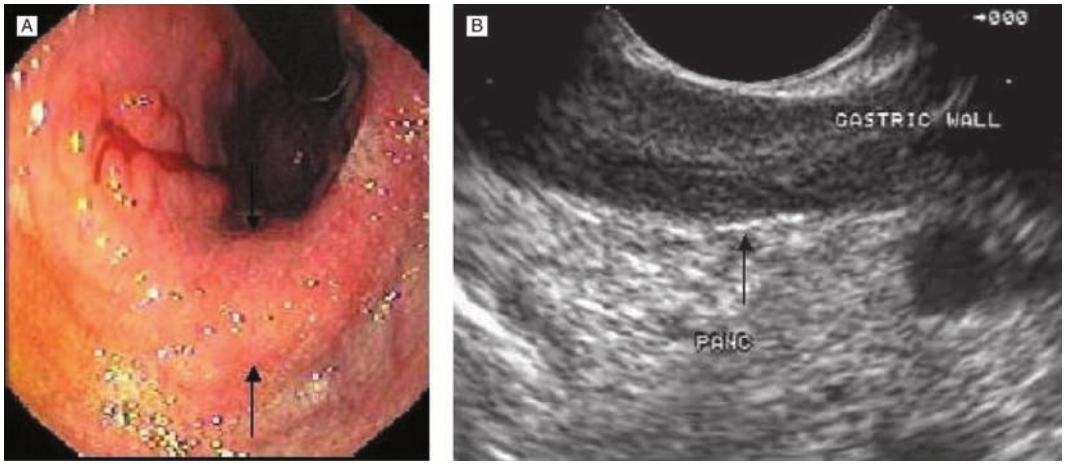


FIGURE 27–2 Gastric cancer: T2N1 lesion. **A.** Endoscopic view. **B.** Endoscopic ultrasound view. (Reproduced with permission from http://www.massgeneral. org/gastro/endo_homepage.htm)

Treatment

Gastric cancer is treated according to the cancer stage at presentation. Reflecting the newest changes in the AJCC staging system, treatment for GEJ and proximal gastric adenocarcinoma smaller than 5 cm from the GEJ is discussed in the esophageal cancer section. Treatment for patients with locally advanced gastric cancer is dichotomized into resectable and unresectable disease. Surgery remains the best chance for long-term survival, but 5-year survival rates after surgery alone are 20% to 50%, and adjunctive therapy, such as chemotherapy or chemoradiotherapy, must be offered. Localized gastric cancer can be classified as clinical T1 disease or higher with or without involved regional lymph nodes. A minimum of 15 examined lymph nodes is recommended for adequate surgical staging.[41] The adjunctive therapy used for the treatment of localized gastric cancer in addition to surgery depends on geographic location in the world. In North America and Europe, results from the Intergroup INT-0116[42] (the adjuvant chemoradiotherapy approach) and Medical Research Council Adjuvant Infusional Chemotherapy (MAGIC)[43] (the perioperative chemotherapy approach) trials established the standard of care in the early 2000s. Most recent trials like FLOT (continuous infusion 5-FU, leucovorin, oxaliplatin, and docetaxel) given perioperatively have also become standard of care. In Asia, however, adjuvant chemotherapy after a D2 nodal dissection is considered the gold standard.[44,45]

Unfortunately, the main therapeutic goal in patients with unresectable locally advanced disease remains symptom palliation. The treatment of unresectable locally advanced and metastatic gastric cancers is discussed in two separate subsections: Unresectable Locally Advanced Gastric, Gastroesophageal Junction, and Esophageal Cancers; and Advanced and Metastatic Gastric, Gastroesophageal Junction, and Esophageal Cancers.

Resectable Disease

Surgery

Surgical resection offers the best chance for long-term survival in patients with localized disease, particularly in combination with postoperative (adjuvant) chemoradiotherapy[42] or perioperative chemotherapy.[43] Even with newer staging modalities, the major barrier to accurately identify patients with potentially resectable disease is the ability to accurately stage disease. In the United States, 67% of patients present with stage III or IV disease, and only 10% present with stage I disease.[46]

By definition, curative resection (also referred to as R0 resection) involves removal of the primary cancer and regional lymph nodes with free margins. The goals of surgery are twofold: local control and (it is hoped) eradication of gastric cancer and (2) attainment of accurate pathologic staging. Considerations for surgical management of gastric cancer are the (1) extent of luminal resection (total vs partial gastrectomy) and (2) extent of lymph node dissection. Total gastrectomy is mainly reserved for proximal gastric cancer and large midgastric tumors or linitis plastica (wherein a large region of the stomach is extensively infiltrated by cancer, resulting in a rigid, thickened fold), whereas partial gastrectomy may be used in distal gastric tumors. Two randomized controlled trials have demonstrated similar survival outcomes for total and partial gastrectomy for distal gastric cancer.[47,48] OS rates improved from 5% for R2 (surgical resection with gross residual disease) to 50% for R0.[47]

Japanese surgeons routinely perform extended lymphadenectomy, whereas in the United States, 54% of patients who underwent primary gastrectomy undergo less than a D1 lymphadenectomy.[42] A D1 lymphadenectomy refers to a limited dissection of the perigastric lymph nodes, whereas D2 refers to the removal of nodes along the hepatic, left gastric, celiac, and splenic arteries, as well as those in the splenic hilum. A D3 lymph node dissection includes lymph nodes located within the porta hepatis and periaortic regions.

Proponents of extended lymphadenectomy argue that only with extended dissection can accurate staging be guaranteed, which also implies accurate prediction of stage-specific survival. Furthermore, with extensive nodal dissection, locoregional relapse rates are lower. Using SEER Project data from 1973 to 2000, Schwarz and Smith[49] evaluated 1377 patients with locally advanced gastric cancer (stages IIIA, IIIB, and IV, M0). The total lymph node (LN) count (or number of negative LNs examined; $P < .0001$) and number of positive LNs ($P < .0001$) were independent prognostic survival predictors. Furthermore, the stage-based survival prediction depended on the total LN number and number of negative LNs. In their earlier analysis of SEER data from 1973 to 1999, these same investigators demonstrated that for every 10 extra LNs dissected, survival improved by 7.6% (T1/2N0), 5.7% (T1/2N1), 11% (T3N0), or 7% (T3N1).[50] The results of this analysis demonstrated that for all T stages, extensive nodal dissection affects survival outcomes. Similarly, a 5-year survival benefit was reported for patients with D2 and D3 dissections compared with D1 lymphadenectomy (60% vs 54%, $P = .041$) in a Taiwanese study involving 221 patients with resectable gastric cancer.[51]

Despite this evidence, prospective studies performed in non-Asian countries were unable to confirm these findings.[41,52–54] The Medical Research Council (MRC) randomly assigned 400 patients with resectable gastric cancer to D1 or D2 nodal dissection. Postoperative morbidity and mortality rates were higher for D2

(46% and 13%) than for D1 (28% and 6%) dissection.[54] Both the initial and long-term follow-up results in the Dutch Gastric Cancer Group study demonstrated a significant increase in morbidity and mortality, with no survival difference between D1 and D2 dissections.[41,53] Although these large prospective studies performed in non-Asian countries could not confirm the initial findings, they went on to suggest that extended lymphadenectomy carries increased rates of morbidity and mortality, with a negligible change in survival.

Despite some disagreement about the benefits of D2 dissection, most experts agree that localized gastric cancer with clinical stage higher than T1b is best treated with multidisciplinary approaches and at high-volume centers, particularly by high-volume surgeons.[55,56] We acknowledge that the literature lacks convincing results in favor of D2 dissection in randomized studies to date that have compared D1 versus D2 dissections; however, the pendulum is swinging in favor of a more thorough nodal dissection by experienced surgeons. A nodal dissection approaching D2 can have the following advantages: accurate nodal staging and removal of more uninvolved nodes, which is associated with prolonged survival.[53,57] A 15-year update of the Dutch trial showed benefit in the D2 group in terms of the hazard ratio (HR) for gastric cancer–related death (0.74; 95% CI, 0.59–0.93; $P = .01$); however, only a few patients were at risk.[58]

Perioperative Chemotherapy

This approach is based on the assumption that neoadjuvant systemic therapy can lead to tumor downstaging, leading to an improved R0 resection rate. This is particularly significant in Western patients in whom the tumors are usually bulky at diagnosis.[59] The MAGIC trial established level 1 evidence for this approach.[43] The study enrolled 503 patients with gastric, GEJ, and esophageal adenocarcinoma.[43] These patients were randomly assigned to receive three cycles of perioperative chemotherapy consisting of epirubicin, cisplatin, and infusional 5-fluorouracil (5-FU) (ECF) followed by surgery, followed by three more cycles of ECF, or surgery followed by observation. In this trial, postoperative chemotherapy proved hard to deliver, with only 34% of patients receiving this treatment, and only 68% of patients underwent a curative resection. Despite this, both progression-free survival (PFS) and OS were improved in the group receiving ECF (HR for progression, 0.66; 95% CI 0.53–0.81; $P < .001$; HR for death, 0.75; 95% CI 0.60–0.93; $P = .009$). Five-year survival rates were 36.3% (95% CI 29.5%–43.0%) among patients in the perioperative chemotherapy group and 23.0% (95% CI 16.6%–29.4%) among those in the surgery group.[43] Taken together, these data suggest that the majority of the benefit may in fact come from the preoperative portion of the chemotherapy.

A second, French study supports the findings of the MAGIC trial. The Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) and the Fédération Francophone de Cancérologie Digestive (FFCD) multicenter phase 3 trial was terminated prematurely for poor accrual and is therefore not adequately powered.[60] Overall, 224 patients with resectable adenocarcinoma of the lower esophagus, GEJ, or stomach (only 25%) were randomly assigned to either perioperative chemotherapy (with cisplatin and 5-FU) and surgery followed by three to four cycles of cisplatin and 5-FU or surgery alone. Only approximately 50% of patients received any postoperative chemotherapy. Despite these issues, the chemotherapy and surgery group had a significantly higher OS (HR for death, 0.69; 95% CI 0.50–0.95; $P = .02$) and disease-free survival (DFS; HR for recurrence or death, 0.65; 95% CI 0.48–0.89; $P = .003$). Five-year survival rates were 38% (95% CI 29%–47%) in the chemotherapy and surgery group compared with 24% (95% CI 17%–33%) in the surgery group. These results are quite similar to those of the MAGIC trial and bring into question the usefulness of the addition of epirubicin to cisplatin and 5-FU.

In contrast, a study by the European Organization for Research and Treatment of Cancer (EORTC 40954) did not demonstrate a benefit from the addition of perioperative chemotherapy.[61] This trial showed a significantly increased R0 resection rate but failed to demonstrate a survival benefit with the addition of chemotherapy; however, it was not sufficiently powered to demonstrate a difference, given its premature termination because of poor accrual.

The Arbeitsgemeinschaft Internistische Onkologie (AIO) German group conducted a multicenter, open-label, randomized phase 2/3 trial (FLOT4) comparing four pre- and four postoperative cycles of conventional ECF versus FLOT in 716 patients with resectable gastric or GEJ adenocarcinoma. Most patients had T3–4 disease (79%–83%) and were node-positive (78%–81%), and a minority had diffuse histology primaries (27%). The OS was significantly improved with FLOT versus ECF (50 vs 35 months; HR 0.77; $P = .012$), with a projected improvement in 5-year OS (45% vs 36%). PFS was also improved with FLOT (30 vs 18 months; HR 0.75; $P = .0036$), as were rates of R0 resection (85% vs 78%), tumor stage T1 or higher (25% vs 15%), and nodal status N0 (49% vs 41%). Rates of adverse events were comparable for the two regimens. The FLOT4 study has established FLOT as the new standard of care for perioperative chemotherapy in patients with resectable gastric cancer who can tolerate a triplet chemotherapy regimen.[62]

The Japanese Clinical Oncology Group (JCOG 0501) published results from their randomized phase 3 trial of gastrectomy with or without neoadjuvant

S-1 plus cisplatin for type 4 (linitis plastica) or large type 3 (>8 cm ulcerative) gastric cancer. Patients were randomly assigned to surgery followed by adjuvant chemotherapy (S-1, days 1–28, q42d for 1 year) (Arm A) or neoadjuvant chemotherapy (NAC) (S-1, 80–120 mg/body, days 1–21 and cisplatin, 60 mg/m2, day 8, q28d, 2 courses) followed by gastrectomy plus the same adjuvant chemotherapy (Arm B). The primary end point was OS. S-1 adjuvant chemotherapy for one year showed remarkable survival results for type 4 or large type 3 gastric cancer, and additional NAC with S-1 plus CDDP was not recommended.[63]

Postoperative Chemoradiotherapy

The indication of adjuvant chemoradiotherapy comes from level 1 evidence of its benefit from the Intergroup INT-0116 trial that showed a significant improvement in OS in the group of patients treated with adjuvant chemoradiotherapy.[42,64] In this trial, 559 patients with stage IB to IV disease were randomly assigned to chemoradiotherapy after surgery or surgery alone. The chemoradiotherapy group received chemotherapy consisting of one 5-day cycle of 5-FU and leucovorin (LV) starting on day 1, followed by chemoradiotherapy beginning 28 days after the start of the initial cycle of chemotherapy. Chemoradiotherapy consisted of 45 Gy of radiation at 1.8 Gy/day 5 days per week for 5 weeks, with 5-FU (400 mg/m2/d) and LV (20 mg/m2/d) on the first four and the last three days of radiotherapy. One month after the completion of radiotherapy, two 5-day cycles of 5-FU (425 mg/m2/d) plus LV (20 mg/m2/d) were given one month apart. The 3-year survival rates were 50% in the chemoradiotherapy group and 41% in the surgery-only group. The HR for death in the surgery-only group, compared with the chemoradiotherapy group, was 1.35 (95% CI 1.09–1.66; $P = .005$). The HR for relapse in the surgery-only group, compared with the chemoradiotherapy group, was 1.52 (95% CI 1.23–1.86; $P < .001$).[42] Recently updated results of this study continue to demonstrate a benefit in terms of both OS and recurrence-free survival (RFS).[65] The major issue of this study was that the majority of patients did not receive an adequate LN dissection. Although a D1 resection was mandated per protocol, more than 50% of patients underwent a D0 resection, and only 10% of patients underwent a D2 nodal dissection. Therefore, it is questioned whether the survival difference occurred because of inadequate surgery rather than from a true benefit of chemoradiotherapy.[42]

Cancer and Leukemia Group B (CALGB) 80101, a US intergroup study, was designed to evaluate postoperative bolus 5-FU and LV with 5-FU plus concurrent radiation (an INT0116 trial treatment regimen) versus postoperative ECF (the MAGIC trial regimen) before and after 5-FU plus concurrent radiation in 546 patients with gastric or GEJ tumors after curative resection.[64] In a preliminary report presented at the 2011 American Society of Clinical Oncology annual meeting, patients receiving ECF had lower rates of diarrhea, mucositis, and grade 4 or worse neutropenia. Overall survival, the primary end point, was not significantly better with ECF (3-year OS, 52% vs 50% for ECF and 5-FU/LV, respectively), regardless of the location of the primary tumor.

The Adjuvant Chemoradiation Therapy in Stomach Cancer (ARTIST) trial compared adjuvant chemoradiotherapy with adjuvant chemotherapy after an R0 resection with D2 dissection in 458 patients.[66] The ARTIST trial was a negative study because its primary end point, 3-year DFS rate, was not statistically different between the two groups. In subgroup analyses, patients with node-positive disease in the adjuvant chemoradiotherapy group had a significantly improved 3-year DFS rate than those in the adjuvant chemotherapy group. The improved DFS among patients with node-positive disease was later confirmed in the recently published update; however, there was no improved OS despite the prolonged follow-up interval.[67] This improved DFS finding may suggest that compared with adjuvant chemotherapy, adjuvant chemoradiotherapy may be beneficial among patients with node-positive resectable gastric cancer, a theory that was tested in the ARTIST-2 trial (see below). Different from INT0116, all patients in the ARTIST-2 trial were required to have a D2 nodal dissection, and the chemotherapy administered to all patients consisted of S-1 versus S-1 and oxaliplatin with or without radiotherapy. Hence, ARTIST-2 was designed to evaluate the benefit of chemoradiotherapy after a D2 nodal dissection.[68,69]

The Dutch phase 3 (CRITICS) trial evaluated the strategy to integrate postoperative chemoradiotherapy with conventional perioperative strategy.[70] Postoperative chemoradiotherapy in addition to preoperative chemotherapy did not improve OS compared with perioperative chemotherapy in patients with resectable gastric cancer treated with adequate preoperative chemotherapy and surgery. In this study, only 60% of all randomly assigned patients could receive the planned postoperative treatment, which was consistent with the MAGIC approach. Optimizing preoperative strategies is the focus of the CRITICS II (NCT02931890) study.[71]

The TOPGEAR trial, which is underway in Australia, Europe, and Canada, directly compares perioperative chemotherapy alone (ECF/ECX/EOX or FLOT) versus preoperative chemoradiotherapy in patients with resectable adenocarcinoma of the stomach and GEJ (NCT01924819).[72] Ajani et al[73] reported the results of several phase 2 studies that demonstrated the

feasibility and effectiveness of a three-step strategy. Thirty-seven patients with locally advanced resectable gastric cancer were treated with trimodality therapy in a phase 2 clinical trial. Chemotherapy consisted of infusional 5-FU, cisplatin, and paclitaxel (FPT); 45 Gy of radiotherapy was administered concurrently with FPT. R0 and pathologic complete response (pathCR) rates were 95% and 30%, respectively. Fourteen percent of patients had only microscopic residual disease. Patients who achieved pathCR or pathologic partial response after preoperative chemoradiotherapy had significantly longer median survival durations than those who did not (63.9 vs 12.6 months; $P = .03$).

As a result of the MDACC's single-institution success with preoperative trimodality therapy, the Radiation Therapy Oncology Group (RTOG) sponsored a multi-institution cooperative study, RTOG 9904. The primary end point was pathCR rate. Forty-nine patients with localized resectable gastric cancer from 20 institutions received 5-FU, LV, and cisplatin (FLP) as induction chemotherapy, followed by concurrent chemoradiotherapy with 5-FU and weekly paclitaxel. The pathCR and R0 resection rates were 26% and 77%, respectively. At one year, more patients who had achieved pathCR (82%) were alive than those who did not (69%).[74] A D2 dissection was performed in 50% of patients. The heterogeneity of different treating institutions minimized the selection bias typical of single-institution results. Outcomes in RTOG 9904 were no better or worse than those of more recent studies, particularly the pathCR and D2 lymphadenectomy rates.

Postoperative Chemotherapy

The benefits of adjuvant chemotherapy after a D2 nodal dissection were initially demonstrated in Japan, and the chemotherapy used was S-1.[44] The Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) trial randomly assigned 1059 patients to one year of S-1 or observation. The updated analysis after 5 years of follow-up has demonstrated consistent results.[75] The OS rate at 5 years was 71.7% in the S-1 group and 61.1% in the surgery-only group (HR 0.669; 95% CI 0.540–0.828). The RFS rate at 5 years was 65.4% in the S-1 group and 53.1% in the surgery-alone group (HR 0.653; 95% CI 0.537–0.793).

Another Asian study, the Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer (CLASSIC) trial, randomly assigned 1035 patients who had undergone D2 gastrectomy to capecitabine plus oxaliplatin for 6 months or observation.[45] The study demonstrated a benefit in patients treated with capecitabine and oxaliplatin for the primary end point of DFS (at 3 years; HR 0.56; 95% CI 0.44–0.72; $P < .0001$) at the prespecified interim analysis. After this analysis, the trial was stopped after a recommendation by the data monitoring committee. The mature OS data were published in *The Lancet Oncology*.[67] By the clinical cutoff date, 103 patients (20%) had died in the adjuvant capecitabine and oxaliplatin group versus 141 patients (27%) in the observation group (stratified HR 0.66; 95% CI 0.51–0.85, $P = .0015$). Estimated 5-year OS was 78% (95% CI 74%–82%) in the adjuvant capecitabine and oxaliplatin group versus 69% (95% CI 64%–73%) in the observation group. Based on these results, CAPOX has been established as another standard postoperative treatment for patients with stage II/III gastric cancer in Asia.

Recently, Japan Clinical Cancer Research Organization (JACCRO) demonstrated the superiority of RFS (HR 0.632) of docetaxel plus S1 (DS) versus S1 alone for stage III GC patients. In the DS group, one 3-week cycle of S1 was given on days 1 to 14, followed by six cycles of S1 (days 1–14) and 40 mg/m2 of docetaxel on day 1 every 3 weeks. This was followed by S1 on days 1 to 28 every 6 weeks for up to one year. Postoperative DS has become the new standard for the curatively resected stage III GC in Japan.[76,77]

The Korean phase 3 trial (ARTIST-II) randomly assigned, in a 1:1:1 ratio, patients with pathologically staged II or III, node-positive, D2-resected gastric cancer, to receive adjuvant S-1 (40–60 mg twice daily 4 weeks on/2 weeks off) for one year, S-1 (2 weeks on and 1 week off) plus oxaliplatin 130 mg/m2 (SOX) for 6 months, or SOX plus chemoradiotherapy 45 Gy (SOXRT). A total of 538 patients were included for this interim efficacy analysis.[78] The DFS at 3 years was found to be 65%, 78%, and 73% in the S-1, SOX, and SOXRT arms, respectively. No difference in DFS between SOX and SOXRT was found (HR 0.910; $P = .667$). The independent monitoring committee ended the trial early, concluding that in patients with curatively D2-resected, stage II/III, node-positive GC, adjuvant SOX was effective in prolonging DFS, when compared with S-1 monotherapy.

Positive results were also reported in another Korean trial, the PRODIGY study.[79] In this trial, 530 patients with newly diagnosed locally advanced gastric or GEJ adenocarcinoma (cT2,3/N[+]M0 or cT4/N[any]M0, per AJCC 7th ed), ECOG PS 0-1, were randomized 1:1 to NAC docetaxel, oxaliplatin, and S-1 (DOS) then surgery and adjuvant S-1 ($n = 266$), or surgery and adjuvant S-1 ($n = 264$). NAC was docetaxel 50 mg/m2 intravenous and oxaliplatin 100 mg/m2 intravenous on day 1, S-1 40 mg/m2 twice by mouth on days 1 to 14 every 3 weeks for 3 cycles. Standard surgery was D2 gastrectomy. DOS and postoperative S-1 showed longer PFS (primary end point) over postoperative S1 in cT2/3-LN positive or cT4 resectable GC.

All major phase 3 trials in localized gastric cancer and the most important ongoing studies in this setting are summarized in Tables 27–3 and 27–4. Given the variability in outcomes in many phase 3 trials, several

Table 27–3 Major Phase 3 Trials for Gastric Cancer in the Localized Setting

Trial	No. of Patients	Treatment Arms	HR for OS (*P* value)	Primary End Point Comparison in Months (Survival Rates in %)
Perioperative Chemotherapy				
Cunningham et al (MAGIC)[43]	503	ECF → surgery → ECF vs surgery	0.75 (.009)	5-y OS: 36.3% vs 23%
Ychou et al (FNLCC/FFCP)[60]	224	CF → surgery → CF vs surgery	0.69 (.02)	5-y OS: 38% vs 24%
Schuhmacher et al (EORTC 40954)[61]	144	CFL → surgery vs surgery (only preoperative CT)	0.16	Underpowered to demonstrate a survival end point because of limited accrual (144/360 patients)
Al-Batran et al (FLOT4)[62]	716	ECF → surgery → ECF vs FLOT → surgery → FLOT	0.77 (.012)	OS: 25 months vs 50 months 5-y OS: 36% vs 45%
Terashima et al (JCOG0501)[63]	300	Surgery → S1 vs S-1+cisplatin → surgery → S1	0.74	3-y OS: 17.5% vs 27.5%
Cunningham et al (MAGIC B/ST03)[80]	1063	ECX+bevacizumab → surgery → ECX+bevacizumab → maintenance bevacizumab vs ECX → Surgery → ECX	1.08 (.36)	3-y OS: 48.1% vs 50.3%
Park et al (ARTIST-2)[78]	538	Surgery → S-1 vs Surgery → S-1+oxaliplatin (SOX) vs Surgery → SOX+CTRT (SOXRT)	0.617 (.016) S-1 vs SOX 0.686 (.057) S-1 vs SOXRT	3-y DFS: 65% vs 78% vs 73%
Postoperative Chemoradiotherapy				
Macdonald et al (INT-0116)[42]	556	Surgery → FL/CTRT (45 Gy+FL)/FL vs surgery	1.32 (.004)	OS: 36 vs 27
Fuchs et al (CALGB 80101)[64]	546	Surgery → ECF/CTRT+FL/ECF vs surgery → FL/CTRT+FL/FL	1.03 (.80)	OS: 38 vs 37
Lee et al (ARTIST)[66]	458	Surgery → XP/XRT/XP vs surgery → XP	1.130 (.5272); N+ patients: HR for DFS, 0.70 (.04)	5-y OS: 75% vs 73%; N+ patients: 3-y DFS: 76% vs 72%
Cats et al (CRITICS)[70]	788	CT → surgery → CT vs CT→ surgery → CTRT	1.01 (.09)	OS: 43 vs 37
Postoperative chemotherapy				
Sasabo et al (ACTS- GC)[75]	1059	Surgery → S-1 vs surgery	0.68 (.003); HR at 5 years: 0.669	3-y OS: 80.1% vs 70.1%; 3-y RFS: 72.2% vs 59.6%
Bang et al (CLASSIC)[45]	1035	Surgery → CapeOx vs surgery	0.56 (< .0001)	3-y DFS: 74% vs 59%
Tsuburaya et al (SAMIT), 2× 2 factorial design[81]	1495	Surgery → UFT vs surgery → S-1 vs surgery → paclitaxel+UFT vs surgery → paclitaxel+S-1	HR for DFS 0.81 (.0048) for monotherapy (0.151 for noninferiority of UFT), 0.92 (.273) for monotherapy vs sequential	3-y DFS: 53% vs 58.2% (UFT vs S-1), 54% vs 57.2% (monotherapy vs sequential)
Yoshida et al (JACCRO GC-07)[77]	915	Surgery →S-1+docetaxel vs surgery →S-1	0.632 (<.001)	3-y RFS: 66% vs 58%

CapeOx, capecitabine and oxaliplatin; CF, cisplatin and 5-fluorouracil; CFL, cisplatin, 5-fluorouracil, and leucovorin; CT, chemotherapy; CTRT, chemoradiotherapy; DFS, disease-free survival; ECF, epirubicin, cisplatin, and 5-fluorouracil; FL, 5-fluorouracil and leucovorin; HR, hazard ratio; OS, overall survival; RFS, recurrence-free survival; SOX, S-1 + oxaliplatin UFT, tegafur and uracil; XP, capecitabine and cisplatin; XRT, capecitabine and radiotherapy.

Table 27–4 List of Ongoing Phase 3 Trials in Localized Gastric Cancer

Trials	No. of Patients	Treatment Arms	Control Arm	Status
Perioperative Chemotherapy				
Ychou et al (FNLCC 94012-FFCD 9703)[60]	250	CF → surgery (only neoadjuvant CT)	Surgery	Active, not recruiting
Postoperative + Preoperative Chemoradiotherapy				
Leong et al (TOPGEAR)[72]	752	ECF → CTRT + 5-FU–based CT → Surgery → ECF	ECF → Surgery → ECF	Recruiting
Kang et al (PRODIGY)[79]	530	CT→ Surgery→ S-1	Surgery → S-1	Active, not recruiting

CF, cisplatin and 5-fluorouracil; CT, chemotherapy; CTRT, chemoradiotherapy; CX, cisplatin and capecitabine; ECF, epirubicin, cisplatin, and 5-fluorouracil; ECX, epirubicin, cisplatin, and capecitabine; 5-FU, 5-fluorouracil; S-1 Ox, S-1 and oxaliplatin.

CHAPTER 27

Table 27–5 Perioperative or Postoperative Therapy for Localized Gastric Cancer: Results of Meta-Analyses

Reference	No. of Studies	No. of Patients	HR for OS	Treatment
Diaz-Nieto et al[82]	34	7,824	0.85	Postoperative chemotherapy
Ronellenfitsch et al[83]	14	2,422	0.81	Perioperative chemo(radio)therapy
Oba et al[84]	14	3,288	DFS: 0.92	Postoperative chemotherapy
Earle et al[84]	13	NR (non-Asian patients)	0.80	Postoperative chemotherapy

DFS, disease-free survival; HR, hazard ratio; NR, not reported yet; OS, overall survival.

meta-analyses have been undertaken (Table 27–5), all of which support a significant survival benefit for perioperative or adjuvant chemotherapy with somewhat better prognosis shown in Asian compared with Western populations,[82–84], including one that was limited to trials from Western (non-Asian) countries.[85] One of the most recent of these analyses evaluated data from 34 randomized trials comparing adjuvant systemic chemotherapy versus surgery alone, conducted in both Asian and Western populations.[82] The risk of death in patients receiving adjuvant chemotherapy was reduced by 15% (HR for death, 0.85; 95% CI 0.80–0.90).

Based on the previously mentioned trials and meta-analyses, postoperative chemoradiotherapy (United States), perioperative chemotherapy (Europe), and adjuvant chemotherapy after a D2 nodal dissection (Asia) can all be regarded as standards of care in the management of localized gastric cancer.

Figure 27-3A summarizes MDACC's approach to localized gastroesophageal cancer.

MD ANDERSON PRACTICE TIPS

RESECTABLE GASTRIC CANCER

- All patients with newly diagnosed gastric cancer undergo a CT imaging and upper endoscopy.
- Patients with resectable gastric cancer also undergo EUS and diagnostic laparoscopy with peritoneal washings.
- MDACC has been developing the practice of multimodality management in a multidisciplinary setting for all patients, but it is especially useful for those with resectable disease. Preoperative trimodality therapy consisting of induction chemotherapy followed by chemoradiotherapy and then surgical resection has been tested and evolved at MDACC over many years.

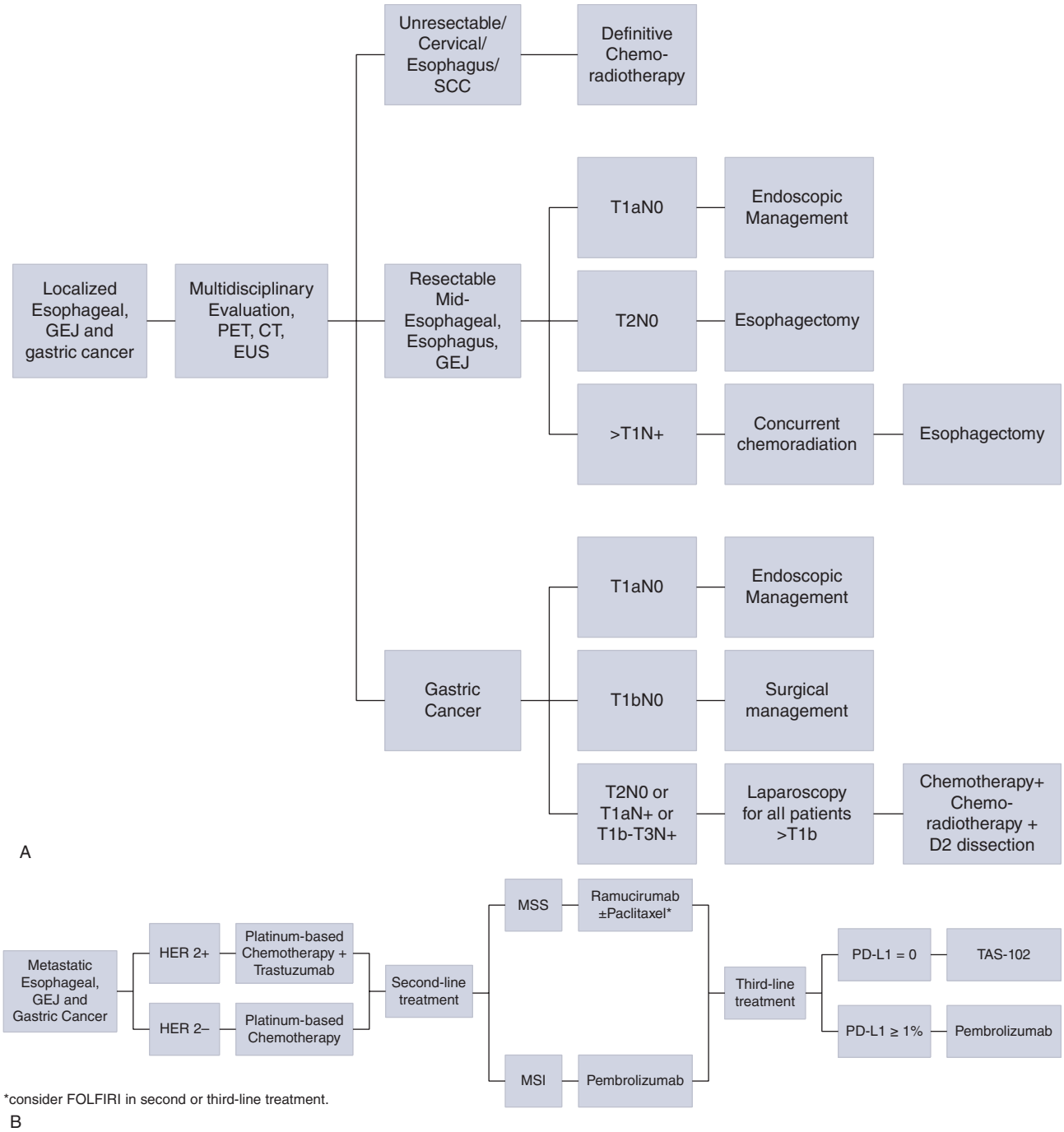


FIGURE 27–3 **The University of Texas MD Anderson Cancer Center Treatment algorithms for (A) localized gastroesophageal cancer and (B) metastatic gastroesophageal cancer. CT, computed tomography; EUS, endoscopic ultrasound; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; PET, positron emission tomography; PS, performance status; SCC, squamous cell carcinoma.**

ESOPHAGEAL AND GASTROESOPHAGEAL JUNCTION CANCERS

Esophageal cancer is estimated to be the eighth most common cause of cancer death among men in the United States and the fifth most common cause of cancer death worldwide.[86] In 2020, the estimated numbers of new cases and deaths from esophageal cancer in the United States are 18,440 and 16,170, respectively.2 Esophageal cancer is three to four times more common in men than in women,[87] with a mean age of 67 years.[88] The lifetime risk of developing esophageal cancer is 1 in 125 for men and 1 in 435 for women.[87] For

classification purposes (AJCC staging, 8th ed), primary tumors of the GEJ and proximal gastric cancer with epicenters extending no more than 2 cm into the stomach are included with esophageal cancers. The incidence of GEJ cancer has continued to increase over the last several decades. In recent years, this trend reached a new plateau, coinciding with the increased incidence of distal esophageal adenocarcinoma since the mid-1990s, a phenomenon confined to North America and other non-Asian countries. Overall, the prognosis of patients with esophageal/GEJ cancer remains poor. Histologic type makes a difference, because SCC has a poorer prognosis than adenocarcinoma. Surgery is still the only chance for cure, and survival can be improved with multimodality therapy.

Epidemiologic Characteristics

Although SCC is the most common histologic type in many parts of the world, it is relatively uncommon outside of Asian and Middle Eastern countries. Squamous cell cancer is 20 times more common in China than in the United States.*89* Esophageal cancer has a poor survival rate; only 19.9% of patients in the United States3 and 10% of patients in Europe[90] survive at 5 years.

Etiologic Characteristics and Risk Factors

The most significant risk factors associated with almost 90% of esophageal SCCs (ESCCs) are tobacco use, alcohol use, and a diet low in fruits and vegetables.[10,91] Smoking and alcohol can synergistically increase the risk of ESCC. Dietary associations with ESCC, such as foods containing N-nitroso compounds, have long been implicated.[92] Betel nut chewing, widespread in certain regions of Asia,[93] and the ingestion of hot foods and beverages (such as tea)[94] in other endemic regions, such as Iran, Russia, and South Africa, have been associated with ESCC. Long-standing achalasia increases the risk of SCC by 16 times.[95] On average, SCC develops 41 years after ingestion of lye. Tylosis, a rare disease associated with hyperkeratosis of the palms of the hands and soles of the feet, is associated with a high rate of ESCC.[96]

Unlike SCC, the risk factors for esophageal adenocarcinoma remain elusive. The strongest and most consistent risk factors include gastroesophageal reflux disease, smoking, obesity,[97] and dietary exposure to nitrosamines; these are found in almost 80% of cases in the United States.[98] According to a Denmark study, more than 50% of esophageal adenocarcinoma cases were found to have no history of symptomatic reflux disease.[99] However, a large study conducted in Sweden demonstrated an association between reflux symptoms and esophageal adenocarcinoma (odds ratio, 7.7) and adenocarcinoma of gastric cardia (odds ratio, 2.0).[100] A high-fat, low-protein, high-calorie diet can also increase the risk. Some data have suggested that interactions between risk factors may be more important than individual risk factors. A study was performed on 305 patients with esophageal adenocarcinoma and 339 age- and sex-matched controls; the strongest individual risk factor identified was reflux.[101]

Barrett esophagus (BE) is generally believed to be a consequence of severe and chronic gastroesophageal reflux disease. The presence of BE is associated with an increased risk of esophageal adenocarcinoma. The median age of BE diagnosis is 40 to 55 years, and it is most common in men.[102]

Clinical Presentation

The presenting symptoms of esophageal cancer usually include dysphagia, weight loss, bleeding, throat pain, and hoarseness. Early symptoms are usually nonspecific, and the patient may present with subtle symptoms, for example, food "sticking" transiently and reflux/regurgitation of food or saliva. This may precede frank dysphagia, which by all accounts is the most common complaint and becomes apparent when the esophageal lumen is narrowed to one-third of its normal diameter. For proximal esophageal tumors, increasing cough may be a sign of tracheoesophageal fistula. Chronic GI blood loss resulting from esophageal cancer may result in iron deficiency anemia.

Pathologic Characteristics

Esophageal cancer includes adenocarcinoma, SCC, mucoepidermoid carcinoma, small cell cancer, sarcoma, adenoid cystic carcinoma, and primary lymphoma. Adenocarcinoma is now more prevalent than SCC in non-Asian countries and primarily develops in the distal esophagus.[103] In general, SCC is found in the upper half of the esophagus, whereas adenocarcinoma predominates closer to the GEJ. This chapter focuses on carcinomas of the esophagus/GEJ, whereas other chapters in this book are dedicated to other types of malignancy of the esophagus/GEJ.

Staging and Prognosis

Esophageal cancer is a treatable disease but is rarely curable. Since the mid-1990s, the histologic type and location of cancer of the upper GI tract have changed. The incidences of proximal gastric, GEJ, and distal esophageal adenocarcinomas have steadily increased up until the last several years, where it now appears to have reached a steady state. The most current version of the AJCC TNM staging (8th edition, Tables 27–6, A–G) now includes primary tumors of the GEJ or proximal gastric cancer extending 2 cm into the stomach as part of esophageal cancer staging.[39]

Table 27–6A American Joint Cancer Committee TNM Staging System for Gastroesophageal Junction and Esophageal Cancers

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia, defined as malignant cells confined to the epithelium by the basement membrane
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b	Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc.
Regional Lymph Nodes (N)	
Nx	Regional nodes cannot be assessed
N0	No regional nodal metastasis
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3	Metastasis in ≥7 regional lymph nodes
Distant Metastases (M)	
M0	No distant metastases
M1	Distant metastases
Grade (G)	
GX	Grade cannot be assessed—stage grouping as G1
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated—stage group as G3 squamous
Location	
Upper	15 to <20 cm
Middle	25 to <30 cm
Lower	30–45 cm

AJCC Prognostic Stage Groups for Esophageal Squamous Cell Carcinoma B. Clinical (cTNM)

When cT is ...	And cN is ...	And M is ...	Then the stage group is ...
Tis	N0	M0	0
T1	N0–1	M0	I
T2	N0–1	M0	II
T3	N0	M0	II
T3	N1	M0	III
T1–3	N2	M0	III
T4	N0–2	M0	IVA
Any T	N3	M0	IVA
Any T	Any N	M1	IVB

C. Pathological (pTNM)

When pT is ...	And pN is ...	And M is ...	And G is ...	And Location is ...	Then the stage group is ...
Tis	N0	M0	N/A	Any	0
T1a	N0	M0	G1	Any	IA
T1a	N0	M0	G2–3	Any	IB
T1a	N0	M0	GX	Any	IA
T1b	N0	M0	G1–3	Any	IB
T1b	N0	M0	GX	Any	IB
T2	N0	M0	G1	Any	IB
T2	N0	M0	G2–3	Any	IIA
T2	N0	M0	GX	Any	IIA
T3	N0	M0	G1–3	Lower	IIA
T3	N0	M0	G1	Upper/Middle	IIA
T3	N0	M0	G2–3	Upper/Middle	IIB
T3	N0	M0	GX	Lower/Upper/Middle	IIB
T3	N0	M0	Any	Location X	IIB
T1	N1	M0	Any	Any	IIB
T1	N2	M0	Any	Any	IIIA
T2	N1	M0	Any	Any	IIIA
T2	N2	M0	Any	Any	IIIB
T3	N1–2	M0	Any	Any	IIIB
T4a	N0–1	M0	Any	Any	IIIB
T4a	N2	M0	Any	Any	IVA
T4b	N0–2	M0	Any	Any	IVA
Any T	N3	M0	Any	Any	IVA
Any T	Any N	M1	Any	Any	IVB

D. Post-neoadjuvant Therapy (ypTNM)

When ypT is ...	And ypN is ...	And M is ...	Then the stage group is ...
T0-2	No	M0	I
T3	N0	M0	II
T0–2	N1	M0	IIIA
T3	N1	M0	IIIB
T0–3	N2	M0	IIIB
T4a	N0	M0	IIIB
T4a	N1–2	M0	IVA
T4a	NX	M0	IVA
T4b	N0–2	M0	IVA
Any T	N3	M0	IVA
Any T	Any N	M1	IVB

AJCC Prognostic Stage Groups for Esophageal Adenocarcinoma E. Clinical (cTNM)

When cT is …	And cN is ...	And M is ...	Then the stage group is ...
Tis	N0	M0	0
T1	N0	M0	I
T1	N1	M0	IIA
T2	N0	M0	IIB

When cT is …	And cN is …	And M is …	Then the stage group is …
T2	N1	M0	III
T3	N0–1	M0	III
T4a	N0–1	M0	III
T1–4a	N2	M0	IVA
T4b	N0–2	M0	IVA
Any T	N3	M0	IVA
Any T	Any N	M1	IVB

F. Pathological (pTNM)

When pT is …	And pN is …	And M is …	And G is …	Then the stage group is …
Tis	N0	M0	N/A	0
T1a	N0	M0	G1	IA
T1a	N0	M0	GX	IA
T1a	N0	M0	G2	IB
T1b	N0	M0	G1–2	IB
T1b	N0	M0	GX	IB
T1	N0	M0	G3	IC
T2	N0	M0	G1–2	IC
T2	N0	M0	G3	IIA
T1	N1	M0	Any	IIB
T3	N0	M0	Any	IIB
T1	N2	M0	Any	IIIA
T2	N1	M0	Any	IIIA
T2	N2	M0	Any	IIIB
T3	N1–2	M0	Any	IIIB
T4a	N0–1	M0	Any	IIIB
T4a	N2	M0	Any	IVA
T4b	N0–2	M0	Any	IVA
Any T	N3	M0	Any	IVA
Any T	Any N	M1	Any	IVB

G. Post-neoadjuvant Therapy (ypTNM)

When ypT is …	And yp N is …	And M is …	Then the stage group is …
T0-2	N0	M0	I
T3	N0	M0	II
T0–2	N1	M0	IIIA
T3	N1	M0	IIIB
T0–3	N2	M0	IIIB
T4a	N0	M0	IIIB
T4a	N1–2	M0	IVA
T4a	NX	M0	IVA
T4b	N0–2	M0	IVA
Any T	N3	M0	IVA
Any T	Any N	M1	IVB

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging System (2020)

Clinical staging uses EGD with EUS, CT, and FDG-PET. In patients with proximal esophageal cancer, additional bronchoscopy is recommended to evaluate potential tracheal invasion or document and palliate tracheoesophageal fistula. Among patients with disease extending into the stomach, most experts agree that laparoscopic peritoneal staging is also necessary to evaluate occult peritoneal seeding that is not well visualized with noninvasive modalities (Figs. 27–4 to 27–9).

In various studies, FDG-PET has been consistently shown to have better specificity than CT at diagnosing metastatic disease and LN status. PET serves the primary purpose of detecting occult metastases that are present in 15% to 20% of patients newly diagnosed with esophageal cancer.[104,106] Multiple studies have been performed in patients with esophageal cancer after preoperative treatment, with PET being examined for predicting prognosis.[104,106] and treatment response.[107] Fluorodeoxyglucose-PET can better reveal bone metastasis than bone scans[108] and commonly reflects images of multiple foci of intense uptake. Studies have shown significant correlations between FDG uptake and tumor invasion depth and LN metastasis and survival rates, with a high degree of accuracy in the neck and upper thoracic and abdominal regions.[109] Unlike with gastric cancer, FDG-PET results have been found to be important predictors of response and prognosis. In a retrospective analysis, Swisher et al reported the results of FDG-PET use in 103 consecutive patients with locally advanced esophageal cancer who

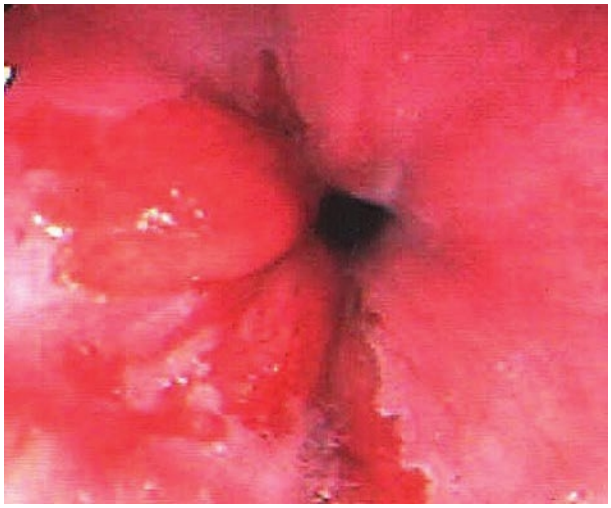


FIGURE 27–4 Barrett esophagus, endoscopic view. (Used with permission from Klaus Monkemuller, MD, University of Alabama at Birmingham, Birmingham, Ala.)



FIGURE 27–5 Esophageal mass, endoscopic view. (Used with permission from Klaus Monkemuller, MD, University of Alabama at Birmingham, Birmingham, Ala.)

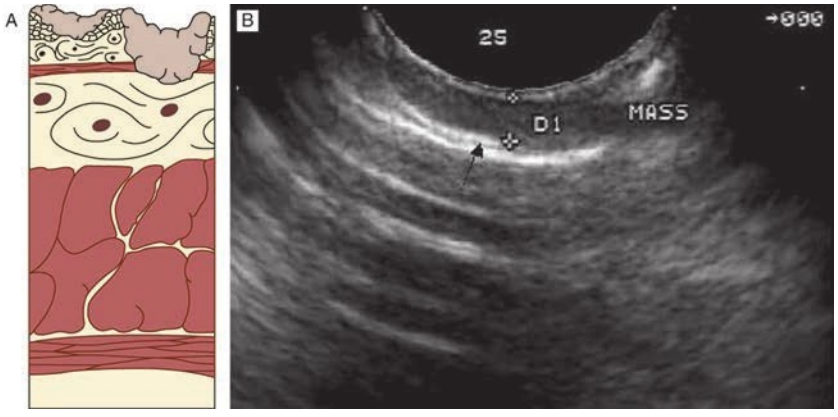


FIGURE 27–6 **A.** Schematic representation of esophagus layers showing depth of tumor invasion. **B.** Endoscopic ultrasound image of T1 esophageal cancer. (Reproduced with permission from http://www.massgeneral.org/gastro/endo_homepage.htm)

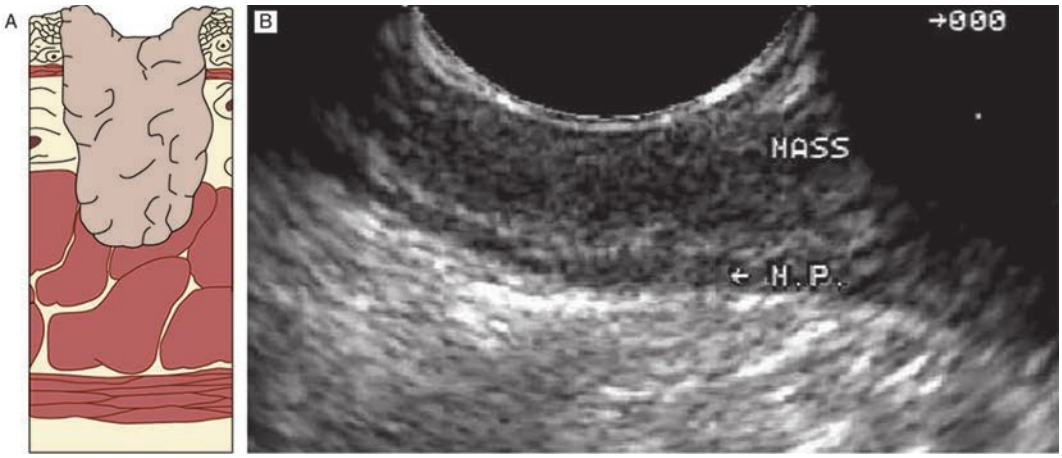


FIGURE 27–7 **A. Schematic representation of esophagus layers showing depth of tumor invasion. B. Endoscopic ultrasound image of T2 esophageal cancer. (Reproduced with permission from http://www.massgeneral.org/gastro/endo_ homepage.htm)**

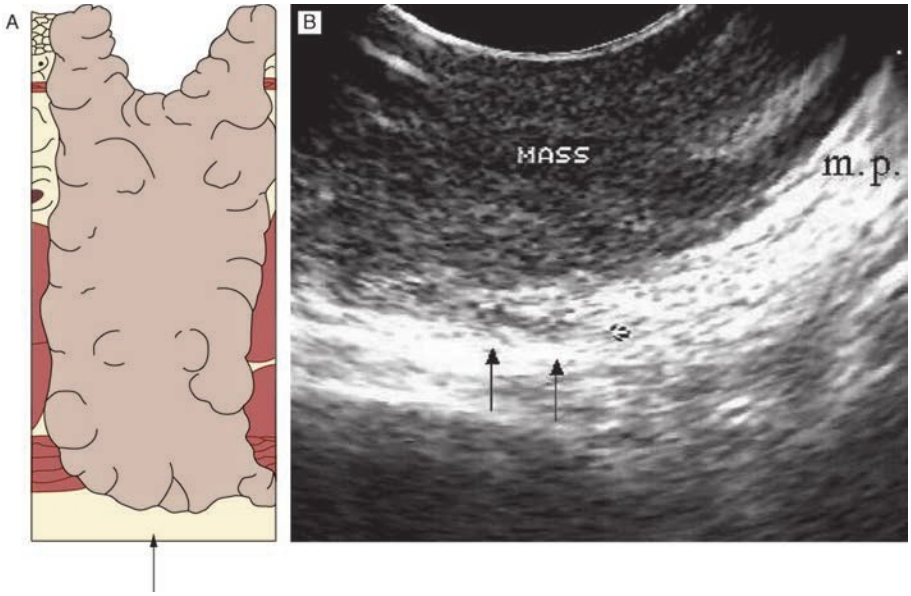


FIGURE 27–8 **A. Schematic representation of esophagus layers showing depth of tumor invasion. B. Endoscopic ultrasound image of T3 esophageal cancer. (Reproduced with permission from http://www.massgeneral.org/gastro/endo_ homepage.htm)**

underwent preoperative chemoradiotherapy.[110] At surgery, 58 patients (56%) had experienced a pathologic response to chemoradiotherapy (surgical pathologic results ≤10% viable residual cancer cells). Pathologic response was associated with FDG-PET standardized uptake value (SUV) (3.1 vs 5.8, $P = .01$). A post-chemoradiotherapy FDG-PET SUV of 4 or higher had the highest accuracy and was an independent predictor of survival (HR 3.5; $P = .04$) on multivariate analysis.[110]

Perhaps the strongest endorsement for using FDG-PET as a predictor of response came from the Metabolic Response Evaluation for Individualization of Neoadjuvant Chemotherapy in Esophageal and Esophagogastric Adenocarcinoma (MUNICON-1) trial. Lordick et al*36* evaluated the feasibility and applicability of FDG-PET in clinical practice in 110 evaluable patients with locally advanced esophageal adenocarcinoma. Patients with adenocarcinoma of the esophagogastric junction types I and II (tumors extending to the esophagus 5 cm above and 2 cm below the GEJ) underwent 2 weeks of induction chemotherapy with platinum and 5-FU (FLP). Fluorodeoxyglucose-PET scans were obtained for all patients at baseline and after induction chemotherapy. Metabolic response

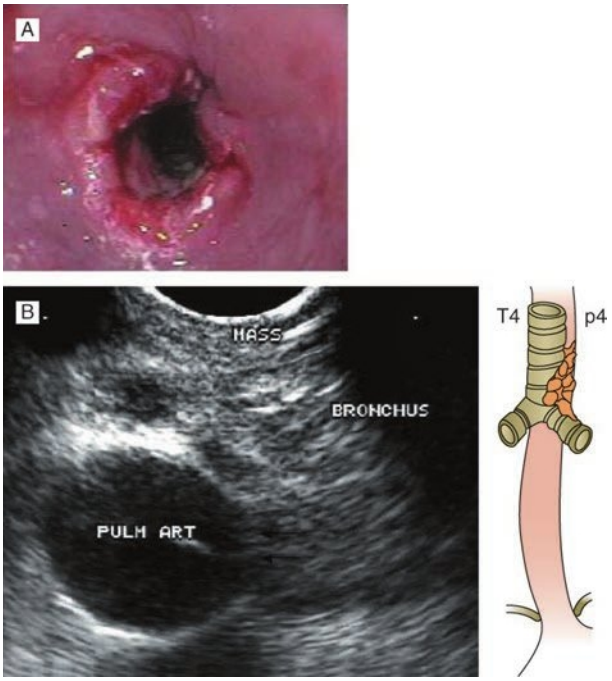


FIGURE 27–9 **A. Endoscopic image of T4 esophageal cancer. B. Endoscopic ultrasound image of the same tumor. (Reproduced with permission from http://www.massgeneral.org/gastro/endo_homepage.htm)**

was defined as an SUV decrease by 35% or more. Responders underwent more chemotherapy with FLP or folinic acid and fluorouracil plus cisplatin and paclitaxel, or folinic acid, 5-FU, and oxaliplatin (FOLFOX) for 12 weeks followed by surgery. Nonresponders discontinued further chemotherapy after the 2 weeks of initial induction chemotherapy and underwent surgery. In this study, there were 54 responders (metabolic response rate, 49%). One-hundred four patients (54 responders and 50 nonresponders) underwent surgery. At 2.3 years of follow-up, the median OS was not reached for responders and was 25.8 months (HR 2.13; $P = .015$) for nonresponders. The median event-free survival durations for responders and nonresponders were 29.7 months and 14.1 months, respectively (HR 2.18; $P = .002$). Major pathologic remissions (<10% residual tumor) were noted in 58% of responders and 0% of nonresponders.*36* In the MUNICON-1 study, the response to induction therapy was valuable for stratifying patients to appropriate therapy, further establishing the clinical utility of FDG-PET in limiting exposure to unnecessary toxicity and maximizing therapeutic benefits. The MUNICON-2 prospective trial was carried out to improve the clinical outcome of metabolic nonresponders using a salvage neoadjuvant radiochemotherapy. In this study, PET nonresponders received salvage neoadjuvant radiochemotherapy, whereas metabolic responders received neoadjuvant chemotherapy for 3 months before surgery. This prospective study showed the feasibility of a PET-guided treatment algorithm. However, by comparing the groups of nonresponding patients in the current trial and the previous published MUNICON I trial, increased histopathologic response was observed after salvage radiochemotherapy, but the primary end point of the study to increase the R0 resection rate was not met.[111]

Treatment

The gold standard for treating high-grade dysplasia and early or superficial esophageal cancer is esophagectomy. However, endoscopic mucosal resection (EMR)/endoscopic submucosal dissection, with or without photodynamic therapy, has become a popular alternative to surgery for early esophageal disease. Endoscopic mucosal resection has been reported in several small prospective case series to be effective, with an initial complete remission rate of 59% to 99%.[112,113] The ideal clinical characteristics for EMR are small (<2 cm diameter), solitary, flat lesions that are confined to the mucosa (T1a). Because EMR has a relatively high recurrence rate, it is recommended that BE and high-grade dysplasia or patients with early esophageal cancer be followed up endoscopically every 3 months during the first year and annually thereafter. Complications associated with EMR are bleeding (4%–46%), perforation (1%), and stricture (20%).[114]

Despite the recognized epidemiologic and clinical differences between ESCCs and adenocarcinomas, there is still inadequate evidence that treatment for esophageal cancer should be based on histologic type. Locally advanced cervical esophageal cancer is preferably managed with definitive chemoradiotherapy. For all other esophageal cancers, current evidence supports the use of preoperative chemoradiotherapy to enhance surgical survival outcome in patients with locally advanced resectable disease.[115] Surgery remains the best chance for long-term survival. Ongoing international clinical research with novel cytotoxic and targeted agents will continue to further define and improve survival outcomes of patients with locally advanced curable esophageal and GEJ cancers. Unfortunately, the main therapeutic goal is symptom palliation in patients with locally advanced, unresectable disease.

Resectable Disease

Surgery

Only 23% of patients with esophageal cancer present with clinically resectable localized disease.[116] Surgical resection is the mainstay of treatment for these patients[117] and should only be recommended as

upfront treatment in T1b/T2 tumors without nodal involvement by EUS. Recent data indicate that the overall 5-year survival rate of patients with esophageal cancer after curative surgery is about 25%.*42,43,*[118] Therefore, preoperative chemotherapy or preoperative chemoradiotherapy have become the mainstay strategies for treatment to improve surgical outcome, whereas definitive chemoradiotherapy has been recommended for patients with cervical tumors or unresectable disease.

Cancers of the middle or lower third of the esophagus (SCC or esophageal adenocarcinoma, except GEJ cancers) generally require total esophagectomy, which is a challenging procedure with a high complication rate. No uniform surgical approaches to curative resection exist, but the most common procedures in North America include transhiatal, transthoracic (Ivor-Lewis), and tri-incisional esophagectomy. For patients with potentially resectable disease, R0 resection is generally believed to be necessary to achieve durable survival.[119] R0 resection is defined as resection of the primary tumor with negative proximal, distal, and circumferential margins. Despite a lack of prospective randomized studies, there is a growing consensus that more extensive nodal dissection is needed; including the removal of all cancerous tissue from the mediastinum improves DFS and OS durations through better control of locoregional recurrence. Also, aggressive lymphadenectomy is generally recommended to increase the accuracy of pathologic staging. In the United States, en bloc resection of the mediastinal and upper abdominal LNs is considered standard for transthoracic esophagectomy, and three-field lymphadenectomy is not considered a standard treatment for patients with esophageal cancer.

Preoperative Chemotherapy

Preoperative chemotherapy theoretically increases the curative resection rates by downsizing and downstaging the primary tumor and LN metastases, reducing the local and distant relapse rates through suppression and elimination of micro-metastases, improving tumor-related symptoms with early initiation of antineoplastic therapy, and appraising in vivo the chemosensitivity of the primary tumor that will influence the choice of chemotherapy in the adjuvant setting. Preoperative therapy is hypothesized to result in tumor downstaging, which allows for higher R0 resection and pathCR rates.[120]

The two largest studies evaluating the role of preoperative chemotherapy were the US Intergroup trial (INT0113)[121] and UK Marsden Royal College (MRC)-OEO-2 randomized controlled trials.[122] Both studies determined the survival benefit of preoperative chemotherapy compared with surgery alone in patients with resectable ESCC and adenocarcinoma. Cisplatin plus 5-FU (CF) was administered in both studies. The two studies had completely divergent findings. INT0113 found no clinical/pathologic benefit or survival improvement with preoperative chemotherapy followed by surgery compared with surgery alone.[121] The median survival was 14.9 months for patients who received preoperative chemotherapy and 16.1 months for those who underwent immediate surgery (P = .53). The recent updated analysis of INT0113 confirmed the lack of benefit of preoperative chemotherapy.[123] The MRC-OEO-2 trial, however, reported a statistically significant improved R0 resection rate (78% vs 70%) and median OS time (17.2 vs 13.3 months) in patients who underwent preoperative chemotherapy.[122] Results of both INT0113 and OEO-2 studies did not help determine the role of preoperative chemotherapy in patients with resectable esophageal cancer. In the United Kingdom and other countries in Europe, preoperative chemotherapy has become the acceptable standard of care.

The three most recent randomized studies of preoperative and perioperative chemotherapy, FNCLCC,[60] UK MAGIC,[43] and UK FLOT trials[124–126] are the strongest validations of the benefits of preoperative and perioperative chemotherapy. These three studies are described in detail in the "Gastric Cancer" section of this chapter. In addition to the FLOT, MAGIC, and French trials, a third Japanese trial on patients with SCC (JCOG 9907) deserves mention because it rendered positive results. Patients were given two cycles of cisplatin and 5-FU (CF) preoperatively. Postoperatively, CF was administered to node-positive patients only. Of the above mentioned three trials, this one showed the highest 5-year survival rate in both arms.[127]

MRC-OEO-5 evaluated the use of preoperative chemotherapy, comparing two preoperative chemotherapy regimens, CF versus ECX (epirubicin, cisplatin, and capecitabine) in resectable esophageal adenocarcinoma.[128] In this study, 879 patients were randomized to receive two cycles of CF or four cycles of ECX before surgery. The median survival was 23.4 months in the CF group and 26.1 months in the ECX group (HR 0.90, P = .19). This trial showed that adding epirubicin to platinum-based therapy and more cycles of chemotherapy did not improve survival. The addition of targeted therapy to perioperative chemotherapy was also not helpful. The MRC ST03 trial*80* demonstrated that the addition of bevacizumab ECX chemotherapy did not prolong OS over chemotherapy alone. Table 27–7 lists the ongoing studies of locally advanced resectable gastric, GEJ, and distal esophageal adenocarcinomas.

Preoperative Radiation

Preoperative radiotherapy was studied in the early 1980s. However, in several phase 3 studies, a benefit similar to that of surgery alone was not shown. In a

Table 27–7 Key Esophageal Cancer Trials

Study	No. of Patients	Treatment Arm Control Arm	HR for OS (*P* value)	OS (%)
Pre- and Perioperative Chemotherapy				
Kelsen et al (INT-113)[121]	467	3 × CF → S S	0.75 (NR)	5-y OS: 36% vs 23%
Allum et al (MRC-OEO-2)[122]	802	2 × CF → S S	0.84 (.03)	5-y OS: 23% vs 17.1%
Ychou et al (ACCORD 7)[60]	169	2/3 × CF → S S	0.69 (.02)	5-y OS: 38% vs 24%
Alderson et al (MRC-OEO-5)[128]	897	2 × CF → S 4 × ECX → S	0.9 (0.19)	3-y OS: 39% vs 42%
Cunningham et al (MRC ST-03)[80]	1100	3 × ECX → S ECX, B → S	1.09 (.36)	3-y OS: 50.3% vs 48.1%
Ando et al (JCOG 9907)[127]	380	S → 2× CF 2 × CF → S	0.73 (.04)	5-y OS: 43% vs 55%
Preoperative Chemoradiotherapy				
Tepper et al (CALGB 9781)[129]	56	2 × CF; 50.4 Gy → S S	1.46-5.69 (NR)	5-y OS: 39% vs 16%
Shapiro et al (CROSS)[115]	366	5 × carboplatin/paclitaxel; 41.4 Gy → S S	0.657 (.003)	5-y OS: 47% vs 34%
Preoperative CT vs Preoperative CRT				
Stahl et al (POET)[130]	119	2.5 × CF, Leu → S 2 × CF, Leu → CE 30 Gy → S	0.67 (.07)	3-y OS: 27.7% vs 47.4%
Postoperative CT				
Ando et al (JCOG 9204)[131]	242	S S → 2 CF	(.13)	5-y OS: 52% vs 61%

B, bevacizumab; CE, cisplatin and etoposide; CF, cisplatin and 5-fluorouracil; CRT, chemoradiotherapy; CT, chemotherapy; ECX, epirubicin, cisplatin, and capecitabine; HR, hazard ratio; Leu, leucovorin; NR, not reported; OS, overall survival, S; surgery.

recent quantitative meta-analysis comprising five randomized trials and 1147 patients, it was again demonstrated that there is no improvement in survival with preoperative radiotherapy alone in potentially resectable esophageal cancer.[132,133]

Preoperative Chemoradiotherapy

In the United States, pre- or perioperative chemotherapy is not as common as preoperative chemoradiotherapy for locally advanced esophageal and GEJ cancers. Preoperative chemoradiotherapy has the goal to improve the pathCR rate, locoregional control, and survival.

The CALGB 9781 trial provided additional support for preoperative chemoradiotherapy, although it was stopped early because of a slow patient accrual rate. Fifty-six patients were randomly assigned to surgery alone (n = 26) or CF chemotherapy and concurrent radiotherapy (n = 30). At a median follow-up of 6 years, an intent-to-treat analysis showed a median OS duration of 4.5 versus 1.8 years (P = .002) in favor of trimodality therapy. The 5-year OS rates were 39% (95% CI 21%–57%) versus 16% (95% CI 5%–33%) in favor of trimodality therapy.[129] Gebski et al[134] reported improved survival with preoperative chemotherapy and chemoradiotherapy. The HR for all-cause mortality with preoperative chemoradiotherapy versus surgery alone was 0.81 (95% CI 0.70–0.93; P = .002), corresponding to a 13% absolute difference in survival at two years, with similar results for different histologic tumor types (SCC: HR 0.84, P = .04; adenocarcinomas: HR 0.75, P = .02). The HR for preoperative chemotherapy was 0.90 (95% CI 0.81–1.00; P = .05), which indicates a 2-year absolute survival benefit of 7%. There was no significant effect on all-cause mortality for preoperative chemotherapy in SCC (HR 0.88; P = .12), but there was a benefit in adenocarcinoma (HR 0.78; P = .014).[134] With chemoradiotherapy, evidence seems to suggest that treating physicians can expect a pathCR rate of 20% to 30%, a median OS

duration of 16 to 24 months, and a therapy-related mortality rate of 5% to 10%.

The Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) trial was a well-executed study that established level 1 evidence for preoperative chemoradiotherapy. Three-hundred sixty-eight patients with localized esophageal cancer (adenocarcinoma or squamous) were randomly assigned to receive either preoperative paclitaxel and carboplatin with concurrent radiation 41.4 Gy (n = 178) or surgery alone (n = 188). With a median follow-up time of 45.4 months, the median OS for preoperative chemoradiotherapy group was 49.4 months versus 24.0 months for the surgery-alone group (HR 0.657, 95% CI 0.495–0.871; P = .003). Five-year OS was again in favor of the chemoradiotherapy group (47%) versus the surgery-alone group (34%).[135] The complete resection rate was higher in the chemoradiotherapy group (92%) versus the surgery-alone group (69%), and 29% of patients in the chemoradiotherapy group had pathCR. In a subgroup analysis, the patients with SCC demonstrated the best outcomes (HR 0.453 for squamous cancer vs 0.732 for adenocarcinoma).[135,136]

The recently published RTOG 1010 study was designed to determine whether trastuzumab increases DFS when combined with trimodality treatment for patients with HER2-overexpressing esophageal adenocarcinoma.[137] This randomized phase 3 trial included patients with newly diagnosed stage T1N1–2, T2–3N0–2 adenocarcinoma of the esophagus involving the mid, distal, or esophagogastric junction and up to 5 cm of the stomach. All patients received chemotherapy of paclitaxel 50 mg/m2 and carboplatin (area under the curve = 2) weekly for 6 weeks, with radiation (50.4 Gy in 28 fractions) followed by surgery. Patients were randomly assigned 1:1 to receive weekly trastuzumab 4 mg/kg for week 1 and then 2 mg/kg weekly × 5 during CXRT then 6 mg/kg for one dose before surgery and 6 mg/kg every 3 weeks for 13 treatments after surgery. The median DFS time was no different at 19.6 months (13.5–26.2) for the CXRT+trastuzumab arm compared with 14.2 months (HR 0.97). The median OS time was 38.5 months for the CXRT+trastuzumab arm compared with 38.9 months for the CXRT arm (HR1.01). This study demonstrated that adding trastuzumab to standard chemotherapy was not better than standard chemotherapy alone in treating localized esophageal adenocarcinoma in patients with trimodality therapy.[137]

Preoperative Chemotherapy Versus Preoperative Chemoradiotherapy

Meta-analyses have been performed to further support the available evidence for preoperative therapy.[134,138,139] Cumulatively, these three meta-analyses determined that the most consistent significant survival benefit resulted from the combination of surgery and preoperative chemoradiotherapy and, to a lesser extent, preoperative chemotherapy.

Since these studies, results from the Preoperative Chemotherapy or Radiochemotherapy in Esophagogastric Adenocarcinoma (POET) trial, presented by Stahl et al,[130] have provided further support for three-step preoperative therapy, although the study was closed prematurely because of slow patient accrual. The POET trial was designed to evaluate the survival outcomes of patients treated with preoperative chemotherapy compared with preoperative chemoradiotherapy. One-hundred nineteen patients were randomly assigned to chemotherapy followed by chemoradiotherapy and surgery (n = 59) or chemotherapy followed by surgery (n = 60); the R0 resection rates were 72% and 70% (P = not significant), the pathCR rates were 16% and 2% (P < .001), and the N0 rates were 64% and 38% (P < .001), respectively. The 3-year OS rate trended toward improvement with induction chemotherapy, chemoradiotherapy, and surgery (47% vs 28% with chemotherapy and surgery; P = .07).[130] Patients in the chemoradiotherapy arm had a significantly higher probability of a pathCR (15.6% vs 2.0%). Postoperative mortality rates did not differ between the chemoradiotherapy and chemotherapy arms (10% vs 4%; P = .26). These results suggest that preoperative chemoradiotherapy confers a survival advantage over preoperative chemotherapy in distal esophageal and GEJ adenocarcinoma.

The use of induction chemotherapy before chemoradiotherapy and surgery has been evaluated in several phase 2 studies.73 Trimodality-eligible patients were randomized to receive no induction chemotherapy (Arm A) or induction chemotherapy (oxaliplatin/FU; Arm B) before oxaliplatin/FU/radiation. Surgery was attempted about 5 to 6 weeks after chemoradiation. The pathCR, postsurgery 30-day mortality, OS, and toxic effects rates were assessed. Results from this study showed that induction chemotherapy produces a nonsignificant increase in the pathCR rate and does not prolong OS.

In Europe and the United Kingdom, the treatment approach varies accordingly to tumor histology. For resectable SCC, patients are commonly treated with preoperative chemoradiotherapy,[140] whereas for resectable adenocarcinomas, either preoperative CRT or perioperative chemotherapy is administered. In the United States, preoperative chemoradiotherapy is the standard of care irrespective of histology.

Postoperative Therapy

Few studies have been performed to evaluate postoperative chemotherapy versus surgery alone. Reflecting the incidence of esophageal cancer during the 1980s and 1990s, these studies included more patients with squamous cell cancer than with adenocarcinoma; this

is a shortcoming of these early studies. In a study by Pouliquen et al, no survival improvement was found in the patients who were administered postoperative chemotherapy (CF).[141]

The second study, a randomized trial, JCOG 9204, compared the outcomes of patients who underwent surgery alone versus patients who underwent surgery followed by adjuvant CF. The 5-year DFS rates favored the postoperative chemotherapy group (55% vs 45%; $P = .037$). However, the difference in the 5-year OS rate was not statistically significant (61% vs 52%; $P = .13$). The duration of adjuvant therapy was suboptimal, and approximately 25% of patients assigned to the postoperative chemotherapy group failed to receive the full course of therapy.[131]

Another retrospective case-control study was designed to evaluate the effect of postoperative chemotherapy in 211 patients who underwent R0 esophagectomy with radical lymphadenectomy. Of 211 patients, 94 received postoperative chemotherapy, whereas the other 117 patients received surgery alone. The OS was compared between the two groups after they were stratified by the numbers of metastasis-positive LNs. In the subgroup of patients with more than eight positive LNs, postoperative chemotherapy significantly improved OS compared with surgery alone. Therefore, the authors suggested that postoperative chemotherapy was beneficial only in patients with more than eight metastatic LNs,[142] reducing the risk of relapse. However, postoperative chemotherapy did not improve OS compared with surgery alone.

Many studies have been performed to evaluate the role of postoperative radiotherapy versus surgery alone. In two studies conducted by Teniere et al,[143] postoperative radiotherapy did not improve survival. Results from two other randomized studies revealed conflicting findings. Xiao et al[144] demonstrated that postoperative radiotherapy improved the 5-year OS in patients with esophageal cancer with stage III disease. In contrast, Fok et al found shorter survival durations in patients who underwent postoperative radiotherapy as a direct result of irradiation-related death and the early appearance of metastatic disease.[145] Thus, the utility of postoperative radiotherapy may be limited. Of these studies, only the one by Zieren et al evaluated quality of life, which was found to be better in the surgery-alone group.

Malthaner et al[139] performed a meta-analysis of 34 randomized controlled trials and six meta-analyses in which patients with locally advanced esophageal cancer underwent pre- or postoperative chemotherapy, radiotherapy, or chemoradiotherapy. No significant difference in survival was observed in the postoperative radiotherapy group.

The available evidence suggests that postoperative chemotherapy or radiotherapy does not result in a benefit. However, few randomized comparisons have been performed with surgery alone versus surgery and postoperative treatment. Extrapolation of the INT-0116 study[42] (described in the gastric section) as supporting evidence for postoperative chemoradiotherapy in esophageal cancer should be performed with caution.

On the basis of the available evidence, patients with esophageal cancer gain limited survival benefit with postoperative chemotherapy and chemoradiotherapy after R0 resection. The limited contribution of postoperative therapy is probably caused by the moderate toxicity, which leads to treatment-related complications or an inability to complete therapy.

The limited ability to deliver therapy after surgery, as demonstrated by results from the INT-0116, MAGIC, and FLOT studies,[42,43] suggests that all effective therapy should be administered before surgery.

The utility of adjuvant checkpoint inhibitor after trimodality therapy in both adenocarcinoma and squamous cell carcinoma patients with esophageal or GEJ cancers is being evaluated in the CHECKMATE 577 study. Results are eagerly awaited.[146]

Definitive Chemoradiotherapy

The potential activity of chemotherapy against micro-metastases and its ability to act as a radiotherapy-sensitizing agent formed the basis for combining chemotherapy and radiotherapy to treat locally advanced cancer. In the RTOG 85-01 study, patients with locally advanced esophageal adenocarcinoma or SCC were randomly assigned to chemoradiotherapy with CF or radiotherapy alone. The 5-year OS rates were 0% and 26% for radiotherapy and chemoradiotherapy, respectively.[147]

A comprehensive review of the pattern of care for esophageal cancer in the United States from 1992 to 1994 surveyed 400 patients with locally advanced esophageal cancer treated at 63 institutions.[148] The study confirmed that using combined concurrent chemoradiotherapy as a nonoperative strategy to achieve superior survival and local tumor control was better than radiotherapy alone.[148] The report also suggested a trend toward survival improvement with chemoradiotherapy before surgery compared with chemoradiotherapy or surgery alone.

In the INT-0123 (RTOG 94-05) study, patients ($n = 236$) were administered concurrent CF (similar to RTOG 85-01) but were assigned randomly to different radiation doses, either 50.4 or 64.8 Gy. No association was found between higher radiation doses and higher median survival (13 vs 18 months for 50.4 vs 64.8 Gy, respectively) or 2-year survival (31% vs 40%, respectively). Higher radiation dose was also more toxic.[149] The reason for the failure of the higher radiation dose to improve survival is unclear.

The multi-institutional RTOG 0113 trial evaluated induction chemotherapy followed by definitive chemoradiotherapy in patients with localized unresectable esophageal cancer. The primary goal was to determine whether any approach would result in more than 78% 1-year OS, surpassing the historical 66% rate from RTOG 94-05. Seventy-two evaluable patients were randomly assigned to receive either induction with fluorouracil, cisplatin, and paclitaxel and then fluorouracil plus paclitaxel with 50.4 Gy of radiation (Arm A) or induction with paclitaxel plus cisplatin and then the same chemotherapy with 50.4 Gy of radiation (Arm B). Both arms of RTOG 0113 were associated with high morbidity, and the study did not meet its 1-year survival end point.[149]

Definitive Chemoradiotherapy Versus Chemoradiotherapy Plus Surgery

Stahl et al[130] performed a randomized comparison of chemotherapy followed by chemoradiotherapy and then surgery (surgical arm, $n = 86$) and chemotherapy followed by chemoradiotherapy and no surgery (nonoperative arm, $n = 86$) in 172 patients with locally advanced ESCC. The median follow-up duration was 6 years. The OS rates were similar for the surgical and nonsurgical arms ($P < .05$). The 2-year local PFS rate was higher in the surgical arm than the nonsurgical arm (64% vs 41%; HR 2.1; 95% CI 1.3–3.5; $P = .003$). The treatment-related mortality rate was significantly higher in the surgical arm (12.8% vs 3.5%; $P = .03$). The clinical tumor response to induction chemotherapy was the only independent prognostic factor for OS (HR 0.30; 95% CI 0.19–0.47; $P < .0001$). The results of this study suggested that adding surgery to chemoradiotherapy improves local tumor control but not survival in patients with locally advanced ESCC. Tumor response to induction chemotherapy is associated with a favorable prognostic group in these high-risk patients, regardless of treatment. Of course, the difficulty of incorporating these results into clinical practice is detecting residual disease or response after preoperative therapy.

Another randomized comparison in only responders to chemoradiotherapy (45 Gy conventional or 60 Gy split-course radiation) was conducted by Bedenne et al.[150] Patients with resectable ESCC were treated with two cycles of CF along with concurrent radiotherapy (conventional/split course). Patients who experienced a response ($n = 259$) were then randomly assigned to surgery or more chemoradiotherapy. The 2-year OS rates were 34% and 40% (HR 0.90; $P = .44$), the median OS durations were 18 and 19 months (P = not significant), the 2-year local control rates were 66% and 57% ($P < .01$), and the 3-month mortality rates were 9.3% and 0.8% ($P = .002$), respectively. The authors concluded that in patients who experience a response to chemoradiotherapy, surgery after chemoradiotherapy resulted in no added benefit over continued chemoradiotherapy.[150]

In a phase 3 study by the Chinese University Research Group for Esophageal Cancer (CURE), investigators from China are comparing the survival benefits of esophagectomy versus chemoradiotherapy. From 2000 to 2004, 80 patients were randomly assigned to esophagectomy ($n = 44$) or chemoradiotherapy ($n = 36$). A two- or three-stage esophagectomy with two-field lymphadenectomy was performed. Chemoradiotherapy consisted of CF and concurrent 50 to 60 Gy of radiation. Tumor response was assessed by EGD, EUS, and CT. Salvage esophagectomies were performed for incomplete response or recurrence. The median follow-up time was 1.4 years. No difference in the early cumulative survival rate was found between the two groups (RR 0.89; 95% CI 0.37–2.17; $P = .45$), nor was there a difference in DFS. Patients treated with surgery only had a slightly higher recurrence rate in the mediastinum, whereas those treated with chemoradiotherapy had a higher rate in the cervical or abdominal region.[151]

Surgery is the foundation of treatment for locally advanced resectable esophageal cancer. Early results from European studies suggested that patients with ESCC will not benefit from surgery after chemoradiotherapy.[152] The caveat of the nonsurgical approach to solid tumors is detecting minimal residual disease. Therefore, until more confirmatory evidence and clinical tools become available for detecting minimal residual disease or molecular or imaging predictive markers in patients who require surgery after preoperative therapy, the treatments for squamous cell cancer and adenocarcinoma will remain similar.

MD ANDERSON PRACTICE TIPS

RESECTABLE GASTRIC CANCER

- All patients with newly diagnosed invasive cancer undergo staging, which includes endoscopic assessment of the location and size of the primary tumor and EUS staging, CT, and/or PET/CT. Patients with cervical or proximal esophageal cancer also undergo bronchoscopy as part of a recommended staging workup.
- Staging laparoscopy is performed in some patients with cardia cancer, but the decision is made on a case-by-case basis.

- Patients with localized disease are discussed at the weekly Esophageal Multidisciplinary Tumor Board.
- Patients with locally advanced cervical esophageal cancer are treated with primary definitive chemoradiotherapy, even those with resectable disease. Salvage surgery is considered only in patients with persistent or locally recurrent disease.
- Currently at MDACC, treatment modalities for locally advanced resectable esophageal cancer include chemoradiotherapy and then surgery. For GEJ adenocarcinoma, postoperative chemoradiotherapy and perioperative chemotherapy are additional options available to patients. With the results of the CROSS trial, we now recognize that a minimum dose of 41.4 Gy may be sufficient in the preoperative setting, although our preference is to use a higher dose (50.4 Gy).

Figure 27–3A summarizes the MDACC approach to resectable gastroesophageal cancer.

ADVANCED AND METASTATIC GASTRIC, GASTROESOPHAGEAL JUNCTION, AND ESOPHAGEAL CANCERS

The prognosis of patients with advanced or metastatic gastric, GEJ, and esophageal cancers is poor; thus, clinicians should be cognizant of the patient's quality of life and weigh the risks and benefits of therapy. The overall 5-year survival rate of metastatic gastric and esophageal cancer patients is less than 5%. The standard of care for advanced disease is systemic chemotherapy. Different frontline combination chemotherapy regimens are available, but no head-to-head comparison has been performed for most of these; thus, the optimal choice is not obvious, and treatment remains regionally variable.

The medical treatment of metastatic gastric and esophageal cancer is primarily palliative and confers a modest effect on OS. Multiple agents are active in the treatment of gastric cancer, including fluoropyrimidines (5-FU, capecitabine, and S-1), anthracyclines, platinum agents, taxanes, irinotecan, and some targeted therapies such as trastuzumab for human epidermal growth factor receptor 2 (HER2)-overexpressing gastric cancers. Combination regimens are associated with higher response rates and, according to one meta-analysis, are also associated with increased survival when compared with single-agent chemotherapies.[153]

First-Line Therapy

Only a minor amount of level 1 evidence exists for the treatment of gastric cancer in the first-line setting. In fact, only docetaxel,[154] cisplatin/oxaliplatin,[155] and trastuzumab[156] are supported by high-level evidence.

A phase 3 trial involving 445 patients with metastatic cancer randomly assigned patients to receive CF or CF plus docetaxel. The investigators found that the addition of docetaxel was superior in terms of response rate (37% vs 25%; $P = .01$), time to tumor progression (5.6 vs 3.7 months; $P < .001$), and OS (9.2 vs 8.6 months; $P = .02$).[154] One could question the clinical significance of a less than 1 month absolute improvement in OS, particularly in the context of significant toxicities, most notably a high rate of febrile neutropenia (30%). Importantly, this regimen should not be used in patients who have a reduced performance status.

The third randomized phase 3 trial enrolled 305 patients in Japan to either S-1 alone or S-1 and cisplatin. Median OS was significantly longer in patients assigned to S-1 plus cisplatin (13.0 months) than in those assigned to S-1 alone (11.0 months; HR for death, 0.77; 95% CI 0.61–0.98; $P = .04$). Progression-free survival was significantly longer in patients assigned to S-1 plus cisplatin than in those assigned to S-1 alone (median PFS, 6.0 vs 4.0 months; $P < .0001$).[157] This trial provided evidence for the superiority of the addition of cisplatin when compared with a fluoropyrimidine alone and established the use of a fluoropyrimidine in addition to a platinum as a reasonable treatment option.

Trastuzumab was the first targeted agent with documented clinical activity in the advanced gastric and gastroesophageal cancer setting. This treatment is useful in the HER2-enriched population; however, only approximately 20% of gastric cancers and 30% of gastroesophageal cancers overexpress HER2, so that a relatively small proportion of patients benefit from the treatment. The ToGA trial randomly assigned 584 patients whose tumors overexpressed HER2 by immunohistochemistry (IHC) or fluorescence in situ hybridization to receive a fluoropyrimidine (5-FU or capecitabine) plus cisplatin with or without trastuzumab. The chemotherapy was administered every 3 weeks for six cycles, and trastuzumab was administered every 3 weeks until disease progression.[156] The investigators found that the addition of trastuzumab to chemotherapy increased OS from 11.1 to 13.8 months (HR 0.74, 95% CI 0.60–0.91; $P = .0046$). The secondary end points of PFS (6.7 vs 5.5 months; $P = .0002$) and

response rate (47.3% vs 34.5%; $P = .0017$) were also improved. On extended follow-up, the HR of OS for the addition of trastuzumab has decreased to 0.80,[158] indicating that although real, the response to trastuzumab may be short lived. The difference in median OS was reduced from 2.7 months to merely 1.4 months, representing an approximate 50% decrease in the effect of trastuzumab, which suggests that only a few patients benefit. Based on this trial, the combination of trastuzumab and chemotherapy has become the standard of care in patients whose tumors overexpress HER2.

In contrast to the positive results with trastuzumab in HER2-overexpressing gastroesophageal cancers, bevacizumab failed to demonstrate an OS benefit when it was added to a combination of cisplatin and fluoropyrimidine in patients with advanced gastric and GEJ adenocarcinoma.[159] A total of 774 patients were randomly assigned, and the median OS was 12.1 months with bevacizumab plus fluoropyrimidine-cisplatin and 10.1 months with placebo plus fluoropyrimidine-cisplatin (HR 0.87, 95% CI 0.73–1.03; $P = .1002$). Both median PFS (6.7 vs 5.3 months; HR 0.80, 95% CI 0.68–0.93; $P = .0037$) and overall response rate (46.0% vs 37.4%; $P = .0315$) were significantly improved with bevacizumab versus placebo.[159] In a preplanned subgroup analysis, the investigators were able to show that a benefit in terms of OS existed for "Pan-American" patients but not for European and Asian patients. This might point to differences in tumor biology but is also dependent on other factors. A subsequent retrospective biomarker analysis of the AVAGAST trial showed that patients with high baseline plasma VEGF-A levels and low baseline expression of neuropilin-1 seemed to have an improved OS. For both biomarkers, subgroup analyses demonstrated significance only in patients from non-Asian regions.[160] It is important to note that neither of these biomarkers has been validated. Unlike the ToGA trial, the AVAGAST trial did not use a biomarker-enriched patient population, underscoring the importance of appropriate patient selection in randomized controlled trials and the use of predictive biomarkers to direct care. Similarly, the AVATAR trial, which included an all Asian patient population, did not show any survival benefit of adding bevacizumab to the cisplatin-capecitabine combination.[161]

Equally disappointing results were also reported from two *EGFR*-targeting trials: the Erbitux (cetuximab) in Combination with Xeloda (capecitabine) and Cisplatin in Advanced Esophagogastric Cancer (EXPAND) and Revised European American Lymphoma (REAL-3) trials.[162,163] A biomarker analysis of the REAL-3 trial did not identify any biomarkers whose presence predicted resistance to modified epirubicin, oxaliplatin, and capecitabine (EOC) and panitumumab; however, only a few biomarkers were evaluated in this study.[164]

The role of lapatinib, a dual *EGFR* and HER2 tyrosine kinase inhibitor (TKI), was investigated in combination with capecitabine plus oxaliplatin (CapeOx) in 545 patients with HER2-positive advanced/metastatic gastroesophageal adenocarcinomas in the TRIO-013/LOGiC trial. The addition of lapatinib to CapeOx did not improve efficacy (OS and PFS) among untreated patients with HER2-positive metastatic gastric cancer.[165] Similarly, the concept of dual HER2 inhibition was studied in the JACOB trial. The JACOB trial was a double-blinded, placebo-controlled, randomized, multicenter, international phase 3 trial evaluating the efficacy and safety of adding pertuzumab to trastuzumab and chemotherapy in first-line treatment of HER2-positive metastatic gastric cancer/GEJ cancer. Unfortunately, adding pertuzumab to trastuzumab and chemotherapy did not significantly improve OS in patients with HER2-positive metastatic gastric or GEJ cancer compared with placebo.[166]

The KEYNOTE 062 study assessed whether in a PD-L1–positive (defined as CPS ≥1), HER2-negative advanced gastric or GEJ adenocarcinoma patient population pembrolizumab was noninferior to cisplatin-based chemotherapy and whether the addition of pembrolizumab to chemotherapy affected outcomes.[167] The investigators found that in patients with a CPS of 1 or higher, pembrolizumab was noninferior to chemotherapy, with a median survival of 10.6 versus 11.1 months (HR 0.91). For patients with a PD-L1 CPS of 10 or more, the survival with pembrolizumab was superior to chemotherapy (HR = 0.69); the median OS was 17.4 months for those receiving pembrolizumab compared with 10.8 months for those receiving chemotherapy. In the combination-therapy arm, the addition of pembrolizumab to chemotherapy added nothing in terms of OS or PFS when compared with chemotherapy alone regardless of patient CPS status. As of this writing, the CHECKMATE-649 (NCT02872116) study addressing the question of whether the addition of nivolumab to standard of care FOLFOX chemotherapy increases OS is ongoing and will soon be reported. The nivolumab/ipilumimab arm of this study was stopped early after an item analysis. Recently, the JAVELIN Gastric 100 study[168] addressed whether maintenance avelumab prolonged OS in patients with metastatic HER2-negative gastric or GEJ cancer in patients who received first-line oxaliplatin-based chemotherapy and did not progress. Reported study results found no difference in OS of patients with PD-L1 1 or higher with a median OS of 16.2 months in avelumab versus 17.2 months in the chemotherapy arm (HR 1.13; $P = .635$). This demonstrates that there is no role for maintenance avelumab in patients who do not progress on standard chemotherapy.

In summary, the standard of care in the first-line setting remains a combination of fluoropyrimidine and platinum-containing chemotherapy, with the addition of trastuzumab in the HER2-enriched population. The results of targeted therapy trials have mostly been disappointing, but none of these trials looked at an appropriately biomarker-enriched population. For immunotherapy, CPS appears to be a better biomarker than PD-L1 score; however, testing methodology and optimal cutoffs need to be better established in gastroesophageal cancers.

Second-Line Therapy

The validity of the use of second-line chemotherapy and its benefit in gastric cancer has long been questioned; however, all recently published trials demonstrated an OS prolongation, albeit very modest, when chemotherapy was compared with best supportive care (BSC).[169–172] A small German phase 3 study compared the efficacy of irinotecan plus BSC to BSC alone in patients with advanced gastric or GEJ adenocarcinoma.[170] Only 40 patients were randomly assigned to treatments, and the study closed early due to poor accrual. The HR for death was 0.48, with a 95% CI of 0.25 to 0.92, favoring the active treatment with irinotecan ($P = .023$). The median survival time was 4.0 months (95% CI 3.6–7.5) in the irinotecan arm and 2.4 months (95% CI 1.7–4.9) in the BSC arm.[170] There were no documented responses to irinotecan in this trial.

The second trial, COUGAR-02, randomized 186 patients to docetaxel plus BSC versus BSC alone. Docetaxel significantly improved OS compared with BSC alone, with a median OS of 5.2 months (95% CI 4.1–5.9) for docetaxel and 3.6 months (95% CI 3.3–4.4) for BSC (HR 0.67, 95% CI 0.49–0.92; $P = .01$).[171] Another study that demonstrated an OS benefit for patients treated with chemotherapy (either docetaxel or irinotecan) versus BSC was published by Kang et al.[173] Median OS was 5.3 months among 133 patients in the chemotherapy arm and 3.8 months among 69 patients in the BSC arm (HR 0.657, 95% CI 0.485–0.891; one-sided $P = .007$). There was no median OS difference between docetaxel and irinotecan (5.2 vs 6.5 months; $P = .116$).*79*

The role of angiogenesis inhibition as a target in gastric cancer was investigated in the Ramucirumab Monotherapy for Previously Treated Advanced Gastric or Gastro-Oesophageal Junction Adenocarcinoma (REGARD) trial, which randomly assigned 355 patients to receive ramucirumab or placebo.[169] This study demonstrated a marginal improvement in median OS (5.2 months in the ramucirumab group and 3.8 months in the placebo group; HR 0.776, 95% CI 0.603–0.998; $P = .047$). Interestingly, the average patient in the study treated with ramucirumab received treatments for 2 weeks longer than the average patient treated with placebo. In the published Ramucirumab in Metastatic Gastric Adenocarcinoma (RAINBOW) trial, ramucirumab was added to weekly paclitaxel as a second-line therapy in 665 patients with advanced or metastatic gastric cancer, demonstrating a significant improvement in both PFS and OS over paclitaxel alone.[172] A statistically significant prolongation of OS was demonstrated (HR 0.81, 95% CI 0.68–0.96; $P = .017$). Median OS times were 9.6 and 7.4 months in the ramucirumab-plus-paclitaxel arm and placebo-plus-paclitaxel arm, respectively. The PFS was also significantly longer for patients receiving ramucirumab plus paclitaxel (HR 0.64, 95% CI 0.54–0.75; $P < .001$) with an overall good safety profile, further supporting its role in combination with chemotherapy.

In the second-line setting, targeted HER2 therapy with TKIs has been a failure.[174,175] Lapatinib has been investigated in a large 420-patient study (TyTAN trial), which randomly assigned HER2-positive patients to lapatinib plus paclitaxel (L+P) versus paclitaxel alone. Median OS was 11.0 months for L+P and 8.9 months for paclitaxel alone in the intent-to-treat population (HR 0.84; $P = .2088$). In a preplanned subgroup analysis, median OS in the HER2 IHC 3+ subgroup was 14.0 months for the combination therapy and 7.6 months for paclitaxel alone (HR 0.59; $P = .0176$).[175] Interestingly, it has recently been demonstrated that although the study mandated IHC HER2 positivity, 35% of patients in the TyTAN trial had tumors classified as IHC 0/1.[175] Antibody-drug conjugates represent a promising class of drugs because of their efficient drug delivery to antigen-expressing tumor cells. Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate comprised of trastuzumab linked to the tubulin inhibitor emtansine by a stable linker. In the GATSBY trial, second-line T-DM1 failed to prolong OS compared with taxane in previously treated HER2-positive gastric cancer.[176]

Equally disappointing, the UK Gefitinib for Oesophageal Cancer Progressing After Chemotherapy (COG) trial in patients with adenocarcinoma of the esophagogastric junction types I/II (tumors extending to the esophagus 5 cm above and 2 cm below the GEJ) in the second-line setting randomized 449 patients to receive gefitinib or placebo.[177]

Multiple studies highlight the importance of identification and targeting of driver mutations and their usefulness in the creation of appropriate biomarkers to direct care.[178,179] *MET* amplification and/or overexpression of its protein product has long been implicated in the pathogenesis of gastric cancer, supporting its role as a poor prognostic factor.*45* Hepatocyte growth factor/MET-targeted treatments were evaluated in patient-selected phase 3 trials (RILOMET-1 and MET

Gastric).[180,181] Both antibodies (rilotumumab and onartuzumab) failed to improve survival in gastric cancer that was IHC-positive for MET expression.

The role of poly (adenosine diphosphate–ribose) polymerase (PARP) inhibitors in gastric cancer was investigated in a phase 2 study in which 124 patients who progressed on fluoropyrimidines (second-line metastatic setting) were randomly assigned to receive olaparib plus paclitaxel versus paclitaxel alone.[182] There was no improvement in PFS, but the addition of olaparib significantly improved OS (HR 0.56, 95% CI 0.35–0.87; P = .010). The subsequently performed phase 3 trial yielded negative results, unfortunately.[183] Overall survival did not differ between treatment groups in the overall patient population (median OS 8.8 months in the olaparib group vs 6.9 months in the placebo group; HR 0.79; P = ·026) or in the ataxia telangiectasia-mutated protein-negative population (12.0 months vs 10.0 months; HR 0.73; P = .25).[183]

The role of immunotherapy has also been assessed in second-line therapy for gastroesophageal cancers. The KEYNOTE-061 trial also failed to show a survival benefit for pembrolizumab over paclitaxel in the second-line setting in patients with a PD-L1 CPS (a proportional assessment of PD-L1 staining on tumor and immune cells) expression >1.[184] Of note, in a post hoc analysis, patients with CPS scores of 5 or more and 10 or more did appear to see benefit. These disappointing results add weight to the hypothesis that only a minority of patients benefit from single-agent immunotherapy. The phase 3 KEYNOTE-181[185] study evaluating pembrolizumab versus physician's choice chemotherapy in patients with advanced esophageal/GEJ adenocarcinoma and SCC who had progressed after first-line therapy failed to meet its primary end point of OS in the intention-to-treat population of patients with a CPS of 1 or more, with median OS of 7.1 months in both arms (HR 0.89; P = .056). They found that in the subgroup of patients with a CPS of 10 or higher, the median survival was 9.3 versus 6.7 months (HR 0.69; P = .0074). In a press release, the FDA granted approval for nivolumab in unresectable advanced, recurrent, or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy. The approval is based on the phase 3 ATTRACTION-3 trial in which patients treated with nivolumab (n = 210) demonstrated superior OS versus those treated with taxane chemotherapy (n = 209) (investigator's choice of docetaxel or paclitaxel) (HR 0.77, 95% CI 0.62–0.96; P = .0189). The median OS was 10.9 months (95% CI 9.2–13.3) for nivolumab compared with 8.4 months (95% CI 7.2–9.9) for docetaxel or paclitaxel.[186] Nivolumab is the first approved immunotherapy in this setting regardless of tumor PD-L1 expression level.[187]

Third-Line Therapy

Apatinib is a small-molecule multitargeted TKI with activity against VEGFR. After showing improved PFS and OS in heavily pretreated patients with metastatic gastric cancer in a phase 2 trial,[188] apatinib was evaluated in a phase 3 trial in 271 patients with advanced gastric cancer.[189] Patients had prior failure to second-line chemotherapy and were stratified according to the number of metastatic sites (≤ or >2 sites). This trial met its primary end point, showing significant improvement in OS and PFS. The median OS time was 6.5 months for apatinib and 4.7 months for placebo (HR 0.71, 95% CI 0.54–0.94; P = .015), and the median PFS was 2.6 months for apatinib and 1.8 months for placebo (HR 0.44; 95% CI 0.33–0.61; P < .0001). This trial further supports the angiogenesis inhibition as a target in this disease.

In addition to treatment with standard cytotoxic chemotherapy and targeted therapy, immune checkpoint inhibitors with antiprogrammed cell death protein 1 monoclonal antibodies (PD-1 inhibitors) have emerged as a therapeutic option in the metastatic setting. As of this writing, the PD-1 inhibitor, pembrolizumab, is approved for all patients with mismatch repair–deficient tumors after failure of first-line cytotoxic chemotherapy. In KEYNOTE-059 Cohort 1, a multicenter, open-label, single-arm phase 2 trial conducted at 67 sites in 17 countries, 259 patients (after failing two or more lines of chemotherapy including cisplatin and 5-FU; patients with HER2-positive tumors must have received treatment with trastuzumab) received a fixed dose of 200 mg pembrolizumab in a 3-weekly cycle. Pembrolizumab showed an objective response rate of 11.6% (95% CI 8.0%–16.1%), with complete response of 2.3% (95% CI 0.9%–5.0%). The response rate was higher in the patients with PD-L1–positive tumors (PD-L1–positive vs PD-L1–negative: 15.5% vs 6.4%). A total of seven (4%) tumors were microsatellite instable–high and the response rates were higher, with an overall response rate of 57.1%. Median PFS was 2.0 months and median OS was 5.6 months. Based on these results, the FDA has approved pembrolizumab as the third-line treatment for PD-L1–positive gastric adenocarcinoma.[190]

Nivolumab, an immune checkpoint inhibitor, was evaluated in the phase 3 ATTRACTION-2 study[191] in patients with gastric or GEJ cancer treated with two or more prior chemotherapy regimens. Patients were randomly assigned (2:1) to receive 3 mg/kg nivolumab or placebo intravenously every 2 weeks. Nivolumab was associated with a significant OS benefit *versus* placebo (OS 5.32 *vs* 4.14 months; P < .0001; 12-month OS 26.6% *vs* 10.9%). Nivolumab reduced mortality risk by 37% compared with placebo. The survival advantage was persistent over time with nivolumab and

irrespective of PD-1/PD-L1 expression. Nivolumab is currently not approved in the United States for metastatic GEJ or gastric cancer.[191]

TAS-102 (trifluridine/tipiracil) is an oral combination drug of two active compounds: trifluridine, a thymidine analog (nucleoside antitumor agent), and tipiracil hydrochloride, a thymidine phosphorylase inhibitor, in a ratio of 1:0.5. In the international phase 3 randomized control trial, the TAGS study, 507 patients with advanced/metastatic gastric adenocarcinomas (including adenocarcinoma of the GEJ) were randomly assigned to TAS-102 or placebo in a 2:1 ratio. In patients with prior gastrectomy, OS (6.0 months vs 3.4 months, HR 0.57, 95% CI 0.41–0.79) and PFS (2.2 months vs 1.8 months, HR 0.65, 95% CI 0.49–0.85) were more favorable among the TAS-102 group versus those receiving placebo. Moreover, the patients who did not have gastrectomy also showed OS (HR 0.80, 95% CI 0.60–1.06) and PFS (HR 0.65, 95% CI 0.49–0.85) benefit to treatment with TAS-102.[192] More patients in the TAS-102 arm achieved disease control compared with the placebo group (44% vs 14%; $P < .0001$).[192]

Table 27–8 lists major phase 3 trials for advanced/metastatic esophageal, GEJ, and gastric cancer involving chemotherapy agents, and Table 27–9 lists trials involving targeted agents in the first-, second-, and third-line settings.

Supportive Measures for Advanced Gastric, Gastroesophageal Junction, and Esophageal Cancers

The goal of symptom palliation is to optimize quality of life. Current or potential signs or symptoms that affect quality of life should be assessed during the initial evaluation of patients with unresectable disease. Available treatment options include palliative radiotherapy without concurrent chemotherapy*197*; chemotherapy; endoscopic palliation with luminal dilation, stents, or laser or chemical ablation; and palliative surgery. Palliative surgery is rarely performed because it is rare that the potential benefits clearly outweigh the risks of surgery. Several special issues to consider in this group of patients include (1) problems specifically associated with primary disease, (2) nutrition, (3) diagnosis and treatment of tracheoesophageal fistulas, and (4) management of oral secretions.

All patients, especially those who present with more than 15% weight loss from their normal baseline, should undergo formal nutritional evaluation, and alternative nutritional support methods should

Table 27–8 Major Phase 3 Gastric Cancer Trials Involving Chemotherapy Agents in the Advanced/Metastatic Setting

Trials	No. of Patients	Treatment Arms	HR for OS (*P* value)	Primary End Point Comparison in Months
Advanced Gastric Cancer: First Line				
Van Cutsem et al (V325 study group)[154]	445	DCF vs CF	TTP: 1.47 (< .001) OS: 1.29 (.02)	TTP: 5.6 vs 3.7 OS: 9.2 vs 8.6
Cunningham et al[155]	1002	ECF vs ECX vs EOF vs EOX	0.80 (.02)	OS: 9.9 vs 9.9 vs 9.3 vs 11.2
Koizumi et al (SPIRITS)[157]	305	S-1 + cisplatin vs S-1	0.77 (.04)	OS: 13.0 vs 11.0
Ajani et al (FLAGS)[193]	1053	Cisplatin + S-1 vs cisplatin + 5-FU	0.92 (.20)	OS: 8.6 vs 7.9
Advanced Gastric Cancer: Second Line				
Thuss-Patience et al (AIO)[170]	40	Irinotecan + BSC vs BSC	0.48 (.012)	OS: 4.0 vs 2.4
Cook et al (COUGAR-02)[171]	168	Docetaxel + ASC vs ASC	0.67 (.01)	OS: 5.2 vs 3.6
Kang et al[173]	202	Docetaxel or irinotecan vs BSC	0.657 (.007)	OS: 5.3 vs 3.8
Higuchi et al (TCOG GI–0801/BIRIP)[194]	130	Biweekly irinotecan + cisplatin vs irinotecan	1.00 (.9823)	PFS: 3.8 vs 2.8 OS: 10.7 vs 10.1

ASC, active symptom control; BSC, best supportive care; CF, cisplatin and 5-fluorouracil; DCF, docetaxel, cisplatin, and 5-fluorouracil; ECF, epirubicin, cisplatin, and 5-fluorouracil; ECX, epirubicin, cisplatin, and capecitabine; EOF, epirubicin, oxaliplatin, and 5-fluorouracil; EOX, epirubicin, oxaliplatin, and capecitabine; 5-FU, 5-fluorouracil; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

Table 27–9 Major Phase 3 Gastric Cancer Trials Involving Targeted Agents in the Advanced/Metastatic Setting

Trials	No. of Patients	Treatment Arms	HR for OS (*P* value)	Primary End Point Comparison in Months
Advanced Gastric Cancer: First Line				
Bang et al (ToGA)[a156]	584	CX/CF + trastuzumab vs CX/CF	0.74 (.0046)	OS: 13.8 vs 11.1
Ohtsu et al (AVAGAST)[159]	774	CF + bevacizumab vs CF	0.87 (.1002)	OS: 12.1 vs 10.1 PFS: 6.7 vs 5.3
Lordick et al (EXPAND)[162]	904	CX + cetuximab vs CX	1.004 (.9547)	OS: 9.4 vs 10.7
Waddell et al (REAL-3)[163]	553	mEOC + panitumumab vs EOC	1.37 (.013)	OS: 8.8 vs 11.3
Hecht et al (LOGiC)[195]	545	CapeOx + lapatinib vs CapeOx + placebo	0.91 (.35)	OS: 12.2 vs 10.5
Tabernero et al (JACOB)[166]	780	Pertuzumab + Trastuzumab + CT vs Placebo + Trastuzumab + CT	0.84 (.057)	OS: 24.4 vs 25
Advanced Gastric Cancer: Second Line				
Fuchs et al (REGARD)[169]	355	Ramucirumab + BSC vs BSC	0.776 (.0473)	OS: 5.2 vs 3.8
Wilke et al (RAINBOW)[172]	665	Paclitaxel + ramucirumab vs paclitaxel	0.81 (.017)	OS: 9.6 vs 7.4
Ohtsu et al (GRANITE-1)[174]	656	Everolimus + BSC vs placebo + BSC	0.90 (.1244)	OS: 5.4 vs 4.3
Satoh et al (TyTAN)[175]	261	Lapatinib + paclitaxel vs paclitaxel	0.84 (.2088)	OS: 11.0 vs 8.9
Dutton et al (COG)[177]	449	Gefitinib vs placebo	0.90 (.29)	OS: 3.73 vs 3.63
Thuss-Patience et al (GATSBY)[176]	415	Standard taxane vs Trastuzumab	1.15 (.86)	OS: 8.6 vs 7.9
Catenacci et al (RILOMET-1)[180]	609	Rilotumumab + epirubicin + cisplatin + capecitabine vs placebo + epirubicin + cisplatin + capecitabine.	1.34 (.003)	OS: 8.8 vs 10.7
Shah et al (MET Gastric)[181]	562	Onartuzumab + mFOLFOX^6 vs placebo + mFOLFOX^6	0.82 (.24)	OS: 11 vs 11.3
Bang et al (GOLD)[183]	643	Olaparib + paclitaxel vs placebo + paclitaxel	0.79 (.026)	OS: 8.8 vs 6.9
Shitara et al (KEYNOTE-061)[184]	592	Pembrolizumab vs paclitaxel	0.82 (.0421)	OS: 9.1 vs 8.3
Kojima et al (KEYNOTE-181)[185]	751	Pembrolizumab vs CT	0.69 (.0074)(when CPS ≥10)	OS: 9.3 vs 6.7(when CPS ≥10)
Advanced Gastric Cancer: Third Line				
Qin et al (apatinib)[189]	271	Apatinib + BSC vs BSC	0.71 (.015)	OS: 6.5 vs 4.7 PFS: 2.6 vs 1.8
Ohtsu et al (GRANITE-1)[174]	656	Everolimus + BSC vs placebo + BSC	0.90 (.1244)	OS: 5.4 vs 4.3
Fuchs et al (KEYNOTE-059 – Cohort 1)[190]	259	Pembrolizumab monotherapy in PD-L1–positive vs PD-L1–negative		OS: 5.8 vs 4.9 OR: 15.5 vs 6.4
Kang et al (ATTRACTION-2)[196]	493	Nivolumab vs placebo	0.63 (.0001)	OS: 5.26 vs 4.14
Shitara et al (TAGS)[192]	507	TAS-102 vs placebo	0.69 (.00029)	OS: 5.7 vs 3.6

[a]HR reduced to 0.8 on follow-up analysis.
BSC, best supportive care; CapeOx, capecitabine and oxaliplatin; CF, cisplatin and 5-fluorouracil; CX, cisplatin and capecitabine; EOC, epirubicin, oxaliplatin, and capecitabine; HR, hazard ratio; mEOC, modified epirubicin, oxaliplatin, and capecitabine; OR, objective response (CR+PR); OS, overall survival; PFS, progression-free survival; TAS-102, trifluridine/tipiracil.

be considered. Adequate nutrition and hydration are crucial to ensure that patients complete the full course of therapy. Jejunostomy feeding tubes (J-tubes), which are inserted primarily via a surgical procedure, can be considered in patients with gastric and GEJ cancer; they can be placed during the initial laparoscopic evaluation. Percutaneous gastrostomy feeding tubes, placed by endoscopic (percutaneous endoscopic gastrostomy) or radiologic (G-tube) guidance, can be considered for esophageal cancer. The continued use of jejunostomy, gastrostomy, or nasogastric feeding tubes is considered the first choice if nutrition cannot be supported orally.

Patients with advanced gastric, GEJ, and esophageal cancers might be candidates for definitive chemoradiotherapy. Chemotherapy agents used in combination with radiotherapy include cisplatin, paclitaxel, carboplatin, oxaliplatin, or 5-FU. Patients with borderline performance status may not be candidates for definitive chemoradiotherapy, even with consistent nutritional support via feeding tubes. Therapy should be based on the patient's most pressing symptoms. Malnutrition should be addressed, whenever feasible, with gastrostomy or a jejunostomy tube. Upper GI bleeding and pain can be palliated with radiotherapy, alone or with endoscopic cauterization. Finally, effective chemotherapy can directly improve symptoms such as dysphagia and pain, as well as indirectly improve nutrition and minimize bleeding risk and aspiration.

Although genetic profiling of tumors (next-generation sequencing) has become a more widely used tool in the treatment of gastric, GEJ, and esophageal cancers, patients are often found to have multiple and nontargetable mutations. Even when a potentially targetable mutation is found and the patient is treated with a given drug, we have found that responses are rare, likely because of our poor knowledge of driver mutations. However, with the advent of more targeted treatments in combination with cytotoxic agents or immunotherapy, we emphasize the enrollment of patients into available clinical trials.

Figure 27–3A and B summarize the MDACC approach to advanced gastric, GEJ, and esophageal cancer.

MD ANDERSON PRACTICE TIPS

ADVANCED GASTRIC, GASTROESOPHAGEAL JUNCTION, AND ESOPHAGEAL CANCERS

- Our approach in the metastatic setting is to provide palliation of symptoms and prolongation of life.
- In HER2-positive gastric cancer, there is an OS benefit with the addition of anti-HER2 therapy to first-line chemotherapy.
- A reasonable option in the first-line setting is a platinum-based doublet with the addition of docetaxel depending on the performance status of the patient.
- In the second line, we use ramucirumab combined with paclitaxel; however, in patients with severe neuropathy, irinotecan-based chemotherapy is also an alternative.
- Since the approval of pembrolizumab in PD-L1–positive gastric cancer, our approach is to use immunotherapy in patients with PD-L1–positive tumors (CPS >1) that have progressed on two lines of chemotherapy.
- Additional options for treatment include TAS102.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer.* 2015;136(5):E359-E386.
2. American Cancer Society. Cancer Facts & Figures 2020. Accessed April 18, 2021. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2020.html
3. National Cancer Institute; Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts. Accessed May 14, 2020. https://seer.cancer.gov/statfacts/
4. Anderson WF, Camargo MC, Fraumeni JF Jr, et al. Age-specific trends in incidence of noncardia gastric cancer in US adults. *JAMA.* 2010;303:1723-1728.
5. Buas MF, Vaughan TL. Epidemiology and risk factors for gastroesophageal junction tumors: understanding the rising incidence of this disease. *Semin Radiat Oncol.* 2013;23:3-9.
6. Alexander GA, Brawley OW. Association of *Helicobacter pylori* infection with gastric cancer. *Mil Med*. 2000;165:21-27.
7. Bosman FT, Carneiro F, Hruban RH, Theise ND. *WHO Classification of Tumours of the Digestive System*. Geneva: World Health Organization, 2010.
8. Correa P. Human gastric carcinogenesis: a multistep and multifactorial process—First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res.* 1992;52:6735-6740.
9. Larsson SC, Wolk A. Red and processed meat consumption and risk of pancreatic cancer: meta-analysis of prospective studies. *Br J Cancer.* 2012;106:603-607.
10. Freedman ND, Abnet CC, Leitzmann MF, et al. A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. *Am J Epidemiol.* 2007;165:1424-1433.
11. Stalnikowicz R, Benbassat J. Risk of gastric cancer after gastric surgery for benign disorders. *Arch Intern Med.* 1990;150:2022-2026.
12. Freedman ND, Chow WH, Gao YT, et al. Menstrual and reproductive factors and gastric cancer risk in a large prospective study of women. *Gut.* 2007;56:1671-1677.
13. Zheng ZH, Sun XJ, Ma MC, et al. [Studies of promoter methylation status and protein expression of E-cadherin gene in associated progression stages of gastric cancer]. *Yi Chuan Xue Bao*. 2003;30:103-108.
14. Oliveira C, Ferreira P, Nabais S, et al. E-Cadherin (CDH1) and p53 rather than SMAD4 and Caspase-10 germline mutations contribute to genetic predisposition in Portuguese gastric cancer patients. *Eur J Cancer.* 2004;40:1897-1903.
15. Kaurah P, MacMillan A, Boyd N, et al. Founder and recurrent CDH1 mutations in families with hereditary diffuse gastric cancer. *JAMA.* 2007;297:2360-2372.
16. Lynch HT, Grady W, Suriano G, Huntsman D. Gastric cancer: new genetic developments. *J Surg Oncol.* 2005;90:114-133; discussion 133.
17. Murphy G, Pfeiffer R, Camargo MC, Rabkin CS. Meta-analysis shows that prevalence of Epstein-Barr virus-positive gastric cancer differs based on sex and anatomic location. *Gastroenterology.* 2009;137:824-833.
18. Kusano M, Toyota M, Suzuki H, et al. Genetic, epigenetic, and clinicopathologic features of gastric carcinomas with the CpG island methylator phenotype and an association with Epstein-Barr virus. *Cancer.* 2006;106:1467-1479.
19. Eslick GD, Lim LL, Byles JE, et al. Association of *Helicobacter pylori* infection with gastric carcinoma: a meta-analysis. *Am J Gastroenterol.* 1999;94:2373-2379.
20. Huang JQ, Sridhar S, Chen Y, Hunt RH. Meta-analysis of the relationship between *Helicobacter pylori* seropositivity and gastric cancer. *Gastroenterology.* 1998;114:1169-1179.
21. Parsonnet J, Forman D. *Helicobacter pylori* infection and gastric cancer—for want of more outcomes. *JAMA.* 2004;291:244-245.
22. Wong BC, Lam SK, Wong WM, et al. *Helicobacter pylori* eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA.* 2004;291:187-194.
23. Ma JL, Zhang L, Brown LM, et al. Fifteen-year effects of *Helicobacter pylori*, garlic, and vitamin treatments on gastric cancer incidence and mortality. *J Natl Cancer Inst.* 2012;104:488-492.
24. Fuccio L, Zagari RM, Eusebi LH, et al. Meta-analysis: can *Helicobacter pylori* eradication treatment reduce the risk for gastric cancer? *Ann Intern Med.* 2009;151:121-128.
25. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature*. 2014;513:202-209.
26. Graham DY, Schwartz JT, Cain GD, Gyorkey F. Prospective evaluation of biopsy number in the diagnosis of esophageal and gastric carcinoma. *Gastroenterology.* 1982;82:228-231.
27. Moss AA, Schnyder P, Marks W, Margulis AR. Gastric adenocarcinoma: a comparison of the accuracy and economics of staging by computed tomography and surgery. *Gastroenterology.* 1981;80:45-50.
28. Amin MB, Greene FL, Edge SB, et al. The *Eighth Edition AJCC Cancer Staging Manual*: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin.* 2017;67:93-99.
29. Rosch T, Lorenz R, Zenker K, et al. Local staging and assessment of resectability in carcinoma of the esophagus, stomach, and duodenum by endoscopic ultrasonography. *Gastrointest Endosc.* 1992;38:460-467.
30. Conlon KC, Karpeh MS Jr. Laparoscopy and laparoscopic ultrasound in the staging of gastric cancer. *Semin Oncol.* 1996;23:347-351.
31. Ikoma N, Blum M, Chiang Y-J, et al. Yield of staging laparoscopy and lavage cytology for radiologically occult peritoneal carcinomatosis of gastric cancer. *Ann Surg Oncol.* 2016;23:4332-4337.
32. Sun L, Su XH, Guan YS, et al. Clinical role of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in post-operative follow up of gastric cancer: initial results. *World J Gastroenterol.* 2008;14:4627-4632.
33. Ott K, Lordick F, Herrmann K, et al. The new credo: induction chemotherapy in locally advanced gastric cancer: consequences for surgical strategies. *Gastric Cancer.* 2008;11:1-9.
34. Ott K, Herrmann K, Lordick F, et al. Early metabolic response evaluation by fluorine-18 fluorodeoxyglucose positron emission tomography allows in vivo testing of chemosensitivity in gastric cancer: long-term results of a prospective study. *Clin Cancer Res.* 2008;14:2012-2018.
35. Swisher SG, Erasmus J, Maish M, et al. 2-Fluoro-2-deoxy-D-glucose positron emission tomography imaging is predictive of pathologic response and survival after preoperative chemoradiation in patients with esophageal carcinoma. *Cancer.* 2004;101:1776-1785.
36. Lordick F, Ott K, Krause BJ, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. *Lancet Oncol.* 2007;8:797-805.
37. Javeri H, Xiao L, Rohren E, et al. The higher the decrease in the standardized uptake value of positron emission tomography after chemoradiation, the better the survival of patients with gastroesophageal adenocarcinoma. *Cancer.* 2009;115:5184-5192.
38. Sim SH, Kim YJ, Oh DY, et al. The role of PET/CT in detection of gastric cancer recurrence. *BMC Cancer.* 2009;9:73.
39. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol.* 2010;17:1471-1474.

40. Talamonti MS, Kim SP, Yao KA, et al. Surgical outcomes of patients with gastric carcinoma: the importance of primary tumor location and microvessel invasion. *Surgery*. 2003;134:720-727; discussion 727-729.
41. Bonenkamp JJ, Hermans J, Sasako M, et al. Extended lymph-node dissection for gastric cancer. *N Engl J Med.* 1999;340:908-914.
42. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med.* 2001;345:725-730.
43. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med.* 2006;355:11-20.
44. Sakuramoto S, Sasako M, Yamaguchi T, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med.* 2007;357:1810-1820.
45. Bang YJ, Kim YW, Yang HK, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. *Lancet.* 2012;379:315-321.
46. Wanebo HJ, Kennedy BJ, Chmiel J, et al. Cancer of the stomach. A patient care study by the American College of Surgeons. *Ann Surg.* 1993;218:583-592.
47. Martin RC 2nd, Jaques DP, Brennan MF, Karpeh M. Extended local resection for advanced gastric cancer: increased survival versus increased morbidity. *Ann Surg.* 2002;236:159-165.
48. Gouzi JL, Huguier M, Fagniez PL, et al. Total versus subtotal gastrectomy for adenocarcinoma of the gastric antrum. A French prospective controlled study. *Ann Surg.* 1989;209:162-166.
49. Schwarz RE, Smith DD. Clinical impact of lymphadenectomy extent in resectable gastric cancer of advanced stage. *Ann Surg Oncol.* 2007;14:317-328.
50. Smith DD, Schwarz RR, Schwarz RE. Impact of total lymph node count on staging and survival after gastrectomy for gastric cancer: data from a large US-population database. *J Clin Oncol.* 2005;23:7114-7124.
51. Wu CW, Hsiung CA, Lo SS, et al. Nodal dissection for patients with gastric cancer: a randomised controlled trial. *Lancet Oncol.* 2006;7:309-315.
52. Danielson H, Kokkola A, Kiviluoto T, et al. Clinical outcome after D1 vs D2-3 gastrectomy for treatment of gastric cancer. *Scand J Surg*. 2007;96:35-40.
53. Hartgrink HH, van de Velde CJ, Putter H, et al. Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch gastric cancer group trial. *J Clin Oncol.* 2004;22:2069-2077.
54. Cuschieri A, Weeden S, Fielding J, et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. *Br J Cancer.* 1999;79:1522-1530.
55. Coupland VH, Lagergren J, Luchtenborg M, et al. Hospital volume, proportion resected and mortality from oesophageal and gastric cancer: a population-based study in England, 2004-2008. *Gut.* 2013;62:961-966.
56. Dikken JL, Dassen AE, Lemmens VE, et al. Effect of hospital volume on postoperative mortality and survival after oesophageal and gastric cancer surgery in the Netherlands between 1989 and 2009. *Eur J Cancer.* 2012;48:1004-1013.
57. Degiuli M, Calvo F. Survival of early gastric cancer in a specialized European center. Which lymphadenectomy is necessary? *World J Surg.* 2006;30:2193-2203.
58. Songun I, Putter H, Kranenbarg EM, et al. Surgical treatment of gastric cancer:15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol.* 2010;11:439-449.
59 Okines A, Verheij M, Allum W, et al. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2010;21(suppl 5):v50-v54.
60. van M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol.* 2011;29:1715-1721.
61. Schuhmacher C, Gretschel S, Lordick F, et al. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for Research and Treatment of Cancer randomized trial 40954. *J Clin Oncol.* 2010;28:5210-5218.
62. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet.* 2019;393:1948-1957.
63. Terashima M, Iwasaki Y, Mizusawa J, et al. Randomized phase III trial of gastrectomy with or without neoadjuvant S-1 plus cisplatin for type 4 or large type 3 gastric cancer, the short-term safety and surgical results: Japan Clinical Oncology Group Study (JCOG0501). *Gastric Cancer.* 2019;22:1044-1052.
64. Fuchs C, Tepper J, Niedzwiecki D, et al. Postoperative adjuvant chemoradiation for gastric or gastroesophageal junction (GEJ) adenocarcinoma using epirubicin, cisplatin, and infusional (CI) 5-FU (ECF) before and after CI 5-FU and radiotherapy (CRT) compared with bolus 5-FU/LV before and after CRT: Intergroup trial CALGB 80101. *J Clin Oncol*. 2011;29:4003-4003.
65. Smalley SR, Benedetti JK, Haller DG, et al. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. *J Clin Oncol.* 2012;30:2327-2333.
66. Lee J, Lim do H, Kim S, et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. *J Clin Oncol.* 2012;30:268-273.
67. Park SH, Sohn TS, Lee J, et al. Phase III trial to compare adjuvant chemotherapy with capecitabine and cisplatin versus concurrent chemoradiotherapy in gastric cancer: final report of the Adjuvant Chemoradiotherapy in Stomach Tumors Trial, including survival and subset analyses. *J Clin Oncol.* 2015;33(28):3130-3136.
68. Dikken JL, van Sandick JW, Maurits Swellengrebel HA, et al. Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS). *BMC Cancer.* 2011;11:329.
69. Leong T, Michael M, Gebski V, et al. TOPGEAR: An international randomized phase III trial of preoperative chemoradiotherapy versus preoperative chemotherapy for resectable gastric cancer (AGITG/TROG/EORTC/NCIC CTG). *J Clin Oncol*. 2012;30(suppl 15).
70. Cats A, Jansen EPM, van Grieken NCT, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. *Lancet Oncol*. 2018;19:616-628.
71. Slagter AE, Jansen EPM, van Laarhoven HWM, et al. CRITICS-II: a multicentre randomised phase II trial of neo-adjuvant chemotherapy followed by surgery versus neo-adjuvant chemotherapy and subsequent chemoradiotherapy followed by surgery versus neo-adjuvant chemoradiotherapy followed by surgery in resectable gastric cancer. *BMC Cancer.* 2018;18:877.
72. Leong T, Smithers BM, Haustermans K, et al. TOPGEAR: a randomized, phase III trial of perioperative ECF chemotherapy with or without preoperative chemoradiation for resectable gastric cancer: interim results from an international, intergroup trial of the AGITG, TROG, EORTC and CCTG. *Ann Surg Oncol*. 2017;24:2252-2258.

73. Ajani JA, Xiao L, Roth JA, et al. A phase II randomized trial of induction chemotherapy versus no induction chemotherapy followed by preoperative chemoradiation in patients with esophageal cancer. *Ann Oncol*. 2013;24:2844-2849.
74. Ajani JA, Winter K, Okawara GS, et al. Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma (RTOG 9904): quality of combined modality therapy and pathologic response. *J Clin Oncol.* 2006;24:3953-3958.
75. Sasako M, Sakuramoto S, Katai H, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. *J Clin Oncol.* 2011;29:4387-4393.
76. Kodera Y, Yoshida K, Kochi M, et al. A randomized phase III study comparing S-1 plus docetaxel with S-1 alone as a postoperative adjuvant chemotherapy for curatively resected stage III gastric cancer (JACCRO GC-07 trial). *J Clin Oncol.* 2018;36:4007-4007.
77. Yoshida K, Kodera Y, Kochi M, et al. Addition of Docetaxel to Oral Fluoropyrimidine Improves Efficacy in Patients With Stage III Gastric Cancer: Interim Analysis of JACCRO GC-07, a Randomized Controlled Trial. *J Clin Oncol.* 2019;37:1296-1304.
78. Park SH, Zang DY, Han B, et al. ARTIST 2: Interim results of a phase III trial involving adjuvant chemotherapy and/or chemoradiotherapy after D2-gastrectomy in stage II/III gastric cancer (GC). *J Clin Oncol.* 2019;37:4001.
79. Kang YK, Yook JH, Park YK, et al. Phase III randomized study of neoadjuvant chemotherapy (CT) with docetaxel(D), oxaliplatin(O) and S-1(S) (DOS) followed by surgery and adjuvant S-1, vs surgery and adjuvant S-1, for resectable advanced gastric cancer (GC) (PRODIGY). *Ann Oncol.* 2019;30:v876-v877.
80. Cunningham D, Stenning SP, Smyth EC, et al. Peri-operative chemotherapy with or without bevacizumab in operable oesophagogastric adenocarcinoma (UK Medical Research Council ST03): primary analysis results of a multicentre, open-label, randomised phase 2-3 trial. *Lancet Oncol.* 2017;18:357-370.
81. Tsuburaya A, Yoshida K, Kobayashi M, et al. Sequential paclitaxel followed by tegafur and uracil (UFT) or S-1 versus UFT or S-1 monotherapy as adjuvant chemotherapy for T4a/b gastric cancer (SAMIT): a phase 3 factorial randomised controlled trial. *Lancet Oncol*. 2014;15:886-893.
82. Diaz-Nieto R, Orti-Rodriguez R, Winslet M. Post-surgical chemotherapy versus surgery alone for resectable gastric cancer. *Cochrane Database Syst Rev*. 2013;9:CD008415.
83. Ronellenfitsch U, Schwarzbach M, Hofheinz R, et al. Perioperative chemo(radio)therapy versus primary surgery for resectable adenocarcinoma of the stomach, gastroesophageal junction, and lower esophagus. *Cochrane Database Syst Rev*. 2013;5:CD008107.
84. Oba K, Paoletti X, Alberts S, et al. Disease-free survival as a surrogate for overall survival in adjuvant trials of gastric cancer: a meta-analysis. *J Natl Cancer Inst.* 2013;105:1600-1607.
85. Earle CC, Maroun JA. Adjuvant chemotherapy after curative resection for gastric cancer in non-Asian patients: revisiting a meta-analysis of randomised trials. *Eur J Cancer.* 1999;35:1059-1064.
86. Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends—an update. *Cancer Epidemiol Biomarkers Prev*. 2016;25:16-27.
87. Colditz GA, editor. *Encyclopedia of Cancer and Society*. SAGE Publications; 2007.
88. Cummings LC, Cooper GS. Descriptive epidemiology of esophageal carcinoma in the Ohio Cancer Registry. *Cancer Detect Prev*. 2008;32:87-92.
89. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin.* 2005;55:74-108.
90. Sant M, Aareleid T, Berrino F, et al. EUROCARE-3: survival of cancer patients diagnosed 1990-94—results and commentary. *Ann Oncol.* 2003;14(suppl 5):v61-v118.
91. Chen ZM, Xu Z, Collins R, et al. Early health effects of the emerging tobacco epidemic in China. A 16-year prospective study. *JAMA.* 1997;278:1500-1504.
92. Keszei AP, Goldbohm RA, Schouten LJ, et al. Dietary N-nitroso compounds, endogenous nitrosation, and the risk of esophageal and gastric cancer subtypes in the Netherlands Cohort Study. *Am J Clin Nutr.* 2013;97:135-146.
93. Wu CM, Lee YS, Wang TH, et al. Identification of differential gene expression between intestinal and diffuse gastric cancer using cDNA microarray. *Oncol Rep.* 2006;15:57-64.
94. Islami F, Pourshams A, Nasrollahzadeh D, et al. Tea drinking habits and oesophageal cancer in a high risk area in northern Iran: population based case-control study. *BMJ*. 2009;338: b929.
95. Ríos-Galvez S, Meixueiro-Daza A, Remes-Troche JM. Achalasia: a risk factor that must not be forgotten for esophageal squamous cell carcinoma. *BMJ Case Rep*. 2015;2015:bcr2014204418.
96. Ribeiro U Jr, Posner MC, Safatle-Ribeiro AV, Reynolds JC. Risk factors for squamous cell carcinoma of the oesophagus. *Br J Surg.* 1996;83:1174-1185.
97. Lindkvist B, Johansen D, Stocks T, et al. Metabolic risk factors for esophageal squamous cell carcinoma and adenocarcinoma: a prospective study of 580,000 subjects within the Me-Can project. *BMC Cancer.* 2014;14:103.
98. Engel LS, Chow WH, Vaughan TL, et al. Population attributable risks of esophageal and gastric cancers. *J Natl Cancer Inst.* 2003;95:1404-1413.
99. Bytzer P, Christensen PB, Damkier P, et al. Adenocarcinoma of the esophagus and Barrett's esophagus: a population-based study. *Am J Gastroenterol.* 1999;94:86-91.
100. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med.* 1999;340:825-831.
101. Zhai R, Chen F, Liu G, et al. Interactions among genetic variants in apoptosis pathway genes, reflux symptoms, body mass index, and smoking indicate two distinct etiologic patterns of esophageal adenocarcinoma. *J Clin Oncol.* 2010;28:2445-2451.
102. Cook MB, Wild CP, Forman D. A systematic review and meta-analysis of the sex ratio for Barrett's esophagus, erosive reflux disease, and nonerosive reflux disease. *Am J Epidemiol.* 2005;162:1050-1061.
103. Brown LM, Devesa SS, Chow WH. Incidence of adenocarcinoma of the esophagus among white Americans by sex, stage, and age. *J Natl Cancer Inst.* 2008;100:1184-1187.
104. Downey RJ, Akhurst T, Ilson D, et al. Whole body 18FDG-PET and the response of esophageal cancer to induction therapy: results of a prospective trial. *J Clin Oncol.* 2003;21:428-432.
105. Kato H, Nakajima M, Sohda M, et al. The clinical application of 18F-fluorodeoxyglucose positron emission tomography to predict survival in patients with operable esophageal cancer. *Cancer.* 2009;115:3196-3203.
106. Skinner HD, McCurdy MR, Echeverria AE, et al. Metformin use and improved response to therapy in esophageal adenocarcinoma. *Acta Oncologica*. 2013;52:1002-1009.
107. Suzuki A, Xiao L, Taketa T, et al. Results of the baseline positron emission tomography can customize therapy of localized esophageal adenocarcinoma patients who achieve a clinical complete response after chemoradiation. *Ann Oncol.* 2013;24:2854-2859.
108. Nakamoto Y, Osman M, Wahl RL. Prevalence and patterns of bone metastases detected with positron emission tomography using F-18 FDG. *Clin Nucl Med*. 2003;28:302-307.
109. Kato H, Kuwano H, Nakajima M, et al. Comparison between positron emission tomography and computed tomography in the use of the assessment of esophageal carcinoma. *Cancer.* 2002;94:921-928.

110. Swisher SG, Maish M, Erasmus JJ, et al. Utility of PET, CT, and EUS to identify pathologic responders in esophageal cancer. *Ann Thorac Surg.* 2004;78:1152-1160; discussion 1152-1160.
111. zum Büschenfelde CM, Herrmann K, Schuster T, et al. (18) F-FDG PET-guided salvage neoadjuvant radiochemotherapy of adenocarcinoma of the esophagogastric junction: the MUNICON II trial. *J Nucl Med.* 2011;52:1189-1196.
112. Prasad GA, Wu TT, Wigle DA, et al. Endoscopic and surgical treatment of mucosal (T1a) esophageal adenocarcinoma in Barrett's esophagus. *Gastroenterology.* 2009;137:815-823.
113. Ciocirlan M, Lapalus MG, Hervieu V, et al. Endoscopic mucosal resection for squamous premalignant and early malignant lesions of the esophagus. *Endoscopy.* 2007;39:24-29.
114. Soetikno RM, Gotoda T, Nakanishi Y, Soehendra N. Endoscopic mucosal resection. *Gastrointest Endosc.* 2003;57:567-579.
115. Shapiro J, van Lanschot JJB, Hulshof M, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *Lancet Oncol.* 2015;16:1090-1098.
116. Siersema PD, van Hillegersberg R. Treatment of locally advanced esophageal cancer with surgery and chemoradiation. *Curr Opin Gastroenterol.* 2008;24:535-540.
117. Hirst J, Smithers BM, Gotley DC, et al. Defining cure for esophageal cancer: analysis of actual 5-year survivors following esophagectomy. *Ann Surg Oncol.* 2011;18:1766-1774.
118. Hofstetter W, Swisher SG, Correa AM, et al. Treatment outcomes of resected esophageal cancer. *Ann Surg.* 2002;236:376-384; discussion 384-375.
119. Rudiger Siewert J, Feith M, Werner M, Stein HJ. Adenocarcinoma of the esophagogastric junction: results of surgical therapy based on anatomical/topographic classification in 1,002 consecutive patients. *Ann Surg.* 2000;232:353-361.
120. Parker EF, Reed CE, Marks RD, et al. Chemotherapy, radiation therapy, and resection for carcinoma of the esophagus. Long-term results. *J Thorac Cardiovasc Surg.* 1989;98:1037-1042; discussion 1042-1034.
121. Kelsen DP, Ginsberg R, Pajak TF, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. *N Engl J Med.* 1998;339:1979-1984.
122. Allum WH, Stenning SP, Bancewicz J, et al. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. *J Clin Oncol.* 2009;27:5062-5067.
123. Kelsen DP, Winter KA, Gunderson LL, et al. Long-term results of RTOG trial 8911 (USA Intergroup 113): a random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer. *J Clin Oncol.* 2007;25:3719-3725.
124. Wagner AD, Grabsch HI, Mauer M, et al. EORTC-1203-GITCG - the "INNOVATION"-trial: Effect of chemotherapy alone versus chemotherapy plus trastuzumab, versus chemotherapy plus trastuzumab plus pertuzumab, in the perioperative treatment of HER2 positive, gastric and gastroesophageal junction adenocarcinoma on pathologic response rate: a randomized phase II-intergroup trial of the EORTC-Gastrointestinal Tract Cancer Group, Korean Cancer Study Group and Dutch Upper GI-Cancer group. *BMC Cancer.* 2019;19:494.
125. Lorenzen S, Pauligk C, Homann N, et al. Feasibility of perioperative chemotherapy with infusional 5-FU, leucovorin, and oxaliplatin with (FLOT) or without (FLO) docetaxel in elderly patients with locally advanced esophagogastric cancer. *Br J Cancer.* 2013;108:519-526.
126. Al-Batran S-E, Homann N, Schmalenberg H, et al. Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO): A multicenter, randomized phase 3 trial. *J Clin Oncol.* 2017;35:4004.
127. Ando N, Kato H, Igaki H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). *Ann Surg Oncol.* 2012;19:68-74.
128. Alderson D, Cunningham D, Nankivell M, et al. Neoadjuvant cisplatin and fluorouracil versus epirubicin, cisplatin, and capecitabine followed by resection in patients with oesophageal adenocarcinoma (UK MRC OE05): an open-label, randomised phase 3 trial. *Lancet Oncol.* 2017;18:1249-1260.
129. Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. *J Clin Oncol.* 2008;26:1086-1092.
130. Stahl M, Walz MK, Stuschke M, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. *J Clin Oncol.* 2009;27:851-856.
131. Ando N, Iizuka T, Ide H, et al. Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus: a Japan Clinical Oncology Group Study—JCOG9204. *J Clin Oncol.* 2003;21:4592-4596.
132. Gignoux M, Roussel A, Paillot B, et al. The value of preoperative radiotherapy in esophageal cancer: results of a study by the EORTC. *Recent Results Cancer Res.* 1988;110:1-13.
133. Arnott SJ, Duncan W, Gignoux M, et al. Preoperative radiotherapy for esophageal carcinoma. *Cochrane Database Syst Rev.* 2005;CD001799.
134. Gebski V, Burmeister B, Smithers BM, et al. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. *Lancet Oncol.* 2007;8:226-234.
135. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med.* 2012;366:2074-2084.
136. Oppedijk V, van der Gaast A, van Lanschot JJ, et al. Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. *J Clin Oncol.* 2014;32:385-391.
137. Safran H, Winter KA, Wigle DA, et al. Trastuzumab with trimodality treatment for esophageal adenocarcinoma with HER2 overexpression: NRG Oncology/RTOG 1010. *J Clin Oncol.* 2020;38:4500-4500.
138. Urschel JD, Vasan H. A meta-analysis of randomized controlled trials that compared neoadjuvant chemoradiation and surgery to surgery alone for resectable esophageal cancer. *Am J Surg.* 2003;185:538-543.
139. Malthaner RA, Wong RK, Rumble RB, Zuraw L. Neoadjuvant or adjuvant therapy for resectable esophageal cancer: a clinical practice guideline. *BMC Cancer.* 2004;4:67.
140. Stahl M, Mariette C, Haustermans K, et al. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2013;24(suppl 6):vi51-vi56.
141. Pouliquen X, Levard H, Hay JM, et al. 5-Fluorouracil and cisplatin therapy after palliative surgical resection of squamous cell carcinoma of the esophagus. A multicenter randomized trial. French Associations for Surgical Research. *Ann Surg.* 1996;223:127-133.
142. Heroor A, Fujita H, Sueyoshi S, et al. Adjuvant chemotherapy after radical resection of squamous cell carcinoma in the thoracic esophagus: who benefits? A retrospective study. *Dig Surg.* 2003;20:229-235; discussion 236-227.
143. Teniere P, Hay JM, Fingerhut A, Fagniez PL. Postoperative radiation therapy does not increase survival after curative resection for squamous cell carcinoma of the middle and lower

esophagus as shown by a multicenter controlled trial. French University Association for Surgical Research. *Surg Gynecol Obstet*. 1991;173:123-130.
144. Xiao ZF, Yang ZY, Liang J, et al. Value of radiotherapy after radical surgery for esophageal carcinoma: a report of 495 patients. *Ann Thorac Surg.* 2003;75:331-336.
145. Fok M, Sham JS, Choy D, et al. Postoperative radiotherapy for carcinoma of the esophagus: a prospective, randomized controlled study. *Surgery*. 1993;113:138-147.
146. Kelly RJ, Lockhart AC, Jonker DJ, et al. CheckMate 577: a randomized, double-blind, phase 3 study of nivolumab (Nivo) or placebo in patients (Pts) with resected lower esophageal (E) or gastroesophageal junction (GEJ) cancer. *J Clin Oncol.* 2017;35:TPS212.
147. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *JAMA.* 1999;281:1623-1627.
148. Coia LR, Minsky BD, Berkey BA, et al. Outcome of patients receiving radiation for cancer of the esophagus: results of the 1992-1994 Patterns of Care Study. *J Clin Oncol.* 2000;18:455-462.
149. Minsky BD, Pajak TF, Ginsberg RJ, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. *J Clin Oncol.* 2002;20:1167-1174.
150. Bedenne L, Michel P, Bouche O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. *J Clin Oncol.* 2007;25:1160-1168.
151. Chiu PW, Chan AC, Leung SF, et al. Multicenter prospective randomized trial comparing standard esophagectomy with chemoradiotherapy for treatment of squamous esophageal cancer: early results from the Chinese University Research Group for Esophageal Cancer (CURE). *J Gastrointest Surg.* 2005;9:794-802.
152. Stahl M. Is there any role for surgery in the multidisciplinary treatment of esophageal cancer? *Ann Oncol.* 2010;21(suppl 7):vii283-vii285.
153. Wagner AD, Grothe W, Haerting J, et al. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. *J Clin Oncol.* 2006;24:2903-2909.
154. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol.* 2006;24:4991-4997.
155. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med.* 2008;358:36-46.
156. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet.* 2010;376:687-697.
157. Koizumi W, Narahara H, Hara T, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol.* 2008;9:215-221.
158. Food and Drug Administration; Office of Medical Products and Tobacco. FDA approves breast cancer treatment that can be administered at home by health care profressional. Accessed April 18, 2021. https://www.fda.gov/news-events/press-announcements/fda-approves-breast-cancer-treatment-can-be-administered-home-health-care-professional
159. Ohtsu A, Shah MA, Van Cutsem E, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. *J Clin Oncol.* 2011;29:3968-3976.
160. Van Cutsem E, de Haas S, Kang YK, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a biomarker evaluation from the AVAGAST randomized phase III trial. *J Clin Oncol.* 2012;30:2119-2127.
161. Shen L, Li J, Xu J, et al. Bevacizumab plus capecitabine and cisplatin in Chinese patients with inoperable locally advanced or metastatic gastric or gastroesophageal junction cancer: randomized, double-blind, phase III study (AVATAR study). *Gastric Cancer.* 2015;18:168-176.
162. Lordick F, Kang YK, Chung HC, et al. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. *Lancet Oncol.* 2013;14:490-499.
163. Waddell T, Chau I, Cunningham D, et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. *Lancet Oncol.* 2013;14:481-489.
164. Okines AF, Gonzalez de Castro D, Cunningham D, et al. Biomarker analysis in oesophagogastric cancer: Results from the REAL3 and TransMAGIC trials. *Eur J Cancer.* 2013;49:2116-2125.
165. Janjigian YY, Maron SB, Chou JF, et al. First-line pembrolizumab (P), trastuzumab (T), capecitabine (C) and oxaliplatin (O) in HER2-positive metastatic esophagogastric adenocarcinoma. *J Clin Oncol.* 2019;37:4011-4011.
166. Tabernero J, Hoff PM, Shen L, et al. Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): final analysis of a double-blind, randomised, placebo-controlled phase 3 study. *Lancet Oncol.* 2018;19:1372-1384.
167. Tabernero J, Cutsem EV, Bang Y-J, et al. Pembrolizumab with or without chemotherapy versus chemotherapy for advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma: The phase III KEYNOTE-062 study. *J Clin Oncol.* 2019;37:LBA4007-LBA4007.
168. Moehler MH, Dvorkin M, Özgüroğlu M, et al. Results of the JAVELIN Gastric 100 phase 3 trial: avelumab maintenance following first-line (1L) chemotherapy (CTx) vs continuation of CTx for HER2– advanced gastric or gastroesophageal junction cancer (GC/GEJC). *J Clin Oncol.* 2020;38:278-278.
169. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet.* 2014;383:31-39.
170. Thuss-Patience PC, Kretzschmar A, Bichev D, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer—a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Eur J Cancer.* 2011;47:2306-2314.
171. Cook N, Marshall A, Blazeby JM, et al. Cougar-02: a randomized phase III study of docetaxel versus active symptom control in patients with relapsed esophago-gastric adenocarcinoma. *ASCO Meeting Abstracts*. 2013;31:4023.
172. Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol.* 2014;15:1224-1235.
173. Kang JH, Lee SI, Lim DH, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. *J Clin Oncol.* 2012;30:1513-1518.
174. Ohtsu A, Ajani JA, Bai YX, et al. Everolimus for previously treated advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 study. *J Clin Oncol.* 2013;31:3935-3943.

175. Satoh T, Xu RH, Chung HC, et al. Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN—a randomized, phase III study. *J Clin Oncol.* 2014;32:2039-2049.
176. Thuss-Patience PC, Shah MA, Ohtsu A, et al. Trastuzumab emtansine versus taxane use for previously treated HER2-positive locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma (GATSBY): an international randomised, open-label, adaptive, phase 2/3 study. *Lancet Oncol.* 2017;18:640-653.
177. Dutton SJ, Ferry DR, Blazeby JM, et al. Gefitinib for oesophageal cancer progressing after chemotherapy (COG): a phase 3, multicentre, double-blind, placebo-controlled randomised trial. *Lancet Oncol.* 2014;15:894-904.
178. Lennerz JK, Kwak EL, Ackerman A, et al. MET amplification identifies a small and aggressive subgroup of esophagogastric adenocarcinoma with evidence of responsiveness to crizotinib. *J Clin Oncol.* 2011;29:4803-4810.
179. Iveson T, Donehower RC, Davidenko I, et al. Rilotumumab in combination with epirubicin, cisplatin, and capecitabine as first-line treatment for gastric or oesophagogastric junction adenocarcinoma: an open-label, dose de-escalation phase 1b study and a double-blind, randomised phase 2 study. *Lancet Oncol.* 2014;15:1007-1018.
180. Catenacci DVT, Tebbutt NC, Davidenko I, et al. Rilotumumab plus epirubicin, cisplatin, and capecitabine as first-line therapy in advanced MET-positive gastric or gastro-oesophageal junction cancer (RILOMET-1): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2017;18:1467-1482.
181. Shah MA, Bang YJ, Lordick F, et al. Effect of fluorouracil, leucovorin, and oxaliplatin with or without onartuzumab in HER2-negative, MET-positive gastroesophageal adenocarcinoma: the METGastric randomized clinical trial. *JAMA Oncol.* 2017;3:620-627.
182. Bang Y-J, S-AI, Lee K-W, et al. Olaparib plus paclitaxel in patients with recurrent or metastatic gastric cancer: a randomized, double-blind phase II study. 2013 ASCO Annual Meeting. *J Clin Oncol.* 2013;31(suppl):abstract 4013.
183. Bang YJ, Xu RH, Chin K, et al. Olaparib in combination with paclitaxel in patients with advanced gastric cancer who have progressed following first-line therapy (GOLD): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2017;18:1637-1651.
184. Shitara K, Özgüroğlu M, Bang YJ, et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. *Lancet.* 2018;392:123-133.
185. Kojima T, Muro K, Francois E, et al. Pembrolizumab versus chemotherapy as second-line therapy for advanced esophageal cancer: phase III KEYNOTE-181 study. *J Clin Oncol.* 2019;37:2-2.
186. Kato K, Cho BC, Takahashi M, et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* 2019;20:1506-1517.
187. US Food and Drug Administration. OPDIVO (nivolumab), Bristol-Myers Squibb Co.
188. Li J, Qin S, Xu J, et al. Apatinib for chemotherapy-refractory advanced metastatic gastric cancer: results from a randomized, placebo-controlled, parallel-arm, phase II trial. *J Clin Oncol.* 2013;31:3219-3225.
189. Qin S. Phase III study of apatinib in advanced gastric cancer: a randomized, double-blind, placebo-controlled trial. *J Clin Oncol*. 2014;32(suppl 15):4003.
190. Fuchs CS, Doi T, Jang RW, et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 Trial. *JAMA Oncol*. 2018;4:e180013-e180013.
191. Chen L-T, Satoh T, Ryu M-H, et al. A phase 3 study of nivolumab in previously treated advanced gastric or gastroesophageal junction cancer (ATTRACTION-2): 2-year update data. *Gastric Cancer.* 2020;23:510-519.
192. Shitara K, Doi T, Dvorkin M, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2018;19:1437-1448.
193. Ajani JA, Rodriguez W, Bodoky G, et al. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. *J Clin Oncol*. 2010;28:1547-1553.
194. Higuchi K, Tanabe S, Shimada K, et al. Biweekly irinotecan plus cisplatin versus irinotecan alone as second-line treatment for advanced gastric cancer: a randomised phase III trial (TCOG GI-0801/BIRIP trial). *Eur J Cancer*. 2014;50:1437-1445.
195. Hecht JR, Bang Y-J, Qin SK, et al. Lapatinib in combination with capecitabine plus oxaliplatin (CapeOx) in HER2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma (AC): the TRIO-013/LOGiC Trial. J Clin Oncol. 2013;31(suppl 18).
196. Kang YK, Boku N, Satoh T, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2017;390:2461-2471.
197. Penniment MG. Full report of the TROG 03.01, NCIC CTG ES2 multinational phase III study in advanced esophageal cancer comparing palliation of dysphagia and quality of life in patients treated with radiotherapy or chemoradiotherapy. *J Clin Oncol*. 2015;33(suppl 3):6.

28 Pancreatic Cancer

Jonathan D. Mizrahi
Anirban Maitra
Robert A. Wolff

KEY CONCEPTS

- Pancreatic cancer has a five-year survival of 10%, and it is expected to become the second leading cause of cancer death in the United States by 2030.
- Modifiable risk factors for pancreatic cancer include tobacco use, obesity, diabetes mellitus (particularly new-onset diabetes), and chronic pancreatitis. Age and family history are well-established, nonmodifiable risk factors.
- *KRAS* mutations and *p16* inactivation are near universal genomic events identified in pancreatic cancers, and histologically, pancreatic adenocarcinomas are characterized by a dense, collagenous stroma.
- High-quality multidetector computed tomography imaging is the gold-standard diagnostic and staging modality, because it can classify pancreatic cancers as resectable, borderline resectable, locally advanced, or metastatic.
- The only potentially curative treatment for pancreatic cancer is surgical resection, which is an option for only 15% to 20% of patients, because most patients are diagnosed at an advanced stage.
- Recent advances in combination chemotherapy, particularly FOLFIRINOX and gemcitabine plus nab-paclitaxel, have increased survival for patients with advanced pancreatic cancer; FOLFIRINOX also improves survival in the adjuvant setting.
- Precision medicine is slowly emerging in pancreatic cancer

When clinicians use the term *pancreatic cancer*, they refer to adenocarcinoma of the pancreas, one of the most challenging malignancies facing oncologists, patients, and caregivers today. This disease is characterized by significant morbidity and a poor prognosis. At the MDACC, we manage pancreatic cancer using a multidisciplinary approach. For patients with localized disease, we generally employ a stepwise multimodality approach. For most patients with locally advanced disease and all patients with metastatic disease, palliation is a high priority. This chapter summarizes our current knowledge about pancreatic cancer, including its epidemiology, risk factors, molecular biology, diagnosis and staging, and clinical strategies for therapy.

HARD FACTS ABOUT PANCREATIC CANCER

Pancreatic adenocarcinoma, the most common pancreatic neoplasm, is an aggressive and often rapidly fatal malignancy. In the United States, it represents 3% of all cancer cases but accounts for 7.5% of all cancer deaths.[1] As of this writing, it is the third leading cause of cancer-related deaths, ranking behind lung and colorectal cancers. The 5-year survival rate has marginally improved over the past few decades (2% in 1974–1976, 6% in 2014) and has recently reached 10% for the first time.[2,3] Over the next decade, deaths caused by pancreatic cancer are projected to increase dramatically, overtaking colorectal cancer as the second leading cause of cancer-related death.

EPIDEMIOLOGY

There are approximately 56,000 new cases of pancreatic cancer each year in the United States and 459,000 cases worldwide.[4] Incidence rates are highest in industrialized societies and Western countries. Of note, the risk of pancreatic cancer among Blacks, in whom pancreatic cancer mortality rates are higher

than most other ethnic groups in the United States, is considerably higher than the rates for African Blacks.[5] The risk of developing pancreatic cancer is low in the first three to four decades of life but increases sharply after the age of 50 years. The average age at the time of diagnosis is 72 years; it is uncommon in persons younger than 40 years. However, there has been an increasing interest in early-onset pancreatic cancer (usually defined as age of onset before 50 years). Our group has recently reported that patients with early-onset pancreatic cancer are more apt to have germline mutations in DNA damage repair pathway genes compared with patients considered to have later onset.[6]

RISK FACTORS FOR PANCREATIC CANCER

Both genetic and environmental factors have been implicated in the risk of pancreatic cancer development. Table 28–1 summarizes these risk factors.

Tobacco

Cigarette smoking is one of the better-established lifestyle risk factors for pancreatic cancer, albeit the odds ratio is lower than that of lung cancer. Overall, cigarette smoking is estimated to account for roughly 25% to 30% of pancreatic cancer cases.[7]

Diabetes Mellitus

Diabetes has been implicated both as an early manifestation of pancreatic cancer and as a predisposing factor. As many as half of pancreatic cancer patients report a history of new-onset diabetes (NOD) or worsening hyperglycemia, and an additional one quarter report impaired glucose tolerance.[8] In these cases, the occult pancreatic cancer is responsible for inducing hyperglycemia, likely through altering peripheral insulin resistance. Changes in glycemic control can occur as early as 36 months before clinical diagnosis, providing an opportunity for earlier detection. However, because only around 1% of NOD is caused by an underlying pancreatic cancer, further enrichment of this high-risk population is needed to conduct meaningful surveillance. Our team is currently leading a multicenter prospective NOD cohort that will accrue 10,000 patients with NOD or hyperglycemia and follow them for the development of incidental pancreatic cancer. Longitudinal collection of biospecimens for biomarker studies aims to better define and enrich this population for pancreatic cancer risk.[9]

Body Mass Index

Epidemiologic studies have also implicated a high body mass index as increasing the risk for pancreatic cancer.[10] Numerous molecular mechanisms—both local (inflammatory mediators produced by abdominal adipocytes within the peri-pancreatic milieu) and systemic (secreted adipokines and hyperinsulinemia)—are

Table 28–1 Acquired and Genetic Risks Factors Associated with Pancreatic Cancer

Acquired Risk Factors	Relative Risk	Comments
Tobacco smoking	2–5	Risk increases with increasing exposure
Diabetes mellitus	2	Not all authorities concur; many patients have altered glucose metabolism on presentation
High body mass index	2	
Chronic pancreatitis	13–18	Not all authorities concur with this degree of increased risk
Inherited Disorders	**Relative Risk**	**Known Defects**
Hereditary pancreatitis	10–53	PRSS1
FAMMM syndrome	22	p16INK/CDKN2
HNPCC	8	MLH1, MSH2, MSH6
Peutz-Jeghers syndrome	13–30	LBK1/STK11
Familial adenomatous polyposis	4–5	APC
Li-Fraumeni syndrome	?	p53
Familial breast and ovarian cancer	3–5	DNA repair pathways, BRCA2

FAMMM, familial atypical mole and melanoma; HNPCC, hereditary nonpolyposis colon cancer.

postulated to contribute toward the increased risk of pancreatic cancer in obesity.[11,12] For example, studies in preclinical models from MDACC have shown the influence of obesity-associated lipocalin-2 levels in accelerating pancreatic carcinogenesis.[13]

Diet

Positive associations have been discovered between pancreatic cancer and meat and carbohydrate intake.[14] However, there is no consensus on the contribution of dietary fat. Epidemiologic studies of pancreatic cancer have shown a protective role for high fruit and vegetable intake.

Chronic Pancreatitis

Early clinical studies have suggested an association between chronic pancreatitis and pancreatic cancer. Studies have suggested that hereditary pancreatitis, in particular, may affect the risk. Mutations of several genes can be associated with hereditary pancreatitis, of which *PRSS1*, encoding for cationic trypsinogen, is the most common.[15]

Familial Pancreatic Cancer and Other Genetic Syndromes

Approximately 10% of patients with pancreatic cancer harbor a germline mutation that predisposes them to pancreatic cancer.[16,17] Notably, only about half of these patients report a family history of pancreatic cancer, and therefore, the National Comprehensive Cancer Network (NCCN) and the American Society for Clinical Oncology (ASCO) both recommend universal germline testing for all patients.[18,19] Known cancer predisposition syndromes that are associated with increased risk of pancreatic cancer include hereditary nonpolyposis colorectal cancer, ataxia-telangiectasia, Peutz-Jeghers syndrome, familial breast and ovarian cancer, and familial atypical multiple-mole melanoma. The most common class of genes associated with familial predisposition to pancreatic cancer are those whose protein products are involved in the cellular DNA repair response, including *BRCA2*, *BRCA1*, *ATM*, and *PALB2*. Of these, BRCA1/2 and PALB2 proteins are key components of homologous recombination through the repair of DNA double-strand breaks. The poly(ADP-ribose) polymerase (PARP) enzyme is integral for single-stranded DNA repair, and inhibition results in DNA breaks that require intact BRCA proteins for repair. Therefore, in the presence of mutant BRCA1/2 or PALB2 proteins, PARP inhibition results in synthetic lethality. As we discuss later, the PARP inhibitor, olaparib, became the first biomarker-based therapy approved for pancreatic cancer based on its clinical benefit in the maintenance setting in germline *BRCA*–mutated patients with disease control on initial platinum-based chemotherapy.[20,21]

MOLECULAR EVENTS IN HUMAN PANCREATIC CARCINOGENESIS

With the advent of next-generation sequencing platforms, several publicly funded initiatives such as the International Cancer Genome Consortium and The Cancer Genome Atlas have comprehensively mapped the genomic landscape of pancreatic cancer across hundreds of tumors.[22–24] These large-scale efforts have not only identified the major recurrent alterations in pancreatic cancer, but also less frequently altered mutations, many of which are "actionable."[25] As much as one quarter of patient tumors may harbor potentially actionable mutations and this information can be returned to the oncologist in a feasible timeframe.[26,27]

Oncogenes in Pancreatic Cancer

Oncogenic mutations of *KRAS* are the defining genetic feature of pancreatic cancer, occurring in about 90% of cases.[24] *KRAS* mutations most commonly involve codon 12 and are usually either a glutamine-to-valine ($KRAS^{G12V}$) or glutamine-to-aspartic-acid ($KRAS^{G12D}$) alteration. The uncommon $KRAS^{G12C}$ mutations are observed in only about 1.5% of pancreatic cancer.[28]

Of note, around 10% of cases are wild-type KRAS. In these cases, it is not uncommon to find alternative drivers, including *NRG1*, *ALK*, or *NTRK* fusions that drive cancer progression,[29] and for which targeted agents are readily available.[30–32] Therefore, the absence of a demonstrable *KRAS* mutation in confirmed pancreatic adenocarcinoma should prompt interrogation for these alternative drivers.[33,34]

Tumor Suppressor Genes in Pancreatic Cancer

The most common recurrently altered tumor suppressor genes in pancreatic cancer are *TP53*, *CDKN2A/p16*, and *DPC4/SMAD4*.[24] *TP53* is the most commonly mutated gene in human cancer, and somatic alterations are present in about 75% of pancreatic cancers. Nearly all pancreatic cancers harbor anomalies of the cyclin-dependent kinase inhibitor gene *CDKN2A/p16*. DPC4/SMAD4 alterations are observed in approximately 55% of pancreatic cancers. In solid tumors, *DPC4/SMAD4* aberrations are somewhat specific for advanced pancreatic cancer.[35]

Potentially Actionable Gene Mutations in Pancreatic Cancer

As of this writing, the most clinically relevant are genes encoding for proteins involved in DNA damage response and repair, including *BRCA2*, *BRCA1*, *PALB2*, *CHEK2*, *ATM*, *RAD51*, among others.[22,24] Although germline mutations of these genes occur in the context of familial pancreatic cancer, approximately 15% of cases harbor somatic loss of function mutations and such cases could be targets for DNA repair targeted therapies, such as PARP inhibitors. Approximately 1% of pancreatic cancer cases harbor mutations in genes involved in a particular class of DNA repair known as mismatch repair, including *MLH1*, *MSH2*, *PMS2*, and *MSH6*, and the corresponding tumors have an exceptionally high tumor mutation burden (so-called "hypermutators").[36] Hypermutator tumors are susceptible to immune checkpoint inhibitor immunotherapy and can be offered this in the first or second line based on recent FDA directives.[37] Finally, one needs to mention the class of genes that encode for protein involved in chromatin regulation (such as *ARID1A*, *PBRM1*, *KDM6A*, *MLL3*, among others) that are cumulatively mutated in 15% to 25% of cases.[38,39] In other solid tumors, there are emerging data to suggest the potential for using immunotherapy combinations against these tumors.[40,41]

Transcriptomic Subtypes of Pancreatic Cancer

Currently, the most widely accepted classification scheme assigns pancreatic cancers into so-called "classical" and "basal-like" subtypes.[24,42] The "classical" phenotype is characterized by the expression of the endodermal transcription factors GATA6 and HNF4A, both of which are absent in the "basal-like" tumors.[43,44] In contrast, basal-like, sometimes called "squamous subtype," is characterized by an aggressive natural history, and emerging data suggest that the basal-like tumors are resistant to FOLFIRINOX.[45]

Pancreatic Cancer Stroma

No discussion of the molecular pathology of pancreatic cancer is complete without alluding to the stroma and immune cell types that comprise the complex tumor microenvironment (TME) in this disease. A credible review of the pancreatic cancer TME is beyond the scope of this chapter, and the reader is pointed to several recent reviews on this topic.[46–48] A few highlights are emphasized. First, the pancreatic cancer stroma is comprised of a multitude of cell types and extracellular matrix proteins.[46] Second, the most common nonimmune cell type is the cancer-associated fibroblast (CAF), and recent single-cell RNA sequencing studies have identified at least three distinct types of CAFs,[49,50] with potentially distinct tumor-promoting versus tumor-suppressive roles. This is important because generic strategies to target the pancreatic cancer CAFs (eg, using small-molecule inhibitors targeting the Hedgehog pathway) have been counterproductive,[51] underscoring the distinct roles played by various CAF populations in constraining or promoting the neoplastic process. Third, the pancreatic cancer TME is characterized by high interstitial pressure, which has been ascribed to the deposition of extracellular matrix proteins like hyaluronic acid and other glycosaminoglycans,[52] and is implicated in reducing the delivery of systemic chemotherapy to the tumor milieu. Although preclinical studies supported the efficacy of reducing interstitial pressure by targeting hyaluronic acid with a pegylated hyaluronidase and facilitating the influx of therapeutic agents,[53,54] the phase 3 clinical trial of this agent (PEG-PH20), in combination with cytotoxic chemotherapy, failed to improve survival in metastatic disease, again reinforcing the complexities of stromal biology in pancreatic cancer.

PATHOLOGY

Pancreatic acinar cells account for approximately 80% of the cell number and volume of the gland; islet cells account for 1% to 2%. The ductal system is composed of single-layer, cuboidal epithelial cells representing 10% to 15% of the gland's structure, with a sparse interlacing network of blood vessels, lymphatics, nerves, and collagenous stroma. In carcinoma, this architecture is markedly altered. The predominant histologic feature is a desmoplastic (fibrous) stroma with atrophic acini, usually preserved islet cell clusters, and a haphazard growth of cancerous ducts (Fig. 28–1). The diagnosis of ductal adenocarcinoma rests on the identification of mitoses; nuclear and cellular pleomorphism; and evidence of perineural, vascular, or lymphatic invasion.[55] Intraductal precursor lesions in the surrounding pancreatic parenchyma are common with two major subtypes. The first and most common (~90% of cancers arise from these precursors) are the microscopic pancreatic intraepithelial neoplasia or PanIN lesions. Histologically, PanIN lesions are graded as "low" and "high" grades. High-grade PanINs often harbor many of the genetic alterations found in frank carcinomas.[56] The macroscopic precursors of ductal adenocarcinomas are mucinous cysts of the pancreas, presenting either as intraductal papillary mucinous neoplasms or mucinous cystic neoplasms.[57] Analogous to PanINs, the cystic lesions also demonstrate low- and high-grade epithelial dysplasia, culminating in invasive neoplasia.



FIGURE 28–1 **Photomicrograph of ductal adenocarcinoma of the pancreas with well-preserved islet cells and pancreatic architecture above and infiltrating tumor with poorly formed glandular structures below.**

Almost all malignant neoplasms of pancreatic origin (95%) arise from the exocrine portion of the gland, with ductal adenocarcinomas being the most common.[58] Pancreatic neuroendocrine tumors arising from the islets of Langerhans are much more infrequent, and primary nonepithelial tumors (eg, lymphomas or sarcomas) are extremely rare. The histologic classification of exocrine pancreatic neoplasms is presented in Table 28–2.

CLINICAL PRESENTATION

The clinical presentation of pancreatic cancer is primarily dependent on the location of the tumor within the pancreas. The majority (85%) develop within the pancreatic head. About 10% are located in the pancreatic body, and 5% are located in the tail. Nonspecific, poorly localized, epigastric or back pain is the most common initial presentation. It is usually caused by invasion or compression of the celiac, splanchnic, or mesenteric plexi. Tumors in the head or neck typically cause pain in the epigastric area or in the right upper quadrant of the abdomen. Cancers of the body may cause unremitting, severe back pain, and tumors in the pancreatic tail may be associated with left upper quadrant pain.

Painless jaundice, another common presentation, is generally associated with tumors in the pancreatic head or uncinate process. When the tumor does not arise in proximity to the intrapancreatic portion of the bile duct, diagnosis may be delayed and characterized by abdominal pain or back pain without jaundice.

Acute pancreatitis, although uncommon, can be caused by a ductal adenocarcinoma in patients with no other reason for acute pancreatitis (lack of gallstones, no history of alcohol or precipitating drugs).[59] Symptoms of chronic pancreatitis are relatively common, including diarrhea, bloating or constipation, abdominal distention, and weight loss. Patients with tail lesions often remain asymptomatic until the development of signs or symptoms of metastatic disease.

Table 28–2 Histologic Classification of Primary Exocrine Pancreatic Tumors

Malignant
Ductal adenocarcinoma
Mucinous cystadenocarcinoma
Acinar carcinoma
Unclassified large cell carcinoma
Small cell carcinoma
Pancreatoblastoma
Benign
Serous cystadenoma
Variable Malignant Potential
Intraductal papillary mucinous tumor
Mucinous cystadenoma
Papillary cystic neoplasm

DIAGNOSIS AND STAGING

Pancreatic cancer can be difficult to diagnose, particularly in patients with nonspecific complaints. Circuitous workups and interventions are not uncommon and may include upper endoscopy, which may be misleading and demonstrate mild esophagitis, gastritis, or duodenitis, with or without evidence of *Helicobacter pylori*. Patients complaining of right upper quadrant pain may undergo ultrasonography, potentially revealing gallstones, prompting cholecystectomy. For patients presenting with complaints of back pain, a musculoskeletal evaluation is commonly done. Most patients ultimately undergo cross-sectional body imaging with the discovery of a pancreatic mass.

For patients who present with obstructive jaundice, suspicion of pancreatic cancer is sufficiently high that the diagnostic workup usually proceeds in an orderly fashion with directed imaging studies. These usually include abdominal ultrasonography, computed tomography (CT) scan of the abdomen, or both.

Tissue Acquisition

With rare exception, all patients seen at MDACC are advised to undergo biopsy to confirm the presence of malignancy and type if it is not performed before referral. Cross-sectional imaging, (our preference is dual-phase multidetector CT), should always be performed before interventional endoscopic or other invasive procedures to prevent procedure-related inflammatory changes, which may confound assessment of the tumor's potential for resection. In patients who present with obstructive jaundice and radiographic evidence of a localized pancreatic mass, endoscopic retrograde cholangiopancreatography and endoscopic ultrasound (EUS) with biopsy are often performed concurrently. EUS-guided biopsies are preferred over percutaneous biopsies in patients who may be candidates for surgical resection to decrease the risk of peritoneal or needle-track seeding, which has been reported among patients undergoing transcutaneous ultrasound– or CT-directed biopsies.[60] Alternatively, when CT or magnetic resonance imaging clearly demonstrates an unresectable, locally advanced cancer, CT- or ultrasound-guided transcutaneous biopsy may substitute for EUS-guided aspiration. If a patient presents with obstructive jaundice and biliary stricture without radiographic evidence of a pancreatic mass, EUS examination is also advised. EUS can also be useful in the evaluation of regional lymph nodes and offers an opportunity for biopsy if the primary tumor is technically difficult to biopsy.

When there is clear radiographic evidence of metastatic disease and an obvious pancreatic mass, we prefer biopsy of a metastatic site, such as the liver. This confirms both the diagnosis and the presence of metastatic disease with one procedure. In addition, core-needle biopsies of metastatic sites can generally be obtained safely and provide sufficient tissue for molecular profiling. Just as the NCCN and ASCO recommend germline testing for patients with pancreatic cancer, the NCCN also encourages molecular and genomic profiling of tumor tissue whenever feasible.[61]

Misdiagnosis of Pancreatic Cancer

It is not uncommon for patients to be misdiagnosed with pancreatic cancer. The most common mistake we see is in the setting of bulky peripancreatic adenopathy mimicking a pancreatic mass. Adenocarcinomas of the pancreas do metastasize to regional lymph nodes, but these are typically small to medium sized. Bulky lymph nodes are more often seen in other pancreatic neoplasms such as acinar cell carcinomas or pancreatic neuroendocrine tumors. Tumors of the esophagus, stomach, duodenum, and sometimes the colon can lead to bulky peripancreatic lymph nodes. Lymphoma, non–small-cell lung cancer, and carcinomas of unknown primary origin may also lead to bulky peripancreatic lymphadenopathy and be mistaken for a primary pancreatic neoplasm. Thin-cut, contrast-enhanced dynamic-phase CT will usually rule out the presence of a primary mass in the pancreas in this setting. Another helpful radiographic finding may be the presence or absence of atrophy of the pancreatic body and tail. Although commonly seen with adenocarcinomas, this finding is usually absent in the setting of neuroendocrine and acinar cell tumors.

High-Quality Computed Tomography

At MDACC, the single most important imaging modality is dynamic-phase CT. This technique is used to objectively define (anatomically) potentially resectable disease and allows for imaging of the pancreas and surrounding vascular structures in arterial and venous phases of intravenous contrast. For optimal pretreatment staging, a CT report in a patient with suspected pancreatic cancer should include the following:

1. The presence or absence of a primary tumor in the pancreas or periampullary region
2. The presence or absence of peritoneal and hepatic metastases
3. Description of the patency of the superior mesenteric vein (SMV) and portal vein (PV) and the relationship of these veins to the tumor
4. Description of the relationship of the tumor to the superior mesenteric artery (SMA), celiac axis, and hepatic artery

Objective radiographic criteria can be used to define a potentially resectable primary tumor of the pancreatic head or uncinate process (Fig. 28–2). The MDACC criteria include: (1) no extrapancreatic disease; (2) a patent SMV and PV (assuming the technical ability to resect and reconstruct this venous confluence); and (3) a definable tissue plane between the tumor and regional arterial structures, including the celiac axis and SMA. A recent meta-analysis has estimated the positive predictive value for resectability based on contrast-enhanced CT imaging is 81%.[62] CT of the chest is now routinely part of our staging workup. Bone scans and brain imaging are rarely indicated and should not be part of routine staging.

Positron Emission Tomography

Positron emission tomographic (PET) scans are not a routine part of our staging. However, they are sometimes

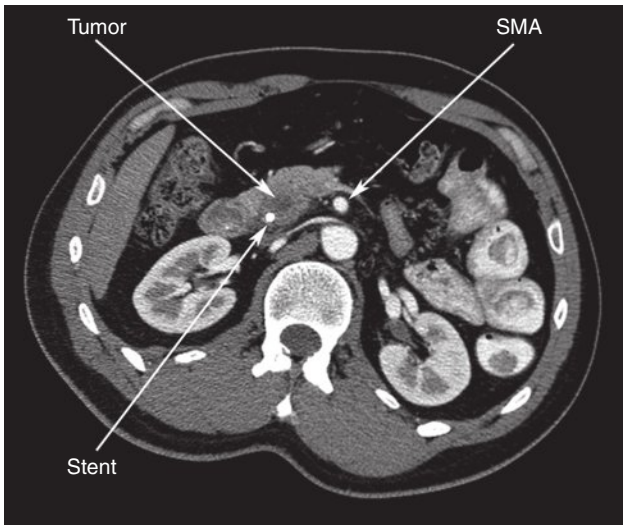


FIGURE 28–2 Computed tomographic image of tumor within the pancreatic head. Note the stent in the bile duct and the subtle low-density mass within the head. The superior mesenteric artery (SMA) has a fat plane completely surrounding it. This defines a potentially resectable tumor.

obtained in the setting of equivocal radiographic findings, such as indeterminate lesions in the liver or lungs. Note that small lesions (<1 cm) may be ^{18}F-fluorodeoxyglucose (FDG)-PET–negative, even when metastatic disease is present.[63] We also find ^{18}FDG-PET useful to evaluate for isolated local recurrence when a patient has undergone previous resection and subsequently exhibits a rising CA19-9 with soft tissue changes in the surgical bed indeterminate for fibrosis or recurrence.

Serum CA19-9 Determinations

CA19-9 measures the specific carbohydrate moiety of the mucin MUC-1.[64] This is the most commonly elevated tumor marker in pancreatic cancer, but it is not specific and may be elevated in other gastrointestinal tumors. Most retrospective analyses generally suggest that a high preoperative CA19-9 level (>500–1000 IU/mL) implies more advanced disease. Serial measurements of CA 19-9 during a course of neoadjuvant therapy is increasingly used to predict who among those with resectable or borderline resectable disease will derive the most benefit from surgical resection.[65,66] Conversely, in patients undergoing surgery as initial therapy, when postoperative CA19-9 levels do not normalize within 8 to 12 weeks postoperatively, early relapse with poor prognosis often ensues.[67] Decreasing CA19-9 levels of 50% or more during induction systemic chemotherapy has been correlated with improved survival.[68] A small subset of patients will have undetectable CA 19-9 levels based on lack of the enzyme fucosyltransferase needed to produce the CA 19-9 antigen, seen in patients who are Lewis antigen–negative (5%–7% of general population).[69]

The TNM System Versus Clinically Oriented Staging

The tumor, node, metastasis (TNM) staging system for pancreatic cancer is outlined in Table 28–3. For patients undergoing resection (who represent the small minority of patients with pancreatic cancer), the TNM system is somewhat useful in providing prognostic information.

TREATMENT STRATEGIES FOR PANCREATIC CANCER

At MDACC, patients are initially staged clinically as having potentially resectable, borderline resectable, locally advanced/unresectable, or metastatic disease (Fig. 28–3). For patients with potentially resectable disease and no contraindications to surgery based on frailty or comorbidities, surgery with curative intent should be pursued. As discussed later, we favor neoadjuvant therapy followed by surgery, over upfront surgery and adjuvant therapy. Patients with metastatic disease and adequate performance status (PS) usually receive systemic therapy. For patients presenting with locally advanced disease, treatment should be individualized and usually initially involves systemic therapy.

Resectable Pancreatic Cancer

It is widely known that surgery holds the only hope of cure for patients with pancreatic cancer. Most cases of resectable pancreatic cancers are comprised of small tumors located in the head of the pancreas. These are removed with a Whipple procedure,[70] more appropriately described as a pancreaticoduodenectomy.

There are two distinct approaches to the management of a patient with potentially resectable pancreatic cancer: (1) proceed with upfront surgery and, if possible, deliver adjuvant therapy for 6 months postoperatively; or (2) deliver neoadjuvant therapy and, if appropriate, proceed with surgical resection thereafter (Fig. 28–4).

Modern Adjuvant Therapy for Resected Pancreatic Cancer

Despite our preference for neoadjuvant therapy over upfront surgery and adjuvant therapy, the majority of patients with resectable pancreatic cancer undergo a surgery-first approach. For those who recover well and have no clinical evidence of early relapse, 6 months of systemic adjuvant therapy remains the standard of

Table 28–3 TNM Criteria for Pancreatic Adenocarcinoma TNM Definitions

No evidence of primary tumor	**T0**	Complete pathologic response to neoadjuvant therapy may result in T0 tumor
Tumor <2 cm in greatest dimension	**T1**	T1 tumors would generally be resectable based on high-quality imaging
Tumor >2 and <4 cm in greatest dimension	**T2**	T2 tumors may be resectable or borderline resectable (nonmetastatic)
Tumor >4 cm in greatest dimension	**T3**	T3 often with extrapancreatic extension and may be borderline resectable
Tumor involves the CA, HA, or SMA	**T4**	Encasement of these vessels define locally advanced disease; <180° = borderline resectable
No regional lymph node metastasis	**N0**	Negative lymph node involvement in 60% of cases after neoadjuvant therapy
Metastasis in one to three regional LNs	**N1**	Positive lymph node involvement occurs in 57% cases with upfront surgery
Metastases in four or more regional LNs	**N2**	Positive lymph node involvement occurs in 57% cases with upfront surgery
No distant metastasis	**M0**	
Distant metastasis	**M1**	Common metastatic sites would include the liver, lung, and peritoneum

Pathologic Staging Classification						
IA	**IB**	**IIA**	**IIB**	**III**	**III**	**IV**
T1	T2	T3	T1-T3	T1-T3	T4	Any T
N0	N0	N0	N1	N2	Any N	Any N
M0	M0	M0	M0	MO	M0	M1
More favorable prognosis: median survival 36 mo	More favorable prognosis: median survival 36 mo	More favorable prognosis: median survival 36 mo	Intermediate survival (median 18–24 mo	Intermediate survival (median 18–24 mo	Locally advanced disease expected survival 14–18 mo	Metastatic disease median survival 9–12 mo

Data from Edge SB, Byrd DR, Byrd DR, et al: AJCC Cancer Staging Manual, 8th ed. New York, NY: Springer; 2017.
LN, lymph node.

care. Since the last edition of this text, results using adjuvant therapy for pancreatic cancer have improved. However, as discussed further below, not all of the improvement in survival observed over time is completely attributable to the improvement of systemic therapy in the adjuvant setting.

A comprehensive history of adjuvant therapy for pancreatic cancer is beyond the scope of this text and focused on the delivery of 5-FU–based chemoradiation which, taken together, were inconclusive as to its survival benefit.[71–73] Gemcitabine monotherapy was subsequently shown to improve disease-free survival (DFS) and overall survival (OS) over surgery alone in a trial conducted by Charité Onkologie (CONKO). CONKO 001 was a randomized phase 3 trial that compared 6 months of gemcitabine with observation alone after curative intent surgery. Investigators showed a significant improvement in DFS and OS with the use of gemcitabine postoperatively (13 and 22.8 months, respectively) compared with surgery alone (6.9 and 20.2 months).[74] Subsequently, the European Society of Pancreatic Cancer (ESPAC) reported on their results in the ESPAC-4 trial, which randomly assigned surgically resected patients to adjuvant gemcitabine with or without capecitabine.[75] The chemotherapy doublet demonstrated an improvement in OS (28 vs 25.5 months; $P = .032$).

More recently, the results of the PRODIGE-24/CCTG study established another new standard of care for the adjuvant setting.[76] Patients were randomized to either 6 months of modified 5-FU, leucovorin, irinotecan, and oxaliplatin (mFOLFIRINOX) or gemcitabine. The combination chemotherapy arm significantly improved DFS from 12.8 to 21.6 months and median OS from 35 to 54.4 months. Despite the impressive survival data from the PRODGE-24/CCTG study, it is

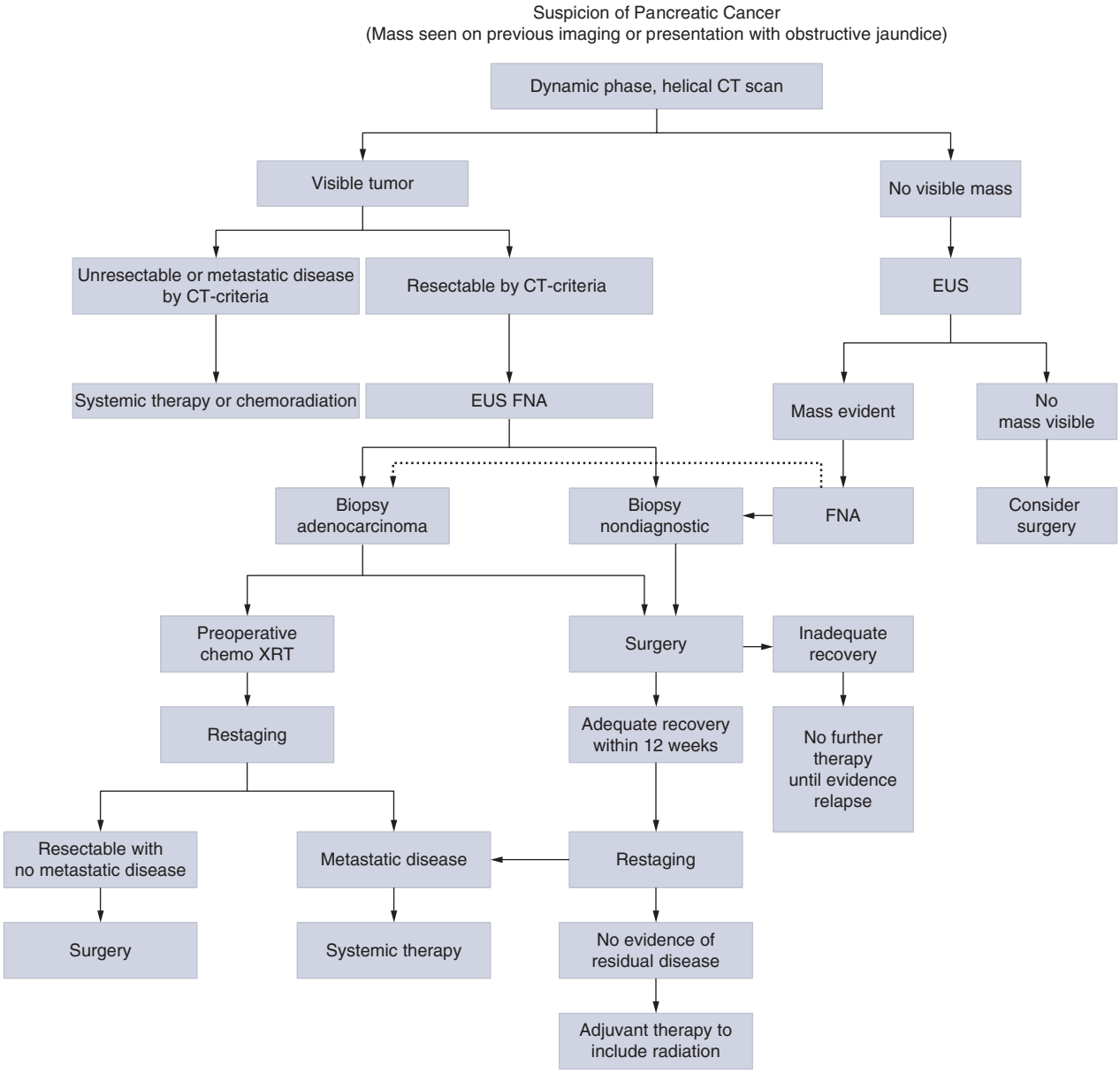


FIGURE 28–3 **General algorithm for diagnostic workup and management of newly diagnosed pancreatic cancer.**

important to recognize that the study patients represented a very select cohort. For example, patients with postoperative CA 19-9 levels greater than 180 U/mL within 21 days of random assignment were excluded. Moreover, enrollment was limited to patients with a World Health Organization PS of 0–1.

The most recent trial of adjuvant therapy for pancreatic cancer was the Adjuvant Pancreatic Adenocarcinoma Clinical Trial (APACT), which compared the combination of gemcitabine and nab-paclitaxel with gemcitabine for 6 months.[77] The primary end point of the study was independently assessed DFS. The results, presented at the ASCO annual meeting in 2019, demonstrated no significant improvement in DFS for the combination over single-agent gemcitabine. Of note, however, there was some improvement in OS for patients receiving gemcitabine and nab-paclitaxel compared with those receiving gemcitabine alone (40 vs 36 months), but this did not meet statistical significance and was not the primary end point.

Table 28–4 summarizes the results of the recently completed adjuvant trials. Note that the survival of patients randomly assigned to gemcitabine has steadily increased from 22.8 months in 2013 to 25 months in 2017 and up to about 35 months in 2018–2019. This suggests that patient selection for trial enrollment has become increasingly stringent from the early 2000s to the present time. Moreover, treatment options

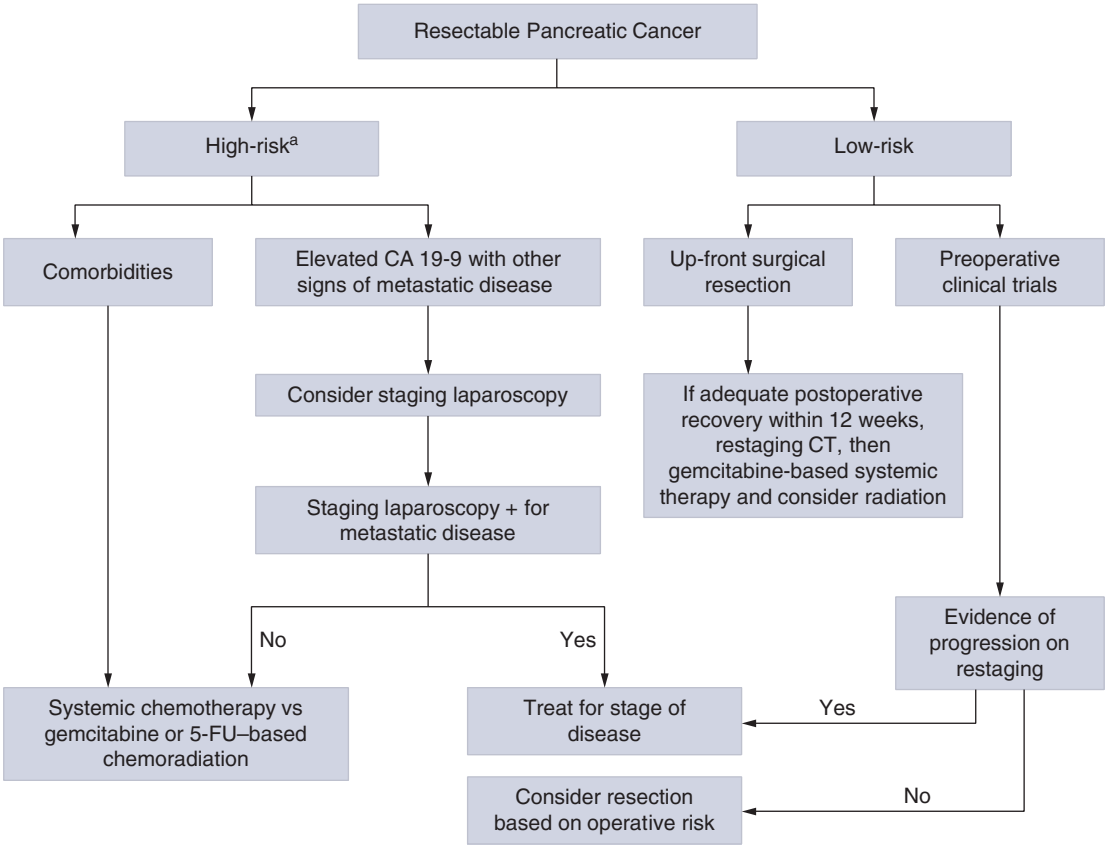


FIGURE 28–4 **Treatment algorithm for the management of resectable pancreatic cancer. [a]High-risk clinical features: suspicion of metastatic disease; CA19-9 >1000 with normal bilirubin; comorbidities suggesting high operative risk.**

available at the time of relapse have slowly expanded during this same time interval.

Challenges Associated with Upfront Surgery Followed by Adjuvant Therapy

In most centers, upfront surgical resection is the mainstay of treatment for potentially resectable pancreatic cancer. However, careful analysis of results from a surgery-first approach uncovers significant potential flaws in sequencing therapy this way.

1. *Surgical morbidity and mortality remain quite high after pancreaticoduodenectomy and impact the delivery of adjuvant therapy.*

Potentially resectable pancreatic cancer is often diagnosed in patients in their 60s to 70s and, given the known risk factors for pancreatic cancer, many patients may have a prior history of tobacco use, diabetes, or obesity, or they may present in a deconditioned state. Any of these comorbidities can increase the risk of postoperative complications, hamper recovery, and reduce the chances of receiving adjuvant therapy. An analysis performed by the American College of Surgeons National Surgical Quality Improvement Program evaluating data from the National Cancer Data Base (NCDB) has reported a rate of serious postoperative complications of 23%. For patients with no serious postoperative complications, the rate of adjuvant therapy delivery was 62%; for those with at least one postoperative complication, the delivery of adjuvant therapy was only 44%.[78] Pancreatic cancer surgery can also result in death. Among roughly 15,000 patients who underwent curative intent surgery for pancreatic cancer, 30-day mortality was only 3.4%, whereas 90-day mortality was twice that, at 7.5%.[79]

2. *Positive surgical margins are associated with inferior prognosis and are quite frequent with upfront surgery.*

Pancreatic cancer is notorious for being locally invasive, and surgical margins at the time of surgical resection are often microscopically positive (R1 resection). In modern trials of adjuvant therapy, the frequency of R1 resections among enrolled patients varies widely between 17% and 60% (Table 28–4). Prospective and retrospective analyses have shown that R1 resections are associated with worse survival compared with R0 resections.[80–82] In ESPAC-4, survival was superior for patients undergoing R0 resection compared with those having an R1 resection, irrespective of assigned therapy, as shown in Table 28–4.[75]

While some have advocated for postoperative radiation as a component of adjuvant therapy for patients

Table 28–4 Results of Upfront surgery in modern adjuvant therapy trials.

Study Year	Number of Patients	Number of Patients Enrolled Per Site Per Year	R1 Resection Rate	Median Survival (Months)	
				Control Arm	Experimental Arm
CONKO 001 2013	364	0.64	17	Observation 20.2	Gemcitabine 22.8
ESPAC 4 2017	730	1.32	60	Gemcitabine Full Cohort 25.5 R0 27.9 R1 23.0	Gemcitabine + capecitabine Full Cohort 28.0 R0 39.5 R1 23.7
PRODIGE/ CCTG 2018	493	1.90	43	Gemcitabine 35.0	FOLFIRINOX 54.4
APACT 2019[a]	866[b]	Not stated	24	Gemcitabine 36.2	Gemcitabine + nab-paclitaxel 40.5

[a]1226 patients were screened for enrollment, 360 (29%) failed screening; of these, 200 (17%) failed based on presence of postoperative radiographic evidence of persistent or metastatic disease, or postoperative CA 19-9 level >100 U/mL.
[b]The primary end point was independently assessed disease-free survival; overall survival was not the primary end point of this trial.

who undergo an upfront R1 resection,[83,84] our view is that neoadjuvant therapy is a more logical strategy to reduce the risk of a positive resection margin.[85]

3. *Upfront surgery results in persistent disease or metastases within the immediate postoperative period.*

The preliminary report of the APACT trial did report on screen failures for enrollment. A total of 1266 patients were evaluated for enrollment in this randomized phase 3 trial, but only 866 (71%) were enrolled. Of the 366 screen failures, 200 (17%) were ineligible based on postoperative radiographic evidence of persistent or metastatic disease, or a postoperative serum CA 19-9 level greater than 100.[77]

In summary, upfront surgery is associated with significant morbidity and mortality, it often leaves microscopic residual disease, and it puts the patient at risk for early relapse in the immediate postoperative period. Thus, based on current estimates, of the patients who undergo upfront surgery with curative intent, as much as 40% to 50% do not receive adjuvant therapy, proven to be a necessary component of treatment.[78]

MDACC Approach to Adjuvant Therapy

As will be discussed in more detail, our institutional bias is to deliver neoadjuvant therapy before considering surgery. Nevertheless, we have a subset of patients who are advised to undergo surgery first as part of their overall treatment plan. In addition, patients present to MDACC in the postoperative period seeking our opinion about a specific plan for adjuvant therapy.

In these circumstances, our approach has several facets.

1. *Assessment of postoperative recovery*

First and foremost, ensuring adequate recovery from surgery is an important step in determining whether the patient has recuperated adequately to consider adjuvant therapy. Patients should be ambulatory and capable of self-care with minimal assistance. At MDACC, adjuvant therapy is generally initiated 8 to 10 weeks postoperatively, although we accept a full 12 weeks of postoperative recovery as the outer bound for embarking on adjuvant therapy. This is based on analysis of results from patients treated on ESPAC trials of adjuvant therapy, which showed no difference in survival for those patients beginning adjuvant therapy at 6 to 8 weeks compared with those starting treatment 12 weeks postoperatively.[86] Moreover, for those patients who did not receive a full six cycles of adjuvant therapy, improved survival was demonstrated if treatment was initiated later (>8 weeks), implying that premature initiation of adjuvant therapy may be detrimental.

2. *Assessment of disease status*

Before initiating adjuvant therapy, patients undergo restaging studies that include measurement of serum tumor markers and CT imaging of the abdomen and pelvis. A specific cutoff for CA 19-9 suggesting persistent disease has not been established, but a postoperative level of 200 or higher should cause concern for the presence of gross residual disease. We recommend postoperative imaging as the patient approaches adequate recovery from surgery, usually 8 to 10 weeks postoperatively.

A. A specific plan for adjuvant therapy

Assuming the patient has adequate recovery and no clinical, biochemical or radiographic evidence of disease on postoperative assessment, the patient's performance status is the primary factor in determining the specific recommendations.

A.Modified (m)FOLFIRINOX:

For patients with very good PS (ECOG 0–1) and no contraindications to treatment with this combination, such as baseline peripheral neuropathy, mFOLFIRINOX delivered once every 2 weeks for six cycles (24 weeks) is the preferred regimen. Note that in the original report of this regimen as adjuvant therapy, the dose of irinotecan was reduced from 180 mg/m^2 to 150 mg/m^2, which improved overall tolerance to the treatment.[76] In the case of progressive peripheral neuropathy during treatment, we have a low threshold to reduce the dose or omit oxaliplatin completely for the remainder of the planned 6 months.

b. Gemcitabine and Capecitabine

For patients with ECOG PS 1–2, treatment with gemcitabine and capecitabine delivered over 24 weeks is generally recommended. In our experience, many patients do not tolerate a 28-day cycle of this regimen (3 weeks on, 1 week off), and if patients have unacceptable toxicity or develop progressive intolerance, we generally switch to treatment on a 21-day cycle. Regardless of cycle length, adjuvant therapy is usually given over 24 weeks.

3. *The Role of Radiation in Resected Pancreatic Cancer*

As a general rule, although final surgical pathology is prognostic, it is not typically used as a major factor in adjuvant treatment planning. The exception to this applies to patients who undergo an R1 resection. In that setting, systemic therapy for at least 4 months is advised. At that juncture, patients may be offered repeat imaging, and if there is no interval development of metastatic disease, chemoradiation may be considered to complete adjuvant therapy. Decisions about the role of postoperative chemoradiation are made by consensus during our weekly multidisciplinary pancreatic cancer conferences.

Neoadjuvant Therapy for Potentially Resectable Disease

At MDACC, our strong preference is for neoadjuvant therapy to be followed by surgery in the appropriate setting. This preference is based on the potential drawbacks associated with upfront surgery outlined previously. Neoadjuvant therapy followed by surgery offers some distinct theoretic advantages over immediate surgery and adjuvant therapy.

- Neoadjuvant therapy allows delivery of chemotherapy or chemoradiation to a relatively well-perfused tumor bed and provides early treatment to microscopic metastases.

Table 28–5 Analyses of R0 Resection Rate and Lymph Node Involvement with Upfront Surgery and Adjuvant Therapy Versus Neoadjuvant Therapy and Surgery

Author Study Details Year	Number of Patients	R0 Resection Rate (%)		Negative Lymph Node Rate (%)	
		Upfront Surgery	Neoadjuvant Therapy	Upfront Surgery	Neoadjuvant Therapy
Roland MDACC/Single Institution 2013	307	85	92	26	50
Youngwirth NCDB 2017	18,243	78	85	43	59
Mokdad NCDB/Propensity Matching 2017	15,237	76	83	23	52
Versteijne Meta-Analysis 2018	3484	67	87	35	56
Versteijne PREOPANC Randomized Trial 2020	246	40	71	22	67

- It can generate meaningful locoregional treatment effect, increasing the chance of a margin-negative resection and reducing the likelihood of positive lymph nodes (Table 28–5).
- It allows for observation of the tumor's underlying biology over time and facilitates the identification of patients with interval development of metastatic disease, sparing them a major surgical procedure which will not be of benefit.
- Neoadjuvant therapy also provides an opportunity to observe the patient's tolerance to nonsurgical treatment and allow for adjustments in its duration or intensity to maximize the patient's chances for recovery from preoperative treatment before surgical intervention.
- Neoadjuvant therapy allows for prehabilitation, which may involve gradual weight loss, improvements in nutrition and glucose control, and exercise to increase cardiovascular and physical fitness.[87]

We have been conducting neoadjuvant trials in potentially resectable pancreatic cancer at MDACC since the early 1990s.[88–92] Our data demonstrated that preoperative therapy is associated with high rates of R0 resections and relatively low local failure rates compared with adjuvant therapy. Subsequent analysis of our survival results in patients undergoing surgery after preoperative therapy has demonstrated increases in OS over time from 1990 to 2014 using four successive time periods, with median OS improving from 24.1 months from 1990 to 1999 to 43 months in 2010 to 2014.[93]

A growing number of comparisons between the use of neoadjuvant therapy followed by surgery and upfront surgery with or without adjuvant therapy have been conducted (Table 28–5).[94–98] All of these analyses conclude that neoadjuvant therapy is more likely to result in an R0 resection compared with upfront surgery and increase the likelihood of negative lymph nodes on final pathology. These analyses have been limited by a lack of randomized data comparing neoadjuvant therapy and subsequent surgery with upfront surgery and adjuvant therapy. The exception is the recently published PREOPANC trial conducted at 16 centers in the Netherlands, summarized in Table 28–5.[98] This study allowed enrollment of patients with resectable or borderline resectable disease (the latter to be discussed below). The study enrolled 246 patients between 2013 and 2017. Patients were randomly assigned to receive three courses of gemcitabine, with the second course given in conjunction with radiation to a dose of 36 Gy delivered over 15 fractions, followed by surgery, followed by four courses of postoperative gemcitabine; or to upfront surgery and six cycles of adjuvant gemcitabine. Based on the intent-to-treat analysis, patients who were assigned to neoadjuvant therapy had a slightly better median OS of 16.0 months compared with 14.3 months for those patients assigned to upfront surgery (P = .096). However, among the patients who underwent surgical resection, there was a clear survival advantage for patients who had received preoperative treatment, 35.2 months versus 19.2 months (P = .029). The PREOPANC trial, although negative for improvement in OS based on intent to treat, showed a survival advantage for those undergoing curative resection and has paved the way for more robust efforts to assess the value of neoadjuvant therapy compared with upfront surgery in pancreatic cancer. Furthermore, investigation of the relative contributions of chemotherapy and chemoradiation in neoadjuvant trials is ongoing.

MDACC Approach to Neoadjuvant Therapy in Patients with Resectable Disease

Patients who are identified before referral as having localized disease are initially seen by one of our surgical oncologists to assess PS and comorbidities and confirm adenocarcinoma from outside specimens or from biopsies obtained here. Routine laboratory studies are obtained to include complete blood counts and coagulation studies, a comprehensive metabolic panel, hemoglobin A1C, and serum tumor markers, specifically carcinoembryonic antigen, CA 19-9, and CA 125. High-quality dynamic-phase pancreatic protocol CT imaging of the chest, abdomen, or pelvis is obtained and reported in a templated format described earlier in the chapter. Patients clinically staged as having potentially resectable disease and considered to be surgical candidates are presented to multidisciplinary pancreatic cancer conferences to consider enrollment in a clinical trial or to develop a preliminary plan for off-protocol therapy.

Outside of a clinical trial, if neoadjuvant therapy is recommended, therapy is generally a well-defined course of induction systemic therapy consisting or 3 to 4 months of mFOLFIRINOX or gemcitabine/nab-paclitaxel. Restaging studies are performed every 2 months during induction chemotherapy. If no interval metastases are noted on restaging, long-, medium-, or short-course capecitabine-based chemoradiation (50.4 Gy over 28 fractions, 36 Gy over 12 fractions, or 30 Gy over 10 fractions, respectively) is delivered. Decisions about the induction chemotherapy are left to the discretion of the treating oncologist and are generally based on comorbidities and PS. Patients with ECOG PS 0–1 are usually treated with mFOLIRINOX and patients with ECOG PS 1–2, or with comorbidities, more often receive gemcitabine and nab-paclitaxel. In terms of the radiation dose and schedule, this is primarily the purview of the treating radiation oncologist with input from the surgeon and medical oncologist. Whenever possible, we advise our patients to receive neoadjuvant chemoradiation at MDACC. However,

we allow the delivery of off-protocol induction chemotherapy in collaboration with the patient's referring oncologist.

Borderline Resectable Pancreatic Cancer

In the late 1990s and early 2000s, the negative prognostic implications of an R1 resection were increasingly appreciated. This coupled with improvements in cross-sectional imaging allowed for the identification of tumors abutting but not encasing critical arterial structures surrounding the pancreas (celiac trunk and SMA). Such tumors were recognized as putting patients at risk for an R1 resection with upfront surgery and, in many centers, were considered locally advanced and unresectable. However, as we and others developed experience with neoadjuvant chemoradiation and observed significant treatment effect on final pathology, it was noted that a subset of patients having tumors with vessel abutment could undergo R0 resection after a period of neoadjuvant therapy. In that context, the concept of borderline resectable pancreatic cancer emerged.[99]

As of this writing, there is variability in definitions of borderline resectable disease, but for the purposes of this text, a borderline resectable tumor is one that puts the patient at high risk for an R1 resection with upfront surgery. A growing number of single-institution reports of neoadjuvant therapy for borderline resectable tumors are being published. Multi-institutional and cooperative group trials specifically designed for patients with borderline resectable disease are now being conducted, with some results already published.[100] Although there is no standard approach to neoadjuvant therapy for borderline resectable disease, some general observations are becoming evident.

1. *Neoadjuvant therapy followed by surgery for borderline resectable disease appears to offer a survival advantage over upfront surgery and adjuvant therapy.*

Using the NCDB, investigators analyzed outcomes of patients with borderline resectable disease treated with upfront surgery and adjuvant therapy and compared them with similar patients treated with neoadjuvant and subsequent surgery.[101] Median OS was superior using a neoadjuvant approach compared with upfront surgery (25.7 vs 19.6 months; $P < .0001$). Moreover, R0 resections were higher using neoadjuvant therapy and the rate of node-positive disease was lower.

2. *Induction gemcitabine/nab-paclitaxel or FOLFIRINOX with or without subsequent chemoradiation are the most common neoadjuvant regimens being reported recently.*

Two studies have reported on clinical outcomes after neoadjuvant therapy and subsequent surgery using FOLFIRINOX compared with gemcitabine and nab-paclitaxel.[102,103] Based on these results, there is no firm conclusion regarding the superiority of one regimen over the other.

3. *The role of radiation in the neoadjuvant treatment of borderline resectable disease is unclear.*

Radiation as a component of neoadjuvant therapy has yet to be firmly established because there are no well-designed randomized trials published to date. There are reports that neoadjuvant chemoradiation may improve R0 and pN0 resections compared with neoadjuvant chemotherapy alone, but no survival advantage has yet been demonstrated .[104] PREOPANC2 is a randomized clinical trial that will compare systemic gemcitabine and gemcitabine-based chemoradiation with FOLFIRINOX alone in patients with resectable and borderline resectable pancreatic cancer.[98] In addition, the Alliance for Clinical Oncology Trial A021501 is comparing FOLFIRINOX × 7 doses followed by SBRT with FOLFIRINOX × 8 doses followed by surgery.[105] Results from these and other trials may clarify the role of neoadjuvant radiation in borderline resectable disease.

MDACC Approach to Borderline Resectable Disease

Whenever possible, patients with borderline resectable pancreatic cancer are enrolled in clinical trials. Outside of a clinical trial, patients with borderline resectable pancreatic cancer are treated using a tailored approach, taking into account PS, comorbidities, baseline CA 19-9 measurements, and presence of indeterminate liver, lung, or peritoneal lesions (Fig. 28–5).

In general, patients with PS 0–1 and no contraindications to FOLFIRINOX are treated with this regimen. Induction chemotherapy is usually delivered over a longer interval (4+ months) compared with patients with potentially resectable disease (3–4 months). For patients with PS 1, comorbidities, or contraindications to FOLFIRINOX, we usually administer gemcitabine and nab-paclitaxel for a similar time frame. We have found that normalization of CA 19-9 levels after completion of neoadjuvant therapy (which for us usually involves chemoradiation after induction chemotherapy), improves the likelihood of a major pathologic response at the time of surgery and increases the chance of long-term survival.[65,66] Therefore, serial CA 19-9 measurements are obtained as patients receive induction chemotherapy. If a patient's clinical or marker response to the first two cycles (8 weeks) of frontline neoadjuvant FOLFIRINOX is considered suboptimal, we will consider a switch in chemotherapy to gemcitabine and nab-paclitaxel. Based on a retrospective analysis, this strategy ultimately allowed surgical resection in 40% to 50% of patients who did not respond to initial FOLFIRINOX.[106] We do not currently know whether a switch to FOLFIRINOX will also salvage the patient's candidacy for surgery if initial treatment with gemcitabine and nab-paclitaxel treatment is ineffective.

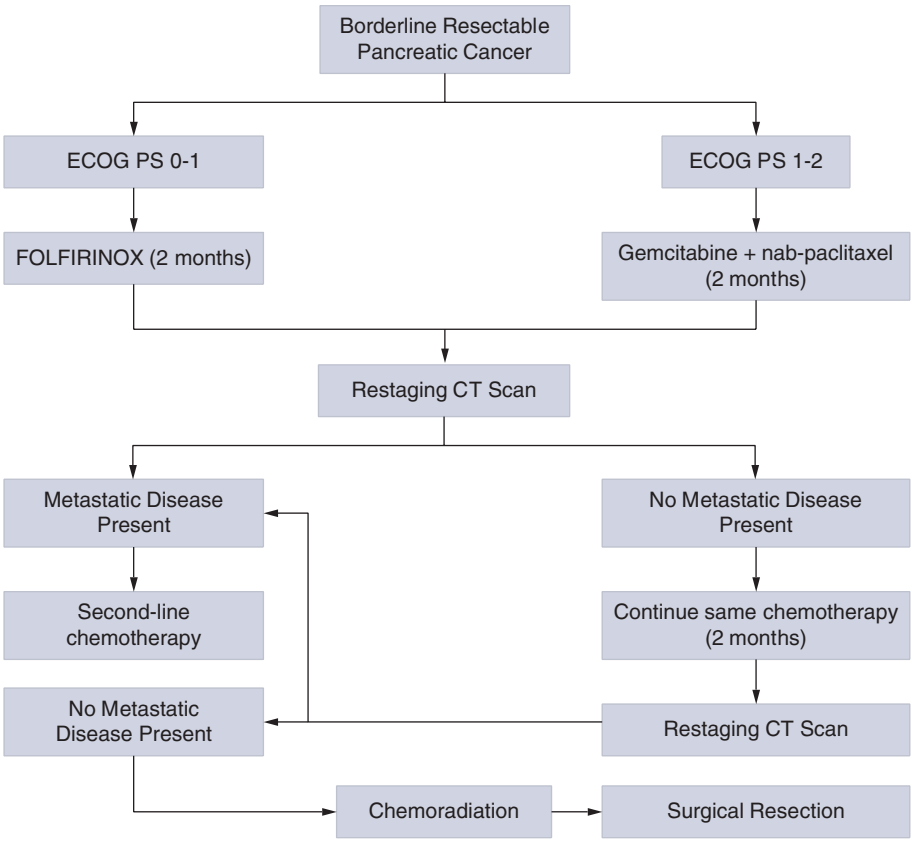


FIGURE 28–5 **Treatment algorithm for the management of borderline resectable pancreatic cancer.**

Neoadjuvant therapy in borderline resectable disease serves to identify the subset of patients with favorable response who should undergo an attempt at surgical resection. Thus, maintaining or improving fitness for surgery remains a priority during neoadjuvant therapy. We take a two-pronged approach. First, we have found that modest de-escalation of FOLFIRINOX or gemcitabine and nab-paclitaxel intensity is well tolerated, generates anticancer effects, and minimizes toxicity that could compromise a patient's surgical candidacy.[107] Second, we have increasingly used formalized prehabilitation as part of our neoadjuvant program to assist patients with nutritional modifications, gradual intentional weight loss, and to provide specific recommendations for exercise to increase cardiovascular fitness and muscle strength.

Management of Patients with Locally Advanced Disease

Patients are defined as having locally advanced pancreatic cancer when there is radiographic evidence of SMA or celiac artery encasement, occlusion of the SMV-PV confluence, or significant involvement of the common hepatic artery originating from the celiac trunk. There should be no clinical or radiographic evidence of metastatic disease. Currently, roughly half of all patients present with locally advanced disease. As with resectable pancreatic cancer, an understanding of certain principles aid in decision making.

- *Locally advanced pancreatic cancer poses unique challenges.* Local tumor progression with worsening pain, new or recurrent biliary obstruction, PV thrombosis, or gastric outlet obstruction represent difficult treatment problems.
- *Assessment of response to therapy can be difficult.* These tumors may be composed of small nests of adenocarcinoma surrounded by large areas of desmoplasia (Fig. 28–6). Even when cytotoxic therapy is effective, the desmoplastic component of the residual mass may not regress, and the overall tumor mass may appear unchanged.
- *All surgical interventions should be considered carefully and based on patient PS and life expectancy.* Palliative nonsurgical procedures may produce results similar to those of aggressive surgery.

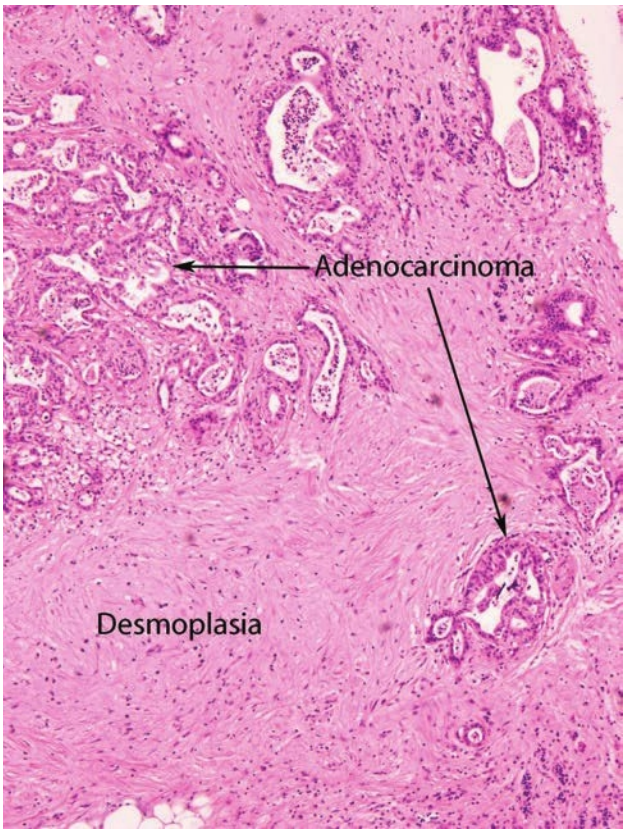


FIGURE 28–6 Photomicrograph of ductal adenocarcinoma of the pancreas with intense desmoplastic reaction. Even if the tumor cells regress in response to therapy, a residual fibrotic mass may remain. This confounds assessment of response to therapy using standard radiographic criteria.

The Evolution of Therapy for Locally Advanced Disease

Concurrent chemoradiation had historically been the initial treatment approach for patients with locally advanced pancreatic cancer. After approval of gemcitabine in 1997, a common practice for management of locally advanced disease was to deliver 5-FU–based chemoradiation followed by systemic gemcitabine as tolerated until disease progression.

Induction Chemotherapy Followed by Chemoradiation

The old paradigm of chemoradiation followed by chemotherapy was challenged by analyses suggesting that induction chemotherapy followed by chemoradiation might be a better strategy.[108–110] Two of these studies showed that approximately 30% of patients with locally advanced pancreatic cancer would develop metastatic disease within 2 to 4 months of starting systemic therapy. This implied that such patients had aggressive tumor biology negating any benefit from local therapy, and therefore the initial use of systemic therapy would serve to identify patients with favorable biology, making them attractive candidates for local control.

Systemic Therapy Alone for Locally Advanced Disease

The strategy of systemic therapy followed by consolidative chemoradiation was challenged by the results of LAP 07.[111] In this trial, patients were randomly assigned to gemcitabine or gemcitabine plus erlotinib (100 mg/d) for 4 months. Participants with controlled disease after induction chemotherapy were subsequently randomly assigned to further chemotherapy for 2 more months or to chemoradiation (54 Gy) with capecitabine 1600 mg/m^2/d). All treatment then ceased. Of the 442 patients initially randomly assigned, 269 patients (61%) entered the second-round randomization phase, thus identifying the subset of patients with unfavorable tumor biology unlikely to benefit from local control. Median OS in the chemotherapy arm was 16.5 months compared with 15.2 months for the chemoradiation group (hazard ratio [HR] 1.03, 95% CI 0.79–1.34; P = .83). It appeared neither radiation nor erlotinib improved survival in this population. However, the administration of radiation delayed the reinitiation of anticancer therapy for progressive disease (3.7 months for the chemotherapy arm, 6.1 months for chemoradiation; P = .02). This potential for a longer chemotherapy-free interval after consolidating chemoradiation may be of value to patients and has been used to justify continued studies of consolidating chemoradiation after a period of systemic therapy. As of this writing, for patients with good PS (ECOG 0–1), the NCCN Pancreatic Cancer Guidelines subcommittee endorses induction chemotherapy (for 4–6 months) for patients with locally advanced disease. If the patient remains with locally advanced, nonmetastatic disease, chemoradiation or SBRT are accepted as subsequent therapeutic options.

MDACC Approach to Locally Advanced Pancreatic Cancer

For patients with adequate PS (ECOG ≤2), outside of a clinical trial, our general approach is to initiate therapy with gemcitabine and nab-paclitaxel rather than FOLFIRINOX. This is based in part on our off-protocol approach to treatment with gemcitabine/nab-paclitaxel (given day 1 and 15 every 28 days) which we find quite tolerable for the majority of our patients.[107] This allows us to consider second-line FOLFIRINOX or 5-FU with liposomal irinotecan if no benefit is observed with first-line gemcitabine and nab-paclitaxel

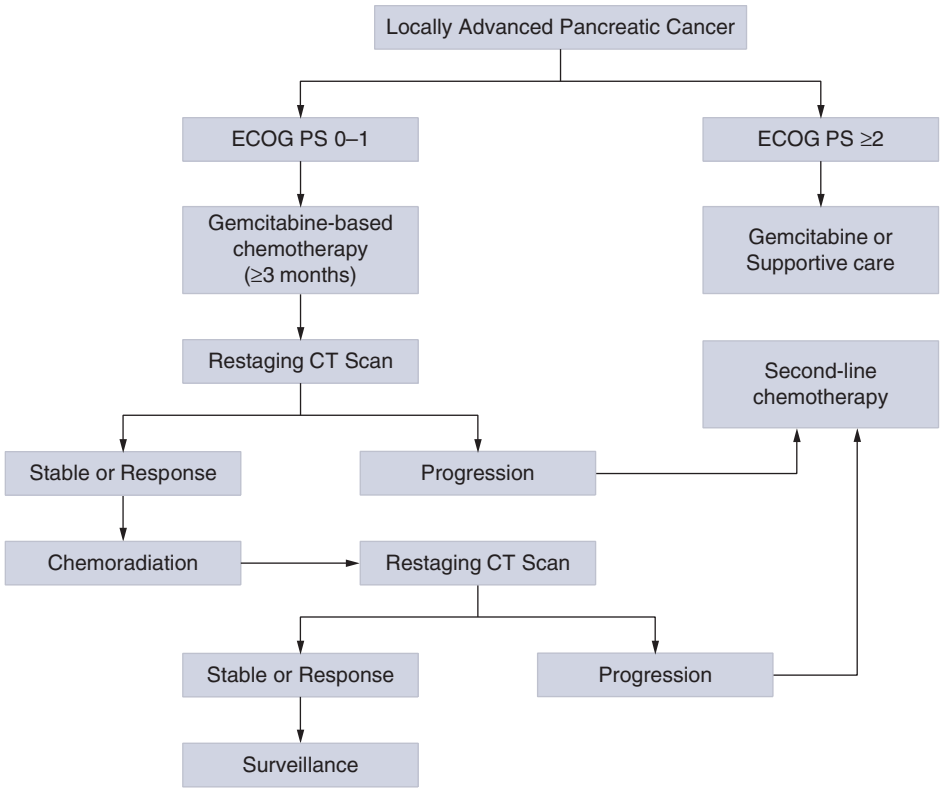


FIGURE 28–7 **Treatment algorithm applied to the management of patients with locally advanced pancreatic cancer.**

and provides another active regimen if interval metastatic disease develops (Fig. 28–7).

The exception to the use of gemcitabine and nab-paclitaxel as frontline therapy in locally advanced disease pertains to patients who are more likely to be reconsidered for surgery after a period of neoadjuvant therapy. These patients usually have PS 0 and limited comorbidities to allow for aggressive neoadjuvant therapy and subsequent surgery. Support for this approach comes from retrospective data reported from the Johns Hopkins Hospital. A total of 415 LAPC patients were included in the study, and 84 patients ultimately underwent resection of the primary tumor (20%) after neoadjuvant therapy. FOLFIRINOX-based therapy and SBRT correlated with increased probability of resection ($P = .006$). Resected patients had better PS, smaller median tumor size ($P = .029$), and lower median CA 19-9 values ($P < .001$. Patients who underwent surgical resection had significant higher median OS compared with those who did not (35.3 vs 16.3 months; $P < .001$).[112] A more recent report also supports FOLFIRINOX (combined with losartan) followed by chemoradiation as a strategy to allow a subset of patients with locally advanced disease to ultimately undergo surgery with curative intent.[113] Our approach is similar for these patients and we generally administer FOLFIRINOX for at least 4 months. For patients who demonstrate a clinical, biochemical, or radiographic response to systemic therapy, we favor consolidating chemoradiation, particularly when surgical resection remains a possibility.

Outside of a clinical trial, we generally administer capecitabine as the radiosensitizer, based on results from the SCALOP trial, a randomized phase 2 trial performed in the United Kingdom. Patients with locally advanced pancreatic cancer who did not have disease progression after 12 weeks of induction chemotherapy with gemcitabine plus capecitabine were randomly assigned to either gemcitabine (300 mg/m^2/week) or capecitabine (830 mg/m^2 twice daily on days of radiotherapy) concurrently with radiation (50.4 Gy in 28 fractions).[114] Median OS was 17.6 months in the capecitabine arm compared with 14.6 months in the gemcitabine arm (adjusted HR 0.68; $P = .185$).[115] Furthermore, for patients who receive chemoradiation we consider maintenance therapy using capecitabine for at least 3 months after completion.

Whenever possible, patients with stable disease or response after a period of systemic therapy, are encouraged to enroll in clinical trials using novel radiosensitizers or radioprotectants.

Of note, if patients do not derive any significant clinical, biochemical, or radiographic response from first- and/or second-line induction chemotherapy, we

generally do not pursue chemoradiation as an alternative strategy. This is also true for patients who remain with relatively high CA 19-9 levels after a trial of systemic therapy. It is our perception that patients with chemoresistant disease harbor tumors that are likewise radioresistant.

For patients with poor PS, supportive care is encouraged, and systemic therapy and radiation are usually contraindicated. In the subgroup of patients with significant pain related to the primary tumor, aggressive use of opioids is initiated, with emphasis on slow-release, long-acting formulations. When poor tolerance to opioids or inadequate pain control occurs with their administration, celiac or splanchnic nerve block is recommended. If adequate pain control is achieved, patients with improving PS can be reconsidered for anticancer therapy.

Localized and Locally Advanced Pancreatic Cancer Summary

Clinical and autopsy data have repeatedly proven that adenocarcinoma of the pancreas is both a locally invasive disease and a systemic disease, and it is estimated that 20% of patients who die as a result of pancreatic cancer succumb to progressive local disease. As a general rule, in patients with localized disease (potentially or borderline resectable, and locally advanced disease), systemic therapy remains the foundation of anticancer therapy and in our view should be delivered before surgery. When appropriate, an array of local therapies should be considered in patients who demonstrate disease response or prolonged local disease stabilization. This might involve ultimate surgical resection, various radiation techniques, or other locally ablative techniques such as irreversible electroporation (if applied properly by experienced clinicians).[116] Moreover, as our systemic therapy continues to evolve and improve, durable local disease control will become increasingly relevant for better patient outcomes.

Management of Metastatic Disease

Compared with patients having other common malignancies, such as cancer of the colon or breast, patients with advanced pancreatic cancer often have more tumor-related symptoms and functional compromise. Therefore, palliation must be a primary goal of therapy. Management of metastatic disease should be guided by the following principles:

- The disease course may be quite dynamic, and the clinical status of a patient can change quickly. Patients therefore require frequent reassessment, regardless of whether they are undergoing cytotoxic therapy.
- Responses to therapy are rarely observed in patients with poor PS or high tumor burden, and combination therapy in these patients is associated with increased toxicity.
- When metastatic disease is confined to the lungs, its course may be more indolent.
- Although newer cytotoxic chemotherapy regimens have improved survival for patients with advanced disease, further advances in the treatment for pancreatic cancer are desperately needed, and patients with good PS should be encouraged to participate in clinical trials.

Gemcitabine-Based Therapy for Advanced Pancreatic Cancer

Gemcitabine

Gemcitabine was the first FDA-approved drug for advanced pancreatic cancer based on a randomized trial. The study compared weekly gemcitabine with bolus weekly 5-FU in previously untreated patients.[117] Patients treated with gemcitabine achieved a higher response rate (5.4% vs 0%) and improvement in median OS compared with those treated with 5-FU (5.65 vs 4.41 months; $P = .0025$). The 1-year survival rate for gemcitabine-treated patients was 18% compared with 2% for those treated with 5-FU. Importantly, more clinically meaningful effects on disease-related symptoms were recorded with gemcitabine therapy compared with 5-FU treatment (24% vs 5%).

Gemcitabine Doublet Therapy

After gemcitabine's approval in 1997, a number of gemcitabine doublets were tested. These trials generally combined gemcitabine with another cytotoxic agent: 5-FU, cisplatin, irinotecan, oxaliplatin, and docetaxel.[118–123] Most doublets showed some modest improvement in objective response rate (15%–20% vs gemcitabine at 10%); alas, no meaningful improvement in survival was observed using cytotoxic doublet therapy in unselected patients.

Similar to cytotoxic doublets, no significant progress has been made combining gemcitabine with molecular targeted agents.[124–129] More recently, the focus of investigation has been aimed at the tumor microenvironment. Early ventures into this arena have likewise been disappointing. Only erlotinib, an oral EGF-R inhibitor, which led to a slightly longer median survival compared with gemcitabine alone (6.24 vs 5.91 months; $P = .038$),[130] has demonstrated improved efficacy in combination with gemcitabine. This is likely explained by the lack of a predictive biomarker for any of the drugs tested and the relative impotence of single-agent gemcitabine as delivered in clinical trials (1000 mg/m^2 over 30 minutes).

Gemcitabine and Capecitabine

In contrast to other cytotoxic drugs, capecitabine, the orally bioavailable fluorinated pyrimidine, has shown modest added benefit compared with treatment with gemcitabine alone. In a phase 3 trial, Cunningham and colleagues randomly assigned patients to receive gemcitabine versus gemcitabine plus capecitabine.[131] The addition of capecitabine to gemcitabine significantly improved overall response rate (19.1% vs 12.4%) and progression-free survival (HR = 0.78) ($P < .03$ and .004, respectively). The combination also showed a trend toward improved OS ($P = .08$). The NCCN Pancreatic Cancer Guidelines subcommittee continues to include this doublet as a reasonable regimen to deliver in patients with advanced disease.

Gemcitabine and Nab-Paclitaxel

In September 2013, the FDA first approved a gemcitabine-based combination chemotherapy regimen with nab-paclitaxel as a standard treatment for advanced pancreatic cancer. This was based on a phase 3 study showing an OS advantage of gemcitabine plus nab-paclitaxel over gemcitabine alone (8.5 months vs 6.7 months; HR for death 0.72; 95% CI 0.62–0.83; $P < .001$).[132] The 1-year survival rates were 35% versus 22%, respectively. The response rate according to independent review was 23% versus 7% in the two groups ($P < .001$). Patients in the combination arm did have increased neutropenia, fatigue, and neuropathy. Importantly, enrollment allowed patients with Karnofsky Performance Status score of at least 70% and suggested that this combination could be used safely in patients with compromised functional status. The gemcitabine and nab-paclitaxel combination therefore is an attractive drug regimen for patients with advanced disease having some degree of frailty or comorbidities, which make triplet drug therapy less attractive.

Gemcitabine and Cisplatin: Good for DNA Damage Repair Deficiency?

As experience with gemcitabine was growing, we and others found that some subsets of patients with advanced disease appeared to have some dramatic responses to gemcitabine and cisplatin. In a retrospective review of clinical data sets from MDACC and the Johns Hopkins group, patients with family or pedigree history of cancer had superior OS when treated with gemcitabine and a platinum analogue over gemcitabine monotherapy. This was especially true in patients with three or more relatives with a history of breast, ovarian, or pancreatic cancers (HR 0.49, 95% CI 0.30–0.80; $P = .003$). As the number of relatives with these cancers increased, the OS rate improved for individuals receiving first-line platinum therapy (HR 0.76, 95% CI 0.65–0.89; $P = .0004$), which was not the case for those receiving other therapies ($P = .98$).[133] Based on preclinical data and such clinical observations, it has been hypothesized that for patients with a strong family history of breast, ovarian or pancreatic cancer, germline mutations of BRCA or other DNA damage repair pathway genes would be more common and more likely sensitive to gemcitabine and platinum therapy. This has been supported by a recent randomized phase 2 trial in which germline BRCA- or PALB2-mutated patients received gemcitabine and cisplatin with or without velaparib.[134] The addition of veliparib did improve the objective response rate from 65% to 74% but this did not reach statistical significance. Nevertheless, the median OS of patients enrolled in this trial was impressive, ranging from 15.5 to 16.4 months. Thus, a strong family history of breast, ovarian, and/or pancreatic cancer, or a documented germline mutation in BRCA1/2 or PALB2 may serve as a predictive biomarker to treatment with gemcitabine and cisplatin. Over time, investigation of platinum-containing regimens in the setting of other mutated DDR genes, such as PALB2, ATM, or ATR, should expand the number of patients who may benefit from this doublet.

Triplet Chemotherapy for Advanced Pancreatic Cancer

FOLFIRINOX

In 2011, investigators in France tested a three-drug chemotherapy regimen consisting of oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) and compared it with gemcitabine in patients with metastatic pancreatic cancer with ECOG PS 0–1.[135] There were 342 patients enrolled and randomly assigned to receive FOLFIRINOX (oxaliplatin, 85 mg/m^2 body surface area; irinotecan, 180 mg/m^2; leucovorin, 400 mg/m^2; and fluorouracil, 400 mg/m^2 given as a bolus followed by 2400 mg/m^2 given as a 46-hour continuous infusion every 2 weeks) or gemcitabine. The median OS was 11.1 months in the FOLFIRINOX group compared with 6.8 months in the gemcitabine group (HR for death 0.57, 95% CI 0.45–0.73; $P < .001$). The objective response rate was also markedly improved in the FOLFIRINOX group, 31.6% versus 9.4% ($P < .001$). FOLFIRINOX is approved for use as frontline therapy in patients with advanced pancreatic cancer having ECOG PS 0–1 and in that population is considered a standard of care.

Gemcitabine, Nab-Paclitaxel, and Cisplatin

Very recently, a gemcitabine triplet combination has been similarly reported as highly active, with overall acceptable toxicity in patients with metastatic disease. This regimen builds on gemcitabine and nab-paclitaxel with the addition of cisplatin for treatment of patients

with advanced disease. In a multicenter phase 1b/2 trial, patients were treated with standard doses of nab-paclitaxel plus gemcitabine plus various doses of cisplatin, 25–50 mg/m^2, on days 1 and 8 of a 21-day cycle.[136] Among the 25 enrolled patients, there were two complete responses (8%), 15 partial responses (62%), four stable disease (17%), and three progressive disease (12%). Median progression-free survival was 10.1 months, with a median OS of 16.4 months. Moreover, 16 patients (64%) were alive at 1 year, 10 (40%) at 2 years, 4 (16%) at 3 years, and 1 (4%) at 4-plus years. On a cautionary note, fatal events occurred in three patients (12%); two were thought to be treatment related. A larger phase 2 trial of this regimen is now underway (NCT03915444).

Second-Line Chemotherapy

Nanoliposomal irinotecan has gained approval in the second-line setting for patients with metastatic pancreatic cancer who received prior gemcitabine-based therapy based on the results of the phase 3 NAPOLI-1 study.[137] In this trial, 417 patients whose disease had progressed on gemcitabine-based chemotherapy were randomized to one of three arms: (1) 5-FU + leucovorin, (2) nanoliposomal irinotecan, or (3) combination of 5-FU + leucovorin + nanoliposomal irinotecan. Median OS in the triplet-therapy group with 5-FU + leucovorin + nanoliposomal irinotecan was 6.1 months, compared with 4.2 months in the 5-FU + leucovorin group (HR 0.67; $P = .012$).

Second-line options for systemic chemotherapy are based largely on a patient's PS at the time of progression. Previously treated patients should be encouraged to participate in clinical trials where available. Outside of a clinical trial, for patients who are treated with first-line gemcitabine plus nab-paclitaxel, those who retain a good PS are usually offered 5-FU + leucovorin + nanoliposomal irinotecan. Rarely, patients with excellent PS may be considered for second-line FOLFIRINOX, although data on the triplet regimen in the pretreated setting are limited. For patients whose disease progresses on first-line FOLFIRINOX and who maintain an adequate PS, gemcitabine plus nab-paclitaxel is an appropriate second-line option.[138]

Future Directions in Systemic Therapy for Pancreatic Cancer

Modern Targeted Therapy in Pancreatic Cancer

For years, targeted therapy in pancreatic cancer proved disappointing predominantly based on the lack of predictable biomarkers. More recent investigations of target therapy have yielded somewhat more positive results.

Targeting Mutations in DNA Repair Proteins

Up to 25% of patients with pancreatic cancer may harbor mutations in genes that play a role in the DNA damage repair (DDR) response.[139–142] The most studied among these are germline BRCA1 and BRCA2 mutations, which occur in as much as 7% of patients with pancreatic cancer.[143,144]

Patients whose tumors are deficient in DDR proteins display heightened susceptibility to DNA-damaging agents, including platinum chemotherapy and radiotherapy. Recent therapeutic focus on inhibitors of PARP, a crucial component of the homologous recombination pathway for single-strand DNA breaks, has identified this class of drugs as being particularly effective in patients with DDR mutations. Early-phase studies evaluating the PARP inhibitors olaparib and rucaparib revealed promising activity in pretreated patients with pancreatic cancer with germline or somatic BRCA1 and BRCA2 mutations.[145,146] Most prominently, the phase 3 POLO trial randomly assigned 154 patients with metastatic pancreatic cancer with germline BRCA1 or BRCA2 mutations whose disease had not progressed on at least 16 weeks of first-line platinum-based chemotherapy to maintenance therapy with either placebo or olaparib.[20] The median PFS in the maintenance olaparib arm was significantly longer than in the placebo arm (7.4 vs 3.8 months, HR 0.53; $P = .004$). As of this writing, there has been no difference in OS between the groups. In December 2019, olaparib was granted FDA approval as a maintenance therapy for this population.[21]

NTRK Fusions

Fusions in the *NTRK* gene are rare but clinically significant molecular events, occurring in up to 1% of patients with pancreatic cancer. This aberration has been demonstrated in case reports to be a potent target with the TRK inhibitor, entrectinib.[147] In 2019, the FDA approved entrectinib in a tumor-agnostic setting for the treatment of patients with advanced solid tumors harboring *NTRK* fusions.[148] As tumor molecular profiling becomes increasingly used, medical oncologists should be aware of this population who have the potential to derive dramatic benefits from targeted therapy.

Stromal Re-engineering and Targeted Therapy

The traditional view of pancreatic cancer stroma has been as a hindrance to delivery of chemotherapy and accounting for the adverse prognosis associated with this cancer. Hedgehog inhibitors were particularly effective in causing stromal depletion.[149] This theory, however, was disproven in the clinical setting, with randomized trials of two hedgehog inhibitors, IPI-926 and vismodegib, failing to improve survival when added to gemcitabine compared with gemcitabine alone. Kalluri et al, from MDACC, recently showed that stromal depletion in genetically engineered mouse models resulted in accelerated tumor growth. In addition, they showed that stromal-depleted pancreatic

cancers were sensitive to the CTLA-4 (cytotoxic T lymphocyte-associated antigen 4) antibody ipilimumab.[150] Similar findings were reported by Rhim et al, who demonstrated that stroma is protective in pancreatic cancer, and deletion of sonic hedgehog accelerated tumor growth; this effect was again reproduced by treatment with smoothened inhibitor.[151] Stroma as a target for therapy continues to be investigated in the clinic.

A recently investigated stromal component is the extracellular matrix component hyaluronan. Enzymatic depletion of hyaluronan by the pegylated hyaluronidase (PEGPH20) resulted in inhibition of cancer growth and prolonged survival when combined with gemcitabine in preclinical studies.[54] Despite early provocative results, PEGPH20 combined with gemcitabine and nab-paclitaxel failed to demonstrate any clinical benefit over treatment with gemcitabine/nab-paclitaxel alone.[152] Even more troubling, in a phase 1b/2 trial conducted by SWOG, PEGPH20 combined with FOLFIRINOX, led to significantly inferior survival compared with FOLFIRINOX alone. The median OS in the mFOLFIRINOX arm was 14.4 months (95% CI 10.1–15.7) versus 7.7 months (95% CI 4.6–9.3) in the experimental arm.[153]

Immunotherapy for Pancreatic Cancer

Immunotherapy has finally come of age, and immune targeting is rapidly changing the course of several cancers. Both innate and adaptive immune systems are involved in the immunosurveillance mechanisms, which include cytotoxic CD8 T-cells, T helper 1 (Th1) cells, dendritic cells, tissue macrophages (M1), and natural killer cells. Cancers must escape these surveillance mechanisms to flourish and degrade health.[154] Preclinical models of pancreatic cancer have informed us that immunosuppressive tumor-associated macrophages, regulatory T-cells, along with scarce effector T-cells (CD8+) occur at even the earliest preinvasive stages and persist through the development of invasive cancer. High concentrations of CD8+ T-cells, when infrequently present in pancreas cancer, are associated with a good prognosis.[155]

Early efforts using modern immunotherapy, specifically checkpoint inhibitors were disappointing. Ipilimumab was investigated in 27 cases of pancreatic adenocarcinoma, and one delayed response occurred.[156] An anti–PD-L1 antibody was studied in an expansion cohort of pancreatic cases ($n = 14$) without any therapeutic responses.[157] These data have highlighted the fact that predictive criteria for checkpoint inhibitors are needed. As of this writing, the only biomarker for potential response to checkpoint inhibition is microsatellite instability, a hallmark of hereditary nonpolyposis colon cancer.[37] Current immunotherapy approaches for pancreatic cancer have taken a variety of forms to include harvest of tumor-infiltrating lymphocytes or leukapheresis of circulating T-cells for ex vivo expansion and reinfusion with or without checkpoint inhibitors or other immune mediators. In addition, some investigators have been evaluating the combination of cytotoxic chemotherapy with checkpoint inhibition with or without a CD40 agonist. Other strategies include integration of cytotoxic checkpoint inhibitors and other immune mediators, pancreatic cancer vaccines, adoptive T-cell transfer, monoclonal antibodies acting at the immune checkpoint level, cytokines, and regulatory T-cell depletion. None of these strategies has a proven benefit thus far and more rigorous preclinical models will be required to accelerate progress with immunotherapy in pancreatic cancer.

MD Anderson Approach to Metastatic Disease

Metastatic pancreatic cancer is characterized by anorexia, cachexia, and pain. Therefore, palliation must always be a major focus for this group of patients and is facilitated by a multidisciplinary approach. Symptomatic relief of biliary obstruction and pain should be addressed before the consideration of systemic therapy. If pain is not well controlled with oral or transdermal opioids, or if these agents are poorly tolerated, patients should undergo an evaluation with an interventional pain specialist to consider celiac or splanchnic plexus neurolysis. In addition to aggressive pain control efforts, other supportive measures should be considered, including appetite enhancers, antidepressants, and central nervous system stimulants.

Biliary obstruction should be relieved by nonsurgical means whenever possible, and we advocate the insertion of expandable metal stents rather than polyethylene biliary stents. Occasionally, percutaneous biliary drainage may be required in the setting of extrahepatic biliary obstruction.

When a patient develops gastric outlet obstruction, we try to estimate the prognosis at that juncture. If life expectancy is greater than 12 weeks, surgical intervention for definitive gastric bypass is considered. For patients with end-stage metastatic disease, the use of duodenal stents is encouraged. For patients with intractable symptomatic ascites, it is important to realize that this may not be caused by carcinomatosis and frequently results from PV or SMV thrombosis. Moderate ascites secondary to portal hypertension may respond to diuretics, including spironolactone, whereas large volume ascites, malignant or otherwise requires repeated paracentesis or an indwelling peritoneal catheter for symptomatic relief. Gastroparesis is another commonly occurring problem that requires promotility agents and dietary and behavioral modification.

MDACC Approach to Systemic Therapy for Advanced Pancreatic Cancer

Systemic therapy for metastatic disease should be actively discouraged in patients with poor PS (ECOG >2) or significant metastatic burden. End-of-life discussions are appropriate at the time of diagnosis. For the majority of patients with newly diagnosed disease, we recommend germline genetic testing and, if feasible, molecular profiling is obtained whenever sufficient tissue is available. When possible, patients with good PS should be treated with systemic therapy in a clinical trial. Off protocol, patients with ECOG PS 0–1 and no contraindications to treatment with FOLFIRINOX are generally advised to receive this regimen as first-line therapy. After progression on FOLFIRINOX, gemcitabine-based regimens like gemcitabine plus nab-paclitaxel are considered. After gemcitabine and nab-paclitaxel, FOLFOX or single-agent capecitabine are preferred. For patients with ECOG PS 1–2, we generally favor gemcitabine and nab-paclitaxel. At the time of disease progression, for those with preserved PS, treatment in a clinical trial is preferred. When this is not available or feasible, treatment with infusional 5-FU and liposomal irinotecan, FOLFIRI, or FOLFOX are all reasonable.

For patients who are not candidates for multiagent chemotherapy, gemcitabine as first-line therapy can be recommended with careful monitoring. At MDACC, our off-protocol approach is to deliver FDR gemcitabine (600–750 mg/m^2) at a rate of 10 mg/m^2 per minute, weekly. Adding erlotinib yields marginal benefit and is not as relevant with the availability of more modern therapy. Nevertheless, when gemcitabine monotherapy is advised, the addition of erlotinib is not unreasonable.

When an objective response or stable disease is observed, chemotherapy is usually continued until there is radiographic or clinical evidence of disease progression, with restaging studies generally performed every 8 to 12 weeks. However, when FOLFIRINOX is being delivered, shifting to a period of maintenance therapy with FOLFIRI or capecitabine may avoid functional impairment from progressive peripheral neuropathy. Gemcitabine-platinum doublets are now generally offered only to patients with BRCA-associated pancreatic cancer.

Summary: Metastatic Disease

Clinically meaningful advances in the treatment of metastatic pancreatic cancer have occurred in the past 5 years. These developments have changed the treatment paradigm for patients with advanced disease, and more patients are experiencing modest improvements in survival and quality of life. Continued efforts to enroll patients with advanced disease into well-designed clinical trials should remain a high priority for oncologists. Finally, attention to palliation should always be a major focus of clinical care.

MD ANDERSON PRACTICE TIPS

- When there are no contraindications to intravenous contrast dye, we prefer high-quality multidetector CT imaging for diagnosis and staging of pancreatic cancer, because it can classify pancreatic cancers as resectable, borderline resectable, locally advanced, or metastatic. Furthermore, our clinicians are comfortable reviewing CT imaging over magnetic resonance imaging and generally rely on CT imaging for restaging purposes.
- On presentation, we recommend germline genetic testing of patients diagnosed with pancreatic cancer, especially those with a family history of breast, ovarian, pancreas, or colon cancer.
- When choosing a site to biopsy for tissue confirmation, we prefer to biopsy a metastatic site versus the tumor in the pancreas. This generally provides more tissue for molecular profiling compared with tissue obtained from fine-needle aspiration of the pancreatic primary.
- Whenever feasible, if insufficient tumor tissue is available for interrogation, we will obtain circulating tumor DNA assay (liquid biopsy) as an alternative to mutational profiling.
- At MDACC, serum tumor markers (most commonly CA 19-9) are routinely followed every 2 to 4 weeks as surrogate markers of response or resistance to therapy. In some patients in whom CA 19-9 levels are undetectable or normal, we have found serum carcinoembryonic antigen or CA 125 levels may occasionally serve as alternative markers.
- Outside a clinical trial, we deliver FOLFIRINOX and gemcitabine/nab-paclitaxel every 2 weeks.
- For patients with localized disease, presentation to our multidisciplinary pancreatic cancer conference is encouraged for input from specialists in medical, surgical, and radiation oncology. Similarly, for patients with limited metastatic disease, input from specialists in radiation oncology, interventional radiology, and surgical oncology is obtained in conference format.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin.* 2019;69(1):7-34.
2. American Cancer Society. Cancer Facts & Figures 2020. American Cancer Society; 2020.
3. Konner J, O'Reilly E. Pancreatic cancer: epidemiology, genetics, and approaches to screening. *Oncology (Williston Park).* 2002;16(12):1615-1622, 31-32; discussion 32-33, 37-38.
4. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68(6):394-424.
5. Liu L, Zhang J, Deapen D, et al. Differences in pancreatic cancer incidence rates and temporal trends across Asian subpopulations in California (1988-2015). *Pancreas.* 2019;48(7):931-933.
6. Bannon SA, Montiel MF, Goldstein JB, et al. High prevalence of hereditary cancer syndromes and outcomes in adults with early-onset pancreatic cancer. *Cancer Prev Res (Phila).* 2018;11(11):679-686.
7. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology.* 2013;144(6):1252-1261.
8. Singhi AD, Koay EJ, Chari ST, Maitra A. Early detection of pancreatic cancer: opportunities and challenges. *Gastroenterology.* 2019;156(7):2024-2040.
9. Maitra A, Sharma A, Brand RE, et al. A prospective study to establish a new-onset diabetes cohort: from the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer. *Pancreas.* 2018;47(10):1244-1248.
10. Aune D, Greenwood DC, Chan DS, et al. Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. *Ann Oncol.* 2012;23(4):843-852.
11. Cascetta P, Cavaliere A, Piro G, et al. Pancreatic cancer and obesity: molecular mechanisms of cell transformation and chemoresistance. *Int J Mol Sci.* 2018;19(11).3331
12. Abbruzzese JL, Andersen DK, Borrebaeck CAK, et al. The interface of pancreatic cancer with diabetes, obesity, and inflammation: research gaps and opportunities: summary of a National Institute of Diabetes and Digestive and Kidney Diseases Workshop. *Pancreas.* 2018;47(5):516-525.
13. Gomez-Chou SB, Swidnicka-Siergiejko AK, Badi N, et al. Lipocalin-2 promotes pancreatic ductal adenocarcinoma by regulating inflammation in the tumor microenvironment. *Cancer Res.* 2017;77(10):2647-2660.
14. Li D, Day RS, Bondy ML, et al. Dietary mutagen exposure and risk of pancreatic cancer. *Cancer Epidemiol Biomarkers Prev.* 2007;16(4):655-661.
15. Zhan W, Shelton CA, Greer PJ, et al. Germline variants and risk for pancreatic cancer: a systematic review and emerging concepts. *Pancreas.* 2018;47(8):924-936.
16. Petersen GM. Familial pancreatic cancer. *Semin Oncol.* 2016;43(5):548-553.
17. Wood LD, Yurgelun MB, Goggins MG. Genetics of familial and sporadic pancreatic cancer. *Gastroenterology.* 2019;156(7):2041-2055.
18. Daly MB, Pilarski R, Yurgelun MB, et al. NCCN Guidelines Insights: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 1.2020. *J Natl Compr Canc Netw.* 2020;18(4):380-391.
19. Stoffel EM, McKernin SE, Brand R, et al. Evaluating susceptibility to pancreatic cancer: ASCO Provisional Clinical Opinion. *J Clin Oncol.* 2019;37(2):153-164.
20. Golan T, Hammel P, Reni M, Van Cutsem E, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. *N Engl J Med.* 2019;381(4):317-327.
21. US Food and Drug Administration. FDA approves olaparib for gBRCAm metastatic pancreatic adenocarcinoma [press release]. December 30, 2019. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-olaparib-gbrcam-metastatic-pancreatic-adenocarcinoma
22. Waddell N, Pajic M, Patch AM, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. *Nature.* 2015;518(7540):495-501.
23. Biankin AV, Waddell N, Kassahn KS, et al. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. *Nature.* 2012;491(7424):399-405.
24. Cancer Genome Atlas Research Network. Integrated genomic characterization of pancreatic ductal adenocarcinoma. *Cancer Cell.* 2017;32(2):185-203.
25. Collisson EA, Bailey P, Chang DK, Biankin AV. Molecular subtypes of pancreatic cancer. *Nat Rev Gastroenterol Hepatol.* 2019;16(4):207-220.
26. Pishvaian MJ, Bender RJ, Halverson D, et al. Molecular profiling of patients with pancreatic cancer: initial results from the Know Your Tumor initiative. *Clin Cancer Res.* 2018;24(20):5018-5027.
27. Aguirre AJ, Nowak JA, Camarda ND, et al. Real-time genomic characterization of advanced pancreatic cancer to enable precision medicine. *Cancer Discov.* 2018;8(9):1096-1111.
28. Li S, Balmain A, Counter CM. A model for RAS mutation patterns in cancers: finding the sweet spot. *Nat Rev Cancer.* 2018;18(12):767-777.
29. Singhi AD, George B, Greenbowe JR, et al. Real-time targeted genome profile analysis of pancreatic ductal adenocarcinomas identifies genetic alterations that might be targeted with existing drugs or used as biomarkers. *Gastroenterology.* 2019;156(8):2242-53 e4.
30. Singhi AD, Ali SM, Lacy J, et al. Identification of targetable ALK rearrangements in pancreatic ductal adenocarcinoma. *J Natl Compr Canc Netw.* 2017;15(5):555-562.
31. Jones MR, Williamson LM, Topham JT, et al. NRG1 gene fusions are recurrent, clinically actionable gene rearrangements in KRAS wild-type pancreatic ductal adenocarcinoma. *Clin Cancer Res.* 2019;25(15):4674-4681.
32. Heining C, Horak P, Uhrig S, et al. NRG1 fusions in KRAS wild-type pancreatic cancer. *Cancer Discov.* 2018;8(9):1087-1095.
33. Solomon JP, Hechtman JF. Detection of NTRK fusions: merits and limitations of current diagnostic platforms. *Cancer Res.* 2019;79(13):3163-3168.
34. Jonna S, Feldman RA, Swensen J, et al. Detection of NRG1 gene fusions in solid tumors. *Clin Cancer Res.* 2019;25(16):4966-4972.
35. Schutte M, Hruban RH, Hedrick L, et al. DPC4 gene in various tumor types. *Cancer Res.* 1996;56(11):2527-2530.
36. Humphris JL, Patch AM, Nones K, et al. Hypermutation in pancreatic cancer. *Gastroenterology.* 2017;152(1):68-74, e2.
37. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. *J Clin Oncol.* 2020;38(1):1-10.
38. Wang W, Friedland SC, Guo B, et al. ARID1A, a SWI/SNF subunit, is critical to acinar cell homeostasis and regeneration and is a barrier to transformation and epithelial-mesenchymal transition in the pancreas. *Gut.* 2019;68(7):1245-1258.
39. Watanabe S, Shimada S, Akiyama Y, et al. Loss of KDM6A characterizes a poor prognostic subtype of human pancreatic cancer and potentiates HDAC inhibitor lethality. *Int J Cancer.* 2019;145(1):192-205.
40. Goswami S, Chen Y, Anandhan S, et al. ARID1A mutation plus CXCL13 expression act as combinatorial biomarkers to predict responses to immune checkpoint therapy in mUCC. *Sci Transl Med.* 2020;12(548).
41. Shen J, Ju Z, Zhao W, et al. ARID1A deficiency promotes mutability and potentiates therapeutic antitumor

immunity unleashed by immune checkpoint blockade. *Nat Med.* 2018;24(5):556-562.
42. Le DT, Wang-Gillam A, Picozzi V, et al. Safety and survival with GVAX pancreas prime and *Listeria monocytogenes*-expressing mesothelin (CRS-207) boost vaccines for metastatic pancreatic cancer. *J Clin Oncol.* 2015;33(12):1325-1333.
43. Brunton H, Caligiuri G, Cunningham R, et al. HNF4A and GATA6 loss reveals therapeutically actionable subtypes in pancreatic cancer. *Cell Rep.* 2020;31(6):107625.
44. O'Kane GM, Grunwald BT, Jang GH, et al. GATA6 expression distinguishes classical and basal-like subtypes in advanced pancreatic cancer. *Clin Cancer Res.* 2020;26(18):4901-4910.
45. Aung KL, Fischer SE, Denroche RE, et al. Genomics-driven precision medicine for advanced pancreatic cancer: early results from the COMPASS Trial. *Clin Cancer Res.* 2018;24(6):1344-1354.
46. Hosein AN, Brekken RA, Maitra A. Pancreatic cancer stroma: an update on therapeutic targeting strategies. *Nat Rev Gastroenterol Hepatol.* 2020;17(8):487-505.
47. Ho WJ, Jaffee EM, Zheng L. The tumour microenvironment in pancreatic cancer—clinical challenges and opportunities. *Nat Rev Clin Oncol.* 2020;17(9):527-540.
48. Helms E, Onate MK, Sherman MH. Fibroblast heterogeneity in the pancreatic tumor microenvironment. *Cancer Discov.* 2020;10(5):648-656.
49. Biffi G, Tuveson DA. Diversity and biology of cancer-associated fibroblasts. *Physiol Rev.* 2021;101(1):147-176.
50. Elyada E, Bolisetty M, Laise P, et al. Cross-species single-cell analysis of pancreatic ductal adenocarcinoma reveals antigen-presenting cancer-associated fibroblasts. *Cancer Discov.* 2019;9(8):1102-1123.
51. Gu J, Saiyin H, Fu D, Li J. Stroma—a double-edged sword in pancreatic cancer: a lesson from targeting stroma in pancreatic cancer with Hedgehog signaling inhibitors. *Pancreas.* 2018;47(4):382-389.
52. DuFort CC, DelGiorno KE, Hingorani SR. Mounting pressure in the microenvironment: fluids, solids, and cells in pancreatic ductal adenocarcinoma. *Gastroenterology.* 2016;150(7):1545-1557, e2.
53. Provenzano PP, Cuevas C, Chang AE, et al. Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. *Cancer Cell.* 2012;21(3):418-429.
54. Jacobetz MA, Chan DS, Neesse A, et al. Hyaluronan impairs vascular function and drug delivery in a mouse model of pancreatic cancer. *Gut.* 2013;62(1):112-120.
55. Hruban RH, Gaida MM, Thompson E, et al. Why is pancreatic cancer so deadly? The pathologist's view. *J Pathol.* 2019;248(2):131-141.
56. Basturk O, Hong SM, Wood LD, et al. A revised classification system and recommendations from the Baltimore Consensus Meeting for Neoplastic Precursor Lesions in the Pancreas. *Am J Surg Pathol.* 2015;39(12):1730-1741.
57. Matthaei H, Schulick RD, Hruban RH, Maitra A. Cystic precursors to invasive pancreatic cancer. *Nat Rev Gastroenterol Hepatol.* 2011;8(3):141-150.
58. Hruban RH, Klimstra DS. Adenocarcinoma of the pancreas. *Semin Diagn Pathol.* 2014;31(6):443-451.
59. Mujica VR, Barkin JS, Go VL. Acute pancreatitis secondary to pancreatic carcinoma. Study Group Participants. *Pancreas.* 2000;21(4):329-332.
60. Rashleigh-Belcher HJ, Russell RC, Lees WR. Cutaneous seeding of pancreatic carcinoma by fine-needle aspiration biopsy. *Br J Radiol.* 1986;59(698):182-183.
61. Tempero MA. NCCN Guidelines Updates: Pancreatic Cancer. *J Natl Compr Canc Netw.* 2019;17(5.5):603-605.
62. Somers I, Bipat S. Contrast-enhanced CT in determining resectability in patients with pancreatic carcinoma: a meta-analysis of the positive predictive values of CT. *Eur Radiol.* 2017;27(8):3408-3435.
63. Kalady MF, Clary BM, Clark LA, et al. Clinical utility of positron emission tomography in the diagnosis and management of periampullary neoplasms. *Ann Surg Oncol.* 2002;9(8):799-806.
64. Pleskow DK, Berger HJ, Gyves J, et al. Evaluation of a serologic marker, CA19-9, in the diagnosis of pancreatic cancer. *Ann Intern Med.* 1989;110(9):704-709.
65. Katz MHG, Varadhachary GR, Fleming JB, et al. Serum CA 19-9 as a marker of resectability and survival in patients with potentially resectable pancreatic cancer treated with neoadjuvant chemoradiation. *Ann Surg Oncol.* 2010;17(7):1794-1801.
66. Tzeng C-WD, Balachandran A, Ahmad M, et al. Serum carbohydrate antigen 19-9 represents a marker of response to neoadjuvant therapy in patients with borderline resectable pancreatic cancer. *HPB (Oxford).* 2014;16(5):430-438.
67. van den Bosch RP, van Eijck CH, Mulder PG, Jeekel J. Serum CA19-9 determination in the management of pancreatic cancer. *Hepatogastroenterology.* 1996;43(9):710-713.
68. Ko AH, Hwang J, Venook AP, et al. Serum CA19-9 response as a surrogate for clinical outcome in patients receiving fixed-dose rate gemcitabine for advanced pancreatic cancer. *Br J Cancer.* 2005;93(2):195-199.
69. Tempero MA, Uchida E, Takasaki H, et al. Relationship of carbohydrate antigen 19-9 and Lewis antigens in pancreatic cancer. *Cancer Res.* 1987;47(20):5501-5503.
70. Whipple AO. The rationale of radical surgery for cancer of the pancreas and ampullary region. *Ann Surg.* 1941;114(4):612-615.
71. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. *Arch Surg.* 1985;120(8):899-903.
72. Smeenk HG, van Eijck CH, Hop WC, et al. Long-term survival and metastatic pattern of pancreatic and periampullary cancer after adjuvant chemoradiation or observation: long-term results of EORTC trial 40891. *Ann Surg.* 2007;246(5):734-740.
73. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med.* 2004;350(12):1200-1210.
74. Javle M, Hsueh CT. Updates in gastrointestinal oncology—insights from the 2008 44th Annual Meeting of the American Society of Clinical Oncology. *J Hematol Oncol.* 2009;2:9.
75. Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *Lancet.* 2017;389(10073):1011-1024.
76. Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. *N Engl J Med.* 2018;379(25):2395-2406.
77. Tempero M, Reni M, Riess H, et al. APACT: phase III, multicenter, international, open-label, randomized trial of adjuvant nab-paclitaxel plus gemcitabine (nab-P/G) vs gemcitabine (G) for surgically resected pancreatic adenocarcinoma. *J Clin Oncol.* 2019;37(suppl 15):4000.
78. Merkow RP, Bilimoria KY, Tomlinson JS, et al. Postoperative complications reduce adjuvant chemotherapy use in resectable pancreatic cancer. *Ann Surg.* 2014;260(2):372-377.
79. Swanson RS, Pezzi CM, Mallin K, et al. The 90-day mortality after pancreatectomy for cancer is double the 30-day mortality: more than 20,000 resections from the national cancer data base. *Ann Surg Oncol.* 2014;21(13):4059-4067.
80. Ghaneh P, Kleeff J, Halloran CM, et al. The impact of positive resection margins on survival and recurrence following resection and adjuvant chemotherapy for pancreatic ductal adenocarcinoma. *Ann Surg.* 2019;269(3):520-529.
81. Strobel O, Hank T, Hinz U, et al. Pancreatic cancer surgery: the new R-status counts. *Ann Surg.* 2017;265(3):565-573.
82. Liu L, Katz MH, Lee SM, et al. Superior mesenteric artery margin of posttherapy pancreaticoduodenectomy and prognosis

in patients with pancreatic ductal adenocarcinoma. *Am J Surg Pathol.* 2015;39(10):1395-1403.
83. Park S, Kim SC, Hong SM, et al. Postoperative radiotherapy for pancreatic cancer with microscopically-positive resection margin. *Anticancer Res.* 2017;37(2):755-764.
84. Suss NR, Talamonti MS, Bryan DS, et al. Does adjuvant radiation provide any survival benefit after an R1 resections for pancreatic cancer? *Surgery.* 2018;163(5):1047-1052.
85. de Geus SWL, Kasumova GG, Sachs TE, et al. Neoadjuvant therapy affects margins and margins affect all: perioperative and survival outcomes in resected pancreatic adenocarcinoma. *HPB (Oxford).* 2018;20(6):573-581.
86. Valle JW, Palmer D, Jackson R, et al. Optimal duration and timing of adjuvant chemotherapy after definitive surgery for ductal adenocarcinoma of the pancreas: ongoing lessons from the ESPAC-3 study. *J Clin Oncol.* 2014;32(6):504-512.
87. Parker NH, Ngo-Huang A, Lee RE, et al. Physical activity and exercise during preoperative pancreatic cancer treatment. *Support Care Cancer.* 2019;27(6):2275-2284.
88. Evans DB, Varadhachary GR, Crane CH, et al. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. *J Clin Oncol.* 2008;26(21):3496-3502.
89. Pisters PW, Wolff RA, Janjan NA, et al. Preoperative paclitaxel and concurrent rapid-fractionation radiation for resectable pancreatic adenocarcinoma: toxicities, histologic response rates, and event-free outcome. *J Clin Oncol.* 2002;20(10):2537-2544.
90. Varadhachary GR, Wolff RA, Crane CH, et al. Preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocarcinoma of the pancreatic head. *J Clin Oncol.* 2008;26(21):3487-3495.
91. Pisters PW, Abbruzzese JL, Janjan NA, et al. Rapid-fractionation preoperative chemoradiation, pancreaticoduodenectomy, and intraoperative radiation therapy for resectable pancreatic adenocarcinoma. *J Clin Oncol.* 1998;16(12):3843-3850.
92. Crane CH, Ellis LM, Abbruzzese JL, et al. Phase I trial evaluating the safety of bevacizumab with concurrent radiotherapy and capecitabine in locally advanced pancreatic cancer. *J Clin Oncol.* 2006;24(7):1145-1151.
93. Cloyd JM, Katz MH, Prakash L, et al. Preoperative therapy and pancreatoduodenectomy for pancreatic ductal adenocarcinoma: a 25-year single-institution experience. *J Gastrointest Surg.* 2017;21(1):164-174.
94. Roland CL, Yang AD, Katz MH, et al. Neoadjuvant therapy is associated with a reduced lymph node ratio in patients with potentially resectable pancreatic cancer. *Ann Surg Oncol.* 2015;22(4):1168-1175.
95. Youngwirth LM, Nussbaum DP, Thomas S, et al. Nationwide trends and outcomes associated with neoadjuvant therapy in pancreatic cancer: an analysis of 18,243 patients. *J Surg Oncol.* 2017;116(2):127-132.
96. Mokdad AA, Minter RM, Zhu H, et al. Neoadjuvant therapy followed by resection versus upfront resection for resectable pancreatic cancer: a propensity score matched analysis. *J Clin Oncol.* 2017;35(5):515-522.
97. Versteijne E, Vogel JA, Besselink MG, et al. Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer. *Br J Surg.* 2018;105(8):946-958.
98. Versteijne E, Suker M, Groothuis K, et al. Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer: results of the Dutch randomized phase III PREOPANC Trial. *J Clin Oncol.* 2020;38(16):1763-1773.
99. Varadhachary GR, Tamm EP, Abbruzzese JL, et al. Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy. *Ann Surg Oncol.* 2006;13(8):1035-1046.
100. Katz MH, Shi Q, Ahmad SA, et al. Preoperative modified FOLFIRINOX treatment followed by capecitabine-based chemoradiation for borderline resectable pancreatic cancer: Alliance for Clinical Trials in Oncology Trial A021101. *JAMA Surg.* 2016;151(8):e161137.
101. Chawla A, Molina G, Pak LM, et al. Neoadjuvant therapy is associated with improved survival in borderline-resectable pancreatic cancer. *Ann Surg Oncol.* 2020;27(4):1191-1200.
102. Dhir M, Zenati MS, Hamad A, et al. FOLFIRINOX versus gemcitabine/nab-paclitaxel for neoadjuvant treatment of resectable and borderline resectable pancreatic head adenocarcinoma. *Ann Surg Oncol.* 2018;25(7):1896-1903.
103. Macedo FI, Ryon E, Maithel SK, et al. Survival outcomes associated with clinical and pathological response following neoadjuvant FOLFIRINOX or gemcitabine/nab-paclitaxel chemotherapy in resected pancreatic cancer. *Ann Surg.* 2019;270(3):400-413.
104. Pietrasz D, Turrini O, Vendrely V, et al. How does chemoradiotherapy following induction FOLFIRINOX improve the results in resected borderline or locally advanced pancreatic adenocarcinoma? An AGEO-FRENCH Multicentric Cohort. *Ann Surg Oncol.* 2019;26(1):109-117.
105. Katz MHG, Ou F-S, Herman JM, et al. Alliance for clinical trials in oncology (ALLIANCE) trial A021501: preoperative extended chemotherapy vs. chemotherapy plus hypofractionated radiation therapy for borderline resectable adenocarcinoma of the head of the pancreas. *BMC Cancer.* 2017;17(1):505.
106. Vreeland TJ, McAllister F, Javadi S, et al. Benefit of gemcitabine/nab-paclitaxel rescue of patients with borderline resectable or locally advanced pancreatic adenocarcinoma after early failure of FOLFIRINOX. *Pancreas.* 2019;48(6):837-843.
107. Gulhati P, Prakash L, Katz MHG, et al. First-line gemcitabine and nab-paclitaxel chemotherapy for localized pancreatic ductal adenocarcinoma. *Ann Surg Oncol.* 2019;26(2):619-627.
108. Krishnan S, Rana V, Janjan NA, et al. Induction chemotherapy selects patients with locally advanced, unresectable pancreatic cancer for optimal benefit from consolidative chemoradiation therapy. *Cancer.* 2007;110(1):47-55.
109. Ko AH, Quivey JM, Venook AP, et al. A phase II study of fixed-dose rate gemcitabine plus low-dose cisplatin followed by consolidative chemoradiation for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys.* 2007;68(3):809-816.
110. Huguet F, Andre T, Hammel P, et al. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. *J Clin Oncol.* 2007;25(3):326-331.
111. Hammel P, Huguet F, van Laethem JL, et al. Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: The LAP07 Randomized Clinical Trial. *JAMA.* 2016;315(17):1844-1853.
112. Gemenetzis G, Groot VP, Blair AB, et al. Survival in locally advanced pancreatic cancer after neoadjuvant therapy and surgical resection. *Ann Surg.* 2019;270(2):340-347.
113. Murphy JE, Wo JY, Ryan DP, et al. Total neoadjuvant therapy with FOLFIRINOX in combination with losartan followed by chemoradiotherapy for locally advanced pancreatic cancer: a phase 2 clinical trial. *JAMA Oncol.* 2019;5(7):1020-1027.
114. Mukherjee S, Hurt CN, Bridgewater J, et al. Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial. *Lancet Oncol.* 2013;14(4):317-326.
115. Hurt CN, Falk S, Crosby T, et al. Long-term results and recurrence patterns from SCALOP: a phase II randomised trial of gemcitabine- or capecitabine-based chemoradiation for locally advanced pancreatic cancer. *Br J Cancer.* 2017;116(10):1264-1270.

116. Ruarus AH, Vroomen L, Geboers B, et al. Percutaneous Irreversible Electroporation in Locally Advanced and Recurrent Pancreatic Cancer (PANFIRE-2): a multicenter, prospective, single-arm, phase II study. *Radiology.* 2020;294(1):212-220.
117. Burris HA 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol.* 1997;15(6):2403-2413.
118. Heinemann V, Boeck S, Hinke A, Labianca R, et al. Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. *BMC Cancer.* 2008;8:82.
119. Kulke MH, Tempero MA, Niedzwiecki D, et al. Randomized phase II study of gemcitabine administered at a fixed dose rate or in combination with cisplatin, docetaxel, or irinotecan in patients with metastatic pancreatic cancer: CALGB 89904. *J Clin Oncol.* 2009;27(33):5506-5512.
120. Heinemann V, Quietzsch D, Gieseler F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. *J Clin Oncol.* 2006;24(24):3946-3952.
121. Heinemann V, Labianca R, Hinke A, Louvet C. Increased survival using platinum analog combined with gemcitabine as compared to single-agent gemcitabine in advanced pancreatic cancer: pooled analysis of two randomized trials, the GERCOR/GISCAD intergroup study and a German multicenter study. *Ann Oncol.* 2007;18(10):1652-1659.
122. Rocha Lima CM, Green MR, Rotche R, et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. *J Clin Oncol.* 2004;22(18):3776-3783.
123. Poplin E, Feng Y, Berlin J, et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol.* 2009;27(23):3778-3785.
124. Philip PA, Benedetti J, Corless CL, et al. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: Southwest Oncology Group-directed intergroup trial S0205. *J Clin Oncol.* 2010;28(22):3605-3610.
125. Philip PA, Goldman B, Ramanathan RK, et al. Dual blockade of epidermal growth factor receptor and insulin-like growth factor receptor-1 signaling in metastatic pancreatic cancer: phase Ib and randomized phase II trial of gemcitabine, erlotinib, and cixutumumab versus gemcitabine plus erlotinib (SWOG S0727). *Cancer.* 2014;120(19):2980-2985.
126. Kindler HL, Friberg G, Singh DA, et al. Phase II trial of bevacizumab plus gemcitabine in patients with advanced pancreatic cancer. *J Clin Oncol.* 2005;23(31):8033-8040.
127. Kindler HL, Karrison TG, Gandara DR, et al. Multicenter, double-blind, placebo-controlled, randomized phase II trial of gemcitabine/cisplatin plus bevacizumab or placebo in patients with malignant mesothelioma. *J Clin Oncol.* 2012;30(20):2509-2515.
128. Van Cutsem E, Vervenne WL, Bennouna J, et al. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. *J Clin Oncol.* 2009;27(13):2231-2237.
129. Kindler HL, Richards DA, Garbo LE, et al. A randomized, placebo-controlled phase 2 study of ganitumab (AMG 479) or conatumumab (AMG 655) in combination with gemcitabine in patients with metastatic pancreatic cancer. *Ann Oncol.* 2012;23(11):2834-2842.
130. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol.* 2007;25(15):1960-1966.
131. Cunningham D, Chau I, Stocken DD, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol.* 2009;27(33):5513-5518.
132. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med.* 2013;369(18):1691-1703.
133. Fogelman D, Sugar EA, Oliver G, et al. Family history as a marker of platinum sensitivity in pancreatic adenocarcinoma. *Cancer Chemother Pharmacol.* 2015;76(3):489-498.
134. O'Reilly EM, Lee JW, Zalupski M, et al. Randomized, multicenter, phase II trial of gemcitabine and cisplatin with or without veliparib in patients with pancreas adenocarcinoma and a germline BRCA/PALB2 mutation. *J Clin Oncol.* 2020;38(13):1378-1388.
135. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med.* 2011;364(19):1817-1825.
136. Jameson GS, Borazanci E, Babiker HM, et al. Response rate following albumin-bound paclitaxel plus gemcitabine plus cisplatin treatment among patients with advanced pancreatic cancer: a phase 1b/2 pilot clinical trial. *JAMA Oncol.* 2019;6(1):125-132.
137. Wang-Gillam A, Li CP, Bodoky G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. *Lancet.* 2016;387(10018):545-557.
138. Mita N, Iwashita T, Uemura S, et al. Second-line gemcitabine plus nab-paclitaxel for patients with unresectable advanced pancreatic cancer after first-line FOLFIRINOX Failure. *J Clin Med.* 2019;8(6):761.
139. Jones S, Hruban RH, Kamiyama M, et al. Exomic sequencing identifies PALB2 as a pancreatic cancer susceptibility gene. *Science.* 2009;324(5924):217.
140. Perkhofer L, Schmitt A, Romero Carrasco MC, et al. ATM deficiency generating genomic instability sensitizes pancreatic ductal adenocarcinoma cells to therapy-induced DNA damage. *Cancer Res.* 2017;77(20):5576-5590.
141. Kobashigawa S, Morikawa K, Mori H, Kashino G. Gemcitabine induces radiosensitization through inhibition of RAD51-dependent repair for DNA double-strand breaks. *Anticancer Res.* 2015;35(5):2731-2738.
142. Smith J, Tho LM, Xu N, Gillespie DA. The ATM-Chk2 and ATR-Chk1 pathways in DNA damage signaling and cancer. *Adv Cancer Res*. 2010;108:73-112.
143. Holter S, Borgida A, Dodd A, et al. Germline BRCA mutations in a large clinic-based cohort of patients with pancreatic adenocarcinoma. *J Clin Oncol.* 2015;33(28):3124-3129.
144. Golan T, Kindler HL, Park JO, et al. Geographic and ethnic heterogeneity in the BRCA1/2 pre-screening population for the randomized phase III POLO study of olaparib maintenance in metastatic pancreatic cancer (mPC). *J Clin Oncol.* 2018;36(suppl 15):4115.
145. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol.* 2015;33(3):244-250.
146. Shroff RT, Hendifar A, McWilliams RR, et al. Rucaparib monotherapy in patients with pancreatic cancer and a known deleterious BRCA mutation. *JCO Precis Oncol*. 2018;2018(2):1-15.
147. Pishvaian MJ, Garrido-Laguna I, Liu SV, et al. Entrectinib in TRK and ROS1 fusion-positive metastatic pancreatic cancer. *JCO Precis Oncol*. 2018(2):1-7.
148. US Food and Drug Administration. FDA approves entrectinib for NTRK solid tumors and ROS-1 NSCLC. 2019. https://

www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-entrectinib-ntrk-solid-tumors-and-ros-1-nsclc
149. Olive KP, Jacobetz MA, Davidson CJ, et al. Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. *Science*. 2009;324(5933):1457-1461.
150. Ozdemir BC, Pentcheva-Hoang T, Carstens JL, et al. Depletion of carcinoma-associated fibroblasts and fibrosis induces immunosuppression and accelerates pancreas cancer with reduced survival. *Cancer Cell.* 2014;25(6):719-734.
151. Rhim AD, Oberstein PE, Thomas DH, et al. Stromal elements act to restrain, rather than support, pancreatic ductal adenocarcinoma. *Cancer Cell.* 2014;25(6):735-747.
152. Van Cutsem E, Tempero MA, Sigal D, et al. Randomized phase III trial of pegvorhyaluronidase alfa with nab-paclitaxel plus gemcitabine for patients with hyaluronan-high metastatic pancreatic adenocarcinoma. *J Clin Oncol.* 2020;38(27):3185-3194.
153. Ramanathan RK, McDonough SL, Philip PA, et al. Phase IB/II randomized study of FOLFIRINOX plus pegylated recombinant human hyaluronidase versus FOLFIRINOX alone in patients with metastatic pancreatic adenocarcinoma: SWOG S1313. *J Clin Oncol.* 2019;37(13):1062-1069.
154. Sideras K, Braat H, Kwekkeboom J, et al. Role of the immune system in pancreatic cancer progression and immune modulating treatment strategies. *Cancer Treat Rev.* 2014;40(4):513-522.
155. Fukunaga A, Miyamoto M, Cho Y, et al. CD8+ tumor-infiltrating lymphocytes together with CD4+ tumor-infiltrating lymphocytes and dendritic cells improve the prognosis of patients with pancreatic adenocarcinoma. *Pancreas.* 2004;28(1):e26-e31.
156. Royal RE, Levy C, Turner K, et al. Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. *J Immunother.* 2010;33(8):828-833.
157. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med.* 2012;366(26):2455-2465.

This page intentionally left blank

29 Biliary Tract Cancer

Shalini Makawita
Sunyoung Lee
Yun Shin Chun
Millicent A. Roach
Eugene J. Koay
Milind Javle

KEY CONCEPTS

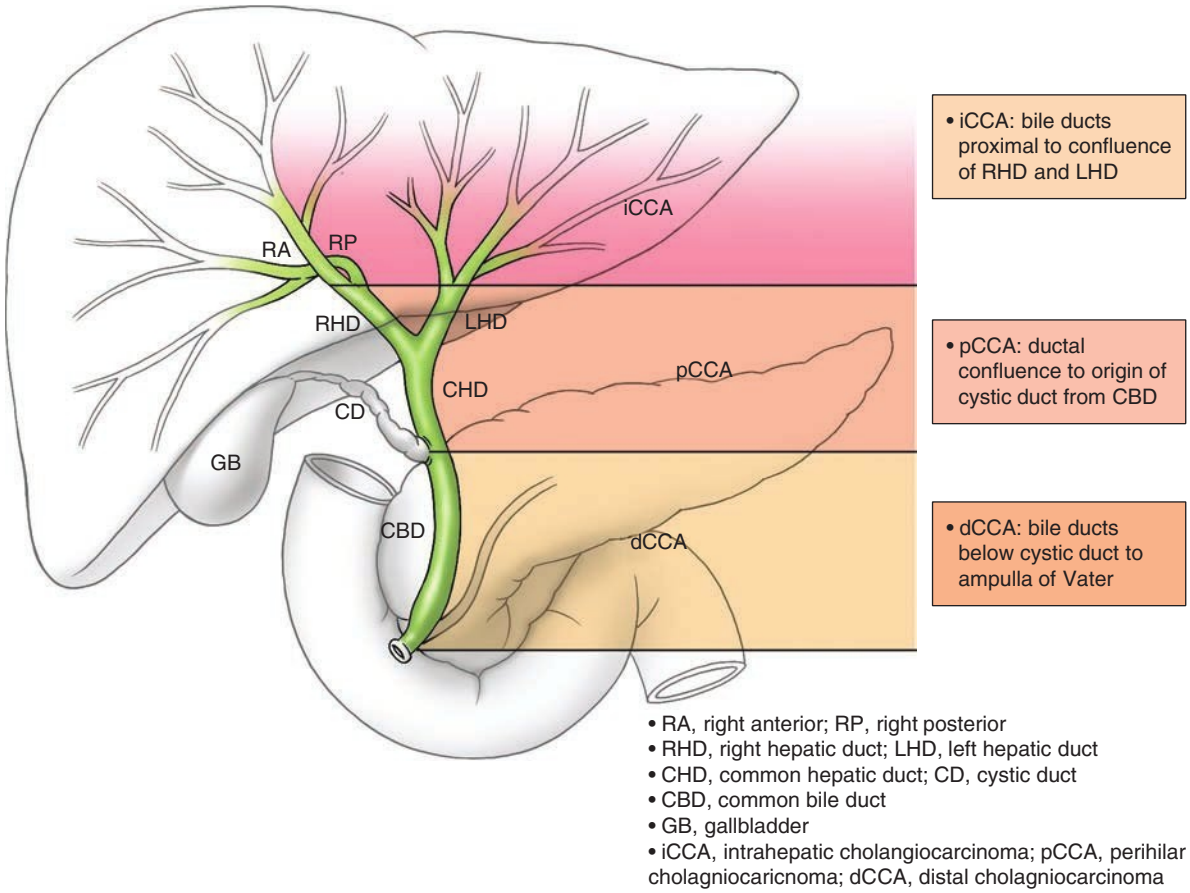
- Biliary tract cancers are rare tumors (prevalence <6/100,000 persons/year) with significant geographic variability.
- Risk factors include cholelithiasis, polyps, porcelain gallbladder, chronic inflammatory states such as inflammatory bowel disease, primary sclerosing cholangitis and nonalcoholic steatohepatitis, genetic syndromes (Peutz-Jeghers or Gardner syndrome), and chronic infection (*Salmonella typhi* carriers, *Opisthorchis viverrine,* and *Clonorchis sinensis,* particularly in Southeast Asia, hepatitis B and C).
- Five-year overall survival rates post R0 resection range from 40% to 50%. High-risk features include positive lymph nodes/margins, vascular invasion, and multifocal disease.
- In localized disease, a multimodality approach is often used:
- In early-stage intrahepatic cholangiocarcinoma, surgical resection with nodal dissection is followed by adjuvant capecitabine or gemcitabine-cisplatin; radiation therapy is given postoperatively for positive margins.
- Neoadjuvant chemotherapy is considered for high-risk features.
- In clinical practice, combination chemotherapy (gemcitabine-cisplatin or gemcitabine-capecitabine) is used adjuvantly, particularly in node-positive disease or R1 resection.
- Systemic therapy in metastatic disease is guided largely by molecular profiling and actionable targets. *FGFR, IDH1, HER2,* and *BRAF* alterations are among the most enriched, and numerous clinical trial options are available for these patients.
- Cholangiocarcinoma has low rates of high microsatellite instability and programmed cell death ligand 1 positivity. It remains overall a "cold tumor," though methods to improve immune cell infiltration and predict responders to immunotherapy are underway.

INTRODUCTION

Biliary Tract Cancers

Biliary tract cancers include gallbladder carcinoma and cholangiocarcinoma, both of which arise from the ductal epithelium. Cholangiocarcinomas are further classified based on their anatomic site as intrahepatic, perihilar, and distal types (Fig. 29–1). Intrahepatic cholangiocarcinoma (ICC) occurs in the bile ducts proximal to the confluence of the right and left hepatic ducts. Perihilar cholangiocarcinoma includes the ductal confluence up to the origin of the cystic duct from the common bile duct, whereas distal cholangiocarcinoma includes the bile duct below the cystic duct origin to the ampulla of Vater. The incidence of these anatomic types varies—perihilar cholangiocarcinoma occurs most frequently, followed by the extrahepatic distal and intrahepatic types. Cholangiocarcinoma has been subclassified by the Liver Cancer Study Group of Japan according to the growth pattern and macroscopic appearance of the tumor into three types as mass-forming, periductal-infiltrating, and intraductal growth types.[1] The mass-forming type has an expansive pattern of growth, whereas the periductal-infiltrating type of tumor extends toward the portal pedicle. The intraductal type spreads along the mucosal layer and is associated with abundant mucin production.

At a microscopic level, cholangiocarcinoma is adenocarcinoma consisting of tubules, acini, solid nests, or trabeculae embedded within a desmoplastic stroma.[2] Other types are exceedingly rare and include



Visual Art: © 2014 The University of Texas MD Anderson Cancer Center

FIGURE 29–1 An overview of cholangiocarcinoma subtypes based on anatomic location. (Reproduced with permission ©2020 The University of Texas MD Anderson Cancer Center.)

adenosquamous and squamous carcinomas that arise in metaplastic epithelium and from liver cysts. Adenocarcinoma, particularly ICC, is radiologically indistinguishable from metastatic tumors from other sites, including those of the stomach, pancreas, lung, or breast. A pattern of immunohistochemical staining is used to distinguish cholangiocarcinoma from other tumor types. The tumor cells typically express cytokeratins AE1/AE3,7, and 19, and epithelial membrane antigen, and display a cytoplasmic positivity for carcinoembryonic antigen (CEA). The absence of a membrane staining for polyclonal CEA and hepatocyte antigen (HepPar 1) aids in distinguishing ICC from hepatocellular carcinoma (HCC) with the pseudoglandular pattern. Other important immunohistochemistry characteristics that distinguish cholangiocarcinoma from other common malignancies are depicted in Table 29–1.[3,4] Most cholangiocarcinomas, particularly the perihilar type have a high degree of desmoplasia, leading to treatment resistance.

Gallbladder malignancies are almost exclusively adenocarcinoma. Rare variants have been described, including papillary adenocarcinoma, mucinous adenocarcinoma, clear cell adenocarcinoma, and signet cell carcinoma. Aggressive histologies of the gallbladder carcinoma include small cell/high grade neuroendocrine carcinoma and squamous histology. These are discussed in detail elsewhere.[5,6]

Epidemiology

Biliary tract cancers are described as rare cancers (a prevalence of less than 6/100,000 persons per year). There is significant geographic heterogeneity in the incidence and prevalence of these cancers worldwide, likely secondary to environmental exposures and genetic susceptibilities. The peak age at diagnosis of cholangiocarcinoma is in the seventh decade of life, and there is a slightly higher incidence in males compared with females. The global incidence of cholangiocarcinoma is depicted in Table 29–2.[7,8]

Several recent studies indicate that the incidence of ICC is rising. Saha et al[9] examined the Surveillance, Epidemiology, and End Results data to assess 40-year

Table 29–1 Pattern of Immunohistochemical Staining in Cholangiocarcinoma

Positive	
AE1/AE3 (or other broad-spectrum keratins, eg, pankeratin)	Diffuse, moderate to strong staining
CK7	Diffuse, moderate to strong staining in most ICC (>90%).
CK17/CK19	Diffuse, moderate to strong staining in most ICC (>80%).
Albumin in situ hybridization (ISH)	Focal to diffuse, moderate to strong staining in most ICC (>90%).
MOC31	Focal to diffuse, moderate to strong staining in most cholangiocarcinoma.
Negative	
CK20	Negative in most ICC. Focal or multifocal, moderate staining can be seen more (<50%) in ICC that arises from large bile ducts. This mirrors the expression in hilar and ECC.
CDX2	Negative in most ICC. Focal or multifocal, weak to moderate staining can be seen (<30%).
TTF1	Negative in most ICC.
GATA3	Negative in most ICC. Focal or multifocal, weak expression can be seen (<10%). If there is diffuse, strong staining for GATA3, other carcinomas, eg, breast and bladder, would have to be excluded.
HepPar-1/arginase-1/glypican-3	Negative in most ICC. If there is robust staining, HCC or combined HCC and cholangiocarcinoma would be a consideration.
SMAD4 (DPC4)	Negative, ie, intact staining, in most ICC.
PAX8	Negative in most ICC.
ER/PR/BRST-2 (GCDFP15)	Negative in most ICC.
NKX3.1/PSA	Negative in ICC.

Table 29–2 Global Incidence Rates of Cholangiocarcinoma

Region	Age- standardized Incidence Rate/100,000 Population
Thailand — North	85
Thailand — South	5.7
China	7.6
South Korea	8.8
Japan	3.5
Germany	3
United Kingdom	2.2
United States	1.6
Australia	0.4
Canada	0.4

trends in the age-standardized incidence of ICC and extrahepatic cholangiocarcinoma (ECC) between 1973 and 2012. They reported that the incidence of ICC increased from 0.44 to 1.18 cases per 100,000 persons, representing an annual percentage change (APC) of 2.30%; this trend has accelerated during the past decade to an APC of 4.36%. In contrast, the incidence of ECC increased modestly from 0.95 to 1.02 per 100,000 persons during the 40-year period (APC, 0.14%). The incidence of cancer of unknown primary origin with histologic features potentially consistent with cholangiocarcinoma decreased by 51% between 1973 and 2012 (APC, –1.87%). Gallbladder carcinoma on the other hand has a different geographic distribution, with high incidence rates reported in South Asia, Latin America, East Asia, and Eastern Europe. The highest mortality rate of gallbladder carcinoma in the world, 35 per 100,000 inhabitants, is found in Southern Chile, which is inhabited by Mapuche Indians.[10] Countries with the top five highest age-standardized incidence rates per 100,000 for males are Bolivia (12.8%), Thailand (9.0%), Republic of Korea (8.4%), Chile (6.6%), and Nepal (6.0%). In the US, an estimated 5000 patients are diagnosed with gallbladder carcinoma annually.[11] There is a strong female predominance with two-thirds of cases and deaths occurring among women. Native American and Alaska Natives have the highest incidence and death rates in the country (3.2 cases and 1.6 deaths per 100,000 people). Gallbladder carcinoma incidence rates are decreasing among all racial and ethnic groups except non-Hispanic Blacks. The incidence rate increased 2.2% per year among non-Hispanic Black men and women in the last decade.[12]

Gallbladder Carcinoma: Risk Factors

The principal risk factor for gallbladder carcinoma is gallstone disease/cholelithiasis. The association between gallstones and cancer has been proven by case-control studies, autopsy studies, and screening surveys. However, the risk of cancer in cholelithiasis is very low at 1%, although 90% of gallbladder carcinoma cases are associated with gallstones. It has been postulated that the chronic inflammation resulting from gallstones leads to epithelial dysplasia and adenocarcinoma. Gallstone size has been correlated with cancer risk, especially with stone size smaller than 3 cm, and the vast majority are composed of cholesterol.[13] These stones are positively correlated with age, female gender, multiparity, genetic factors, high body mass index, and family history of gallstones. Gallbladder diseases like adenomyomatosis, polyps, and porcelain gallbladder are associated with a high risk of cancer.

Other conditions associated with gallbladder carcinoma include inflammatory bowel disease, including Crohn disease and ulcerative colitis, Peutz-Jeghers syndrome, multiple familial polyposis (Gardner syndrome), and anomalous pancreatobiliary junction, particularly in East Asia. Chronic infections, including *Salmonella typhi* carrier state has also been linked with gallbladder carcinoma, independent of the presence of gallstones.[14]

Cholangiocarcinoma: Risk Factors

Cholangiocarcinoma is rare in the Western world, but more common in Asia. In most cases in the West, this disease is rare, sporadic, and without an identifiable risk factor. Higher incidence in Asia is caused by a greater risk of liver fluke infections with *Opisthorchis viverrini* and *Clonorchis sinensis*, particularly in Southeast Asia. Hepatolithiasis and choledochal cysts are also more likely to be associated with cholangiocarcinoma in Asian countries.[15] Other infectious risk factors include hepatitis B in Asia and hepatitis C in the West. Other important factors include primary sclerosing cholangitis (PSC) associated with inflammatory bowel disease, cirrhosis, alcoholism, obesity, fatty liver disease, and smoking. Cirrhosis and nonalcoholic steatohepatitis are most commonly associated with ICC, whereas liver fluke infections are more likely to be associated with perihilar cholangiocarcinoma.[16]

In the Western countries, PSC is an important risk factor for cholangiocarcinoma. The annual incidence of cholangiocarcinoma in PSC is around 1%, with a reported lifetime incidence of 20%.[17] The median time from PSC diagnosis to detection of cholangiocarcinoma is relatively short, at 4 to 6 years. There are no clear predictive factors identifiable in patients with PSC that correlate with an increased risk of cancer, and there are inconsistent data regarding cirrhosis as a risk factor in this setting. Given the high risk, most guidelines recommend surveillance with annual or biennial imaging (ultrasound, magnetic resonance imaging, or magnetic resonance cholangiopancreatography) and laboratory workup including CA 19-9 levels.[18]

Genetic Epidemiology of Biliary Cancers

As discussed above, biliary cancers have unique epidemiologic trends, and considerable research has ensued to identify a genetic basis of these cancers. The largest experience in this field is a genome wide association study from Tata Memorial Hospital, in Mumbai, India.[19] The study included 1042 patients with gallbladder carcinoma and 1709 control patients and demonstrated significant single-nucleotide polymorphisms (SNPs) in the chromosomal region containing the hepatobiliary phospholipid transporter genes, *ABCB1* and *ABCB4*. A smaller Japanese genome wide association study noted that the SNP rs7504990 in the deleted in colon cancer (*DCC*) gene is associated with an increased risk of gallbladder carcinoma.[20] Other genomic variations noted in gallbladder carcinoma include variations in cytochrome P450 enzymes, some of which play a key role in estrogen metabolism, which may explain the female predominance.[21] Bile acids are important for cholesterol homeostasis and the polymorphisms of CYP7A1, which encodes for a rate-limiting step in the bile acid synthesis pathway and may lead to gallbladder carcinogenesis.[22]

It is believed that cholangiocarcinoma may be related to dysregulation of genes involved in inflammation. Genomic variation in the interleukin (IL)-6 receptor (IL-6R), rs8192284 in exon 9 of IL-6R is associated with liver fluke–related cholangiocarcinoma in Thailand. SNPs in IL-8 gene and IL-1 receptor antagonist have been associated with susceptibility to biliary tract cancers.[23] Although the above variants individually have a low risk, collectively these may be important for prediction of individual risk and for future surveillance strategies.

STAGING

Staging of biliary tract cancers requires high-quality, multiphasic computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and pelvis to evaluate the extent of primary tumor and identify metastases, particularly in the lymph nodes, liver, and peritoneum. CT of the chest, with or without contrast, should be performed to evaluate for pulmonary and lymph node metastases. For patients with biliary obstruction, high-quality cross-sectional imaging should be performed before placement of biliary

stents, which can interfere with tumor visualization. Positron emission tomography (PET)/CT may be considered when CT or MRI findings are equivocal.

Staging laparoscopy as a standalone procedure is not routinely recommended. For patients scheduled for surgical resection of biliary tract tumors, staging laparoscopy has been shown to identify an unresectable disease in 17% of patients, with a higher yield in patients with gallbladder carcinoma and elevated serum CA 19-9.[24] Therefore, diagnostic laparoscopy before open resection can be considered for patients at risk for radiologically occult metastases, particularly peritoneal implants.

The eighth edition of the American Joint Committee on Cancer Staging Manual has separate staging systems for gallbladder carcinoma, ICC, perihilar bile duct cancer, and distal bile duct cancer (Table 29–3).[25] For gallbladder carcinoma, the T category is based on the depth of invasion into the gallbladder wall and extension to surrounding structures. For ICC, tumor size, number, and vascular invasion define the T stage. The T category for perihilar cholangiocarcinoma reflects the central location of these tumors, which can invade the portal vein, hepatic artery, and contralateral bile duct and/or vasculature. For distal cholangiocarcinoma, the T stage is based on the depth of tumor invasion, measured in millimeters.

In biliary tract cancers, regional lymph nodes are defined as those in the hepatoduodenal ligament. With the exception of ICC, the N category is separated by the number of positive regional nodes, with N1 defined as one to three regional nodes and N2 as four or more regional nodes. M1 disease includes distant lymph node metastases, including aortocaval and celiac lymph nodes.

SURGERY FOR BILIARY TRACT CANCERS

The goals of surgery are to evaluate for radiologically occult distant metastases which contraindicate surgery, resect the primary tumor with negative margins, and perform regional lymphadenectomy for adequate staging. Preoperative biopsy is not mandatory before surgery and can be difficult to obtain, particularly in patients with malignant biliary strictures. Transperitoneal biopsy is contraindicated in patients with perihilar cholangiocarcinoma who may otherwise be candidates for liver transplantation because of the risk of peritoneal seeding.[26] In most patients, suspicious clinical presentation and radiologic features, with or without elevated CA 19-9, are sufficient for preoperative diagnosis. In rare patients, a differential diagnosis of immunoglobulin (Ig)G4-associated cholangitis (IAC) presents a diagnostic and therapeutic dilemma. IAC is a fibroinflammatory disorder characterized by IgG4-positive plasma cell infiltration of the bile duct wall and elevated serum IgG4 levels in 74% of patients.[27] Concurrent autoimmune pancreatitis is found in 92% of patients. Imaging features of IAC include long, multifocal strictures and smooth margins of the bile duct lumen.[28] In contrast, cholangiocarcinoma is characterized by a solitary, irregular lesion with eccentric thickening of the bile duct wall.

Estimated 5-year overall survival (OS) rates after R0 resection are reportedly 43%, 40%, 48.5%, and 44% in gallbladder carcinoma, ICC, perihilar cholangiocarcinoma, and distal bile duct cancer, respectively.[29–32] Predictors of worse survival after surgery include lymph node metastases, positive resection margin, vascular invasion, and multifocal disease. Contraindications to surgery include distant metastases, local invasion into critical vasculature that cannot be reconstructed, poor performance status, and insufficient functional liver remnant volume. In selected patients with locally advanced disease or poor prognostic factors, such as lymph node metastases or multifocal diseases, neoadjuvant therapy may be considered, particularly in the setting of a clinical trial. Systemic therapy before surgery may allow assessment of tumor biology, treatment of micrometastases, downsizing of tumors, and increased chance of R0 resection.[33,34]

Gallbladder Cancer

Among patients undergoing definitive surgery for gallbladder carcinoma, 61% of patients are diagnosed incidentally with cancer after laparoscopic cholecystectomy for a presumed benign gallbladder disease.[29] For T1a tumors, simple cholecystectomy is sufficient. For incidentally diagnosed T1b–T3 tumors, reresection, also termed *radical cholecystectomy*, is recommended. Radical cholecystectomy entails resection of the gallbladder bed, typically partial hepatectomy of segments 4B/5, and hepatoduodenal ligament lymphadenectomy. Bile duct resection is reserved for patients who otherwise would have a positive cystic duct margin. Routine resection of port sites from prior laparoscopic cholecystectomy is not recommended.[35]

Intrahepatic Cholangiocarcinoma

Major or minor hepatectomy may be required for R0 resection of ICC, depending on the anatomic extent of a disease. ICC often presents as a large mass invading the hepatic vein, inferior vena cava, and/or portal vein, requiring extended resection. Criteria for resectability of hepatic tumors include adequate vascular inflow and outflow, biliary drainage, and sufficient functional remnant liver volume.[36] For patients with inadequate liver volume, portal vein embolization is a strategy that induces hypertrophy of the remnant liver to enable safe hepatectomy.

Table 29–3 Staging System[a]

Stage		Disease site			
		Gallbladder cancer	**Intrahepatic cholangiocarcinoma**	**Perihilar bile duct**	**Distal bile duct**
I	IA	T1N0: Invades lamina propria or muscular layer	T1aN0: Solitary tumor ≤ 5 cm without vascular invasion	T1N0: Tumor confined to bile duct, with extension up to muscle layer or fibrous tissue	T1N0: Invades bile duct wall with depth < 5mm
	IB		T1bN0: Solitary tumor >5 cm without vascular invasion		
II	IIA	T2aN0: Invades perimuscular connective tissue on peritioneal side without involvement of serosa (visceral peritoneum)	T2No: Solitary tumor with intrahepatic vascular invasion, or multiple tumors, with or without vascular invasion	T2N0: Invades beyond wall of bile duct to surrounding adipose tissue or adjacent hepatic parenchyma	T1N1: 1-3 regional nodes, or T2N0: invades bile duct wall with depth 5-12 mm
	IIB	T2bN0: Invades perimuscular connective tissue on hepatic side without extension into the liver			T2N1, or T3N0; invades bile duct wall with depth >12 mm, or T3N1
III	IIIA	T3 N0: Tumor perforates serosa and/or directly invades liver and/or other adjacent organ or structure, ie., extrahepatic bile duct, colon	T3N0: Tumor perforating visceral peritoneum	T3N0: Invades unilateral branches of portal vein or hepatic artery	T1-3,N2: ≥ 4 regional nodes
	IIIB	T1-3, N1: 1-3 regional lymph nodes	T4N0: Direct invasion of local extrahepatic structures, or any T, N1: regional lymph node metastasis	T4N0: Invades main PV or branches bilaterally, or CHA, or unilateral 2nd-order biliary radicles with contralateral PV or HA involvement	T4, any N: Tumor involves celiac axis, superior mesenteric artery, and /or common hepatic artery
	IIIC	–	–	Any T, N1: 1-3 regional nodes	–
IV	IVA	T4, N0-1: Tumor invades main portal vein or hepatic artery, or invades ≥ 2 extrahepatic organs or structures	Any T, any No, M1	Any T, N2: ≥ 4 regional nodes	Any T, any N, M1
	IVB	T1-4, N2: 4 ≥ regional nodes, or M1		Any T, any N, M1	

[a]Text describes underlined T or N category.
CHA, common hepatic artery; HA, hepatic artery; PV, portal vein.
Data from Edge SB, Byrd DR, Byrd DR, et al: AJCC Cancer Staging Manual, 8th ed. New York, NY: Springer; 2017

Perihilar Cholangiocarcinoma

Perihilar cholangiocarcinoma, also termed *hilar cholangiocarcinoma* or *Klatskin tumor*, is technically challenging to resect because of its central location and frequent involvement of the portal vein, hepatic artery, and second-order bile duct tributaries of both hepatic ducts. Major hepatectomy and bile duct resection with reconstruction are required, and in some patients, vascular resection and reconstruction are needed. Preoperative biliary drainage and normalization of serum bilirubin are necessary before major hepatectomy. Endoscopic biliary stents carry a risk of ascending cholangitis, whereas percutaneous transhepatic biliary drainage is associated with a risk of peritoneal seeding.[37,38] For patients with potentially resectable tumors, consultation with a hepatobiliary surgeon and high-quality axial imaging are recommended before placement of biliary stents.

In patients with unresectable tumors, liver transplantation after neoadjuvant therapy is associated with a post-transplant 5-year recurrence-free survival rate of 65%.[39] Eligibility criteria for liver transplantation include radial diameter smaller than 3 cm and absence of a metastatic disease, including nodal metastases.

Distal Bile Duct Cancer

The standard surgical procedure to achieve margin-negative resection and adequate lymph node harvest is pancreaticoduodenectomy (PD), which is associated with significant morbidity and mortality. In highly selected patients with localized mid–bile duct cancer who are not candidates for PD, segmental bile duct resection with lymphadenectomy has been shown to result in comparable survival as PD.[40]

RADIATION THERAPY

Previous studies have shown that the majority of patients with unresectable ICC die from liver failure caused by vascular compromise (portal vein or hepatic vein obstruction) or biliary obstruction.[41,42] In a retrospective study of 362 patients with unresectable ICC, local tumor progression led to liver failure in 89% patients, half of whom died from tumor-related biliary obstruction and the rest from vascular compromise or a combination of both.[43] Although a higher proportion of patients with ECC die from extrahepatic disease than those with ICC, local tumor-related complications remain an important factor in patient survival.[42] For both ICC and ECC, radiation therapy (RT) plays an important role in achieving local control of the primary tumor.

In recent decades, multiple advances in radiation delivery technologies have made the delivery of high doses of radiation to the upper abdomen safe and effective through multiple radiation modalities: stereotactic body RT (SBRT), intensity-modulated RT (IMRT), proton therapy, and image-guided radiation, which have been reviewed previously.[44–47]

Growing Evidence for Radiation Therapy in the Treatment of Biliary Cancers

Through a series of clinical trials, RT techniques, dose constraints, and specific indications were established that have demonstrated that RT can effectively ablate small liver tumors.[48] Traditional SBRT can achieve excellent results for small hepatic tumors (<5 cm), but it may not be an effective strategy for large liver tumors (>7 cm). The ablative doses are defined as those that can achieve 2-year local tumor control rates greater than 90% and are termed *stereotactic ablative RT*. Studies have shown that SBRT in 3 to 5 fractions can lead to high biliary stricture rates and toxicity to the central hepatobiliary tract and should be avoided.[49] An RT dose of 58 Gy in 15 fractions is considered safe for the biliary tree. Delivery of lower RT doses has resulted in inadequate tumor control in primary ICC and proven insufficient for liver metastases.[50]

In a retrospective study involving 34 patients with 42 lesions, including 31 unresectable ICC and 11 hilar cholangiocarcinomas treated with a median SBRT dose of 30 Gy in three fractions, an actuarial 4-year local control of 79% was achieved.[51] The median OS was 17 months, and the median progression-free survival (PFS) was 10 months. However, 12% (4/34) of patients experienced grade III adverse effects, including duodenal ulceration, cholangitis, and liver abscess.[51] A phase 2 trial of 128 patients included 46 patients with ICC, 35 with HCC, and 47 with colorectal liver metastases.[52] All patients received high-dose conformal RT with a median dose of 60.75 Gy (1.5 Gy per fraction, twice daily) and concurrent hepatic artery floxuridine. The median OS was 15.8 months for all patients, and 13.3 months for patients with ICC.

A retrospective dose-response analysis of patients treated with definitive IMRT for unresectable ICC at MDACC identified 79 patients, most of whom had large tumors (median size 7.9 cm).[41] Eighty-nine percent of patients (n = 70) had received systemic chemotherapy before RT. The median RT dose was 58.05 Gy (range 35–100) in 3 to 30 fractions, with median biologic equivalent dose (BED) of 80.5 Gy. The 1-year and 3-year OS rates were 87% and 44%, respectively, and the median OS after diagnosis was 30 months.[41] RT dose was the single most important prognostic factor, with a higher total dose correlating with improved local control (P = .03) and OS (P = .02). No significant treatment-related toxicities were reported. These results suggest that BED of 80.5 Gy or greater may be

ablative for large ICC tumors, with long-term OS rates comparing favorably to surgical resection. This requires careful treatment planning with attention to organ motion control, protection of surrounding organs, daily image guidance, and incorporation of conformal RT techniques such as IMRT and proton therapy.

A prospective study of hypofractionated proton RT for patients with either HCC or ICC further validated the findings of MDACC's retrospective analysis. In a study of 44 patients with HCC, 37 patients with ICC, and two patients with mixed HCC and ICC, patients received 15 fractions of radiation to a maximum of 67.5 Gy in 15 fractions.[53] The 2-year local control for ICC was 94.1%, and the 2-year OS for ICC was 46.5%. Encouraging results were also noted for HCC. Toxicities in both ICC and HCC were very low. This study led to two phase 3 randomized trials, NRG GI001 for ICC (hypofractionated radiation vs observation after initial chemotherapy; NCT02200042) and NRG GI003 for HCC (protons vs photons; NCT03186898). The NRG GI001 was terminated because of lack of patient accrual, and the NRG GI003 study is ongoing.

The results of escalated-dose RT in unresectable ECC have not been as clearly favorable as those for ICC. In 1990, a multicenter, retrospective study of patients with ECC reported an improved median survival in patients receiving more than 40.0 Gy compared with those receiving 40.0 Gy or less.[54] A retrospective analysis of 52 patients with unresectable ECC treated between 1957 and 2000 at MDACC shed light on the limitations of conventional dosing in preventing local progression.[55] Although the study was limited in its statistical power by its small patient number, it did suggest a possible association between increasing radiation dose and improved local control.

However, in a modern retrospective cohort of patients with unresectable ECC (2001–2015), there was no dose-response relationship.[42] In this study, RT was given at a median dose of 50.4 Gy with a range of BED between 36–98 Gy (median 59.5). The cohort was split into an escalated-dose RT (EDRT) group (>50.4 Gy in 28 fractions, BED >59.5) and a conventional-dose group (BED ≤59.5). The EDRT group did not demonstrate improved OS or freedom from local progression, and showed worse freedom from distant progression. In addition, EDRT was associated with the onset of grade 3 or higher lymphopenia, which has been shown to portend poor prognosis in other disease sites.[56] Toxicity rates were comparable between radiation dose groups. Thus, although dose escalation has shown promising results in unresectable ICC, the results with ECC suggest that higher RT doses do not provide the same local control and OS benefits. The proximity of ECC tumors to the bowel limit the ability to completely cover the tumor with higher doses of radiation and may explain the differences in outcomes.

In contrast to the locally advanced setting, consolidative chemoradiation has shown promise in the earlier-stage resectable setting. SWOG's S0809 study investigated the use of gemcitabine and capecitabine followed by consolidative chemoradiation.[57] This study is discussed below and showed that survival rates were similar between R0 and R1 resection groups after radiotherapy.

In summary, there is benefit in the use of adjuvant and definitive RT to achieve local control and prolonged survival for patients with ICC and ECC. The assessment of response in these settings can be challenging, and rigorous standards remain to be defined. There is also a strong rationale to combine RT with systemic therapy to achieve both local and distant control. In recent years, various molecular targets have been identified for cholangiocarcinoma. Preclinical data combining RT with targeted agents in these different molecular settings of cholangiocarcinoma may be fruitful; clinical trials in these areas are needed.

SYSTEMIC THERAPY

Neoadjuvant Therapy

The rationale for neoadjuvant therapy includes tumor downstaging, treatment of micrometastatic disease, and assessment of tumor biology before resection.[58–60] Neoadjuvant therapy enhances the R0 margins rate and prevents distant metastases, both of which are associated with improved clinical outcomes.[61–66] For example, a study of patients who had neoadjuvant chemoradiation showed 100% of the margin-negative surgical resection (R0) versus 54% in those who did not have neoadjuvant therapy. Survival benefit was manifested in a study comparing patients who received neoadjuvant concurrent chemoradiation with those who did not, and the 5-year survival rate was superior (53 vs 23%).[67] Intrahepatic, combined intrahepatic and extrahepatic, and extrahepatic recurrence rates were 60.9%, 18.6%, and 21.0% in resected ICC.[68] The sites of recurrence in 41% to 60% of resected hilar cholangiocarcinoma were distant metastases[69,70] and in 85% of patients with recurrent gallbladder carcinoma.[70] In a study of 401 patients,[71] the cumulative recurrence rate was higher in R1 than in R0 resections (86 vs 57% at 5 years; $P < .001$). Other studies show that patients with a R0 resection had longer median OS and recurrence-free survival, and lower recurrence probability than those with a R1 resection.[72–75]

The ideal systemic chemotherapy regimen in the neoadjuvant setting is unclear. The combination of gemcitabine and cisplatin has been the most frequently used chemotherapy regimen for resectable cholangiocarcinoma since the validation of clinical efficacy by

the ABC-02 trial.[76] FOLFIRINOX (5-fluorouracil, irinotecan, and oxaliplatin) resulted in favorable antitumor activity in locally advanced or metastatic biliary tract cancer.[77] More recently, the combination of gemcitabine, cisplatin, and nab-paclitaxel was tested in advanced biliary tract cancers, and it showed promising OS and PFS superior to historical controls treated with gemcitabine-cisplatin alone.[34] Objective response rates (ORR) in patients who received the doublet and triplet chemotherapy were 26.1%[76] and 45%,[37] respectively. This superior efficacy has led to the frequent use of the triple chemotherapy in the neoadjuvant setting at MDACC. The National Comprehensive Cancer Network (NCCN) officially listed the triple combination as one of the neoadjuvant chemotherapy options (NCCN Guidelines, v. 2.2020). As of this writing, a neoadjuvant clinical trial of gemcitabine, cisplatin, and nab-paclitaxel is underway at MDACC along with seven other institutions (NCT03579771).

Adjuvant Therapy

Cholangiocarcinoma has a high recurrence rate at distant sites after a curative surgical resection, and this suggests the importance of adjuvant therapy in addition to neoadjuvant therapy (perioperative therapy). Two large studies compared survival in patients who underwent curative-intent resection alone, chemotherapy alone, chemotherapy with RT, and RT alone.[78,79] Overall, adjuvant therapy did not provide statistically significant survival benefit with a trend toward better survival—the median recurrence-free survival (odds ratio [OR] 0.74, 0.55–1.01). Chemotherapy (OR 0.39, 0.23–0.66) and chemoradiation therapy (OR 0.61, 0.38–0.99) showed statistically significant survival benefit, but RT alone did not, with an OR of 0.98 (0.67–1.43). This study clearly demonstrated that any form of adjuvant therapies had survival advantage in patients with R1 resection or a lymph node–positive disease: margin-positive and node-positive patients had the ORs of 0.36 (0.19–0.68) and 0.49 (0.30–0.80), respectively. Radiation therapy alone showed benefit in patients with R1 resection (OR 0.33, 0.14–0.81). A meta-analysis including 15 studies and 5060 patients revealed that adjuvant chemotherapy was associated with improved OS with a HR of 0.66 (0.55–0.79).[80] Survival benefit was larger in high-risk patients with positive margins and lymph nodes.[81] Based on these strong clinical data, adjuvant therapy has been generally recommended in all the patients who undergo surgical resection for ICC, ECC, and gallbladder carcinoma. However, phase 3 evidence was lacking until recently.

A randomized, phase 3 study (PRODIGE 12-ACCORD 18-UNICANCER GI) compared the efficacy of adjuvant gemcitabine and oxaliplatin, and it did not show statistically significant clinical benefit with a trend toward better survival, with the median recurrence-free survival of 30.4 versus 18.5 months with a HR of 0.88 (0.62–1.25).[82] The median OS was 75.8 versus 50.8 months with a HR of 1.08 (0.70–1.66). Most patients included in this study had a R0 resection (86%). However, this trial was underpowered and may have missed a positive outcome because of low patient numbers and heterogeneity of biliary cancers that were included. Another study from Japan in patients with intravenous (IV) mitomycin C with 5-fluorouracil, followed by oral fluorouracil compared survival with those who had surgical resection alone.[79] It revealed that patients who had resected gallbladder carcinoma had a statistically significant 5-year survival rate and disease-free survival, whereas patients with pancreatic cancer, cholangiocarcinoma, and ampullary cancer did not have survival benefit.

Adjuvant 5-fluorouracil or gemcitabine was compared after surgical resection with observation in an open-label, phase 3, randomized, controlled clinical trial in patients with resected periampullary cancers (ESPAC-3 trial).[83] This study included patients with cholangiocarcinoma (ampullary 297 and bile duct 96), both node-positive and -negative diseases, and R0 and R1 resections. 5-fluorouracil 425 mg/m^2 IV was administered 1 to 5 days every 28 days, and gemcitabine 1000 mg/m^2 IV once a week for 3 weeks of every 4 weeks for 6 months. The median OS in the chemotherapy and observation groups was 43.1 and 35.2 months (HR 0.86, 95% CI 0.66–1.11), respectively. After adjusting for independent prognostic variables, a HR was 0.75 (P = .03). When compared with the observational group, the gemcitabine group (HR 0.77, 95% CI 0.57–1.05) had better survival than the 5-fluorouracil group (HR 0.95, 95% CI 0.71–1.28). Of note, a R1 resection was a poor prognostic indicator, with a HR of 1.98.

Capecitabine monotherapy was investigated in a randomized, controlled, phase 3 study for patients with cholangiocarcinoma or gallbladder carcinoma who had undergone a surgical resection (BILCAP trial).[84] Patients assigned to capecitabine 1250 mg/m^2 twice daily on days 1 to 14 of a 21-day cycle for eight cycles, and clinical outcomes were compared with patients who did not receive adjuvant chemotherapy under observation. The study included patients with R0 and R1 resections; positive and negative lymph nodes; tumor grades I, II, and III; and ICC and ECC and gallbladder carcinoma. This trial did not meet its primary end point. The median OS by intention-to-treat was 51.1 months (95% CI 34.6–59.1) in the capecitabine arm compared with 36.4 months (95% CI 29.7–44.5) in the observation arm (HR 0.81, 95% CI 0.63–1.04; P = .097). However, the survival benefit was significant after adjusting for nodal status, disease grade, and sex (HR 0.71, 95% CI 0.55–0.92; P = .010). The most common adverse events from capecitabine

were hand-foot syndrome (20%), diarrhea (8%), and fatigue (8%). In an unplanned subset analysis, no statistical benefit was noted with capecitabine for patients with hilar cholangiocarcinoma or muscle-invasive gallbladder carcinoma.

Although there are no prospective randomized clinical trials that are available to compare the efficacy of monotherapy with combination chemotherapy, most clinicians use combination chemotherapy (eg, gemcitabine + cisplatin or gemcitabine + capecitabine), particularly in patients with a node-positive disease or R1 resection because combination therapy is better established in the advanced or metastatic setting.[76] The NCCN guidelines recommend capecitabine as a preferred medication in the adjuvant setting. Combination regimens including 5-fluorouracil (or capecitabine) plus oxaliplatin (or cisplatin), gemcitabine plus capecitabine (or cisplatin) are potential alternatives, as is gemcitabine or 5-fluorouracil (or capecitabine) monotherapy.

Concurrent Chemoradiation

Adjuvant chemotherapy alone discussed above demonstrated improved survival in the BILCAP trial. Traditionally, in the US, a combination of concurrent chemoradiation and chemotherapy has been used in patients with high-risk features (positive node, R1 resection, or lymphovascular and perineural invasion).[85–87] Adjuvant concurrent chemoradiation, sequential chemotherapy followed by RT, and chemotherapy alone were compared in resected ICC.[88] This study demonstrated that patients had better clinical outcomes when RT was added in the adjuvant setting. A HR for overall mortality at advanced pathologic stages III and IV were 0.55 (0.41–0.74) and 0.92 (0.70–1.33), respectively, in patients who received concurrent chemoradiation and chemotherapy followed by radiation, compared with those who only received chemotherapy.

Capecitabine (1650 mg/m^2/day) and 5-fluorouracil (225 mg/m^2/day) are widely used as a radiosensitizer in gastrointestinal malignancies including pancreatic adenocarcinoma, rectal cancer, and cholangiocarcinoma.[89,90] These agents are known to cause direct and abscopal effects when combined with RT.[89,91] Capecitabine is more frequently used than 5-fluorouracil because of the convenience of oral administration and elimination of catheter-related complications.[92]

In ECC and gallbladder carcinoma, a phase 2 clinical trial investigated adjuvant capecitabine and gemcitabine followed by concurrent chemoradiation therapy (SWOG S0809).[57] The study included patients with stages pT2–4, lymph node–positive and –negative diseases, and R0 and R1 margins. Treatment consisted of four cycles of gemcitabine (1000 mg/m^2 IV on days 1 and 8) and capecitabine (1500 mg/m^2/d on days 1–14, in divided doses twice daily) every 21 days. After reimaging, patients not experiencing disease progression then received capecitabine (1330 mg/m^2/d, in divided doses twice daily, 7 days per week) concurrent with radiotherapy (45 Gy to regional lymph nodes including retro-pancreaticoduodenal, celiac, and portal vein nodes and 54–59.4 Gy to a preoperative tumor bed). The median OS was 35 months, and that of patients with R0 and R1 resections was 34 and 35 months (not statistically different); the 2-year survival rate was 67% and 60% in R0 and R1 resections (not statistically different). The median disease-free survival was 26 and 23 months in R0 and R1 resections, respectively. This study demonstrates that patients who received concurrent chemoradiation after combination chemotherapy have similar OS and disease-free survival in R0 and R1 resections.

In summary, adjuvant capecitabine is regarded as the standard of care after surgical resection of biliary tract cancer based on the BILCAP trial. The role of adjuvant capecitabine for hilar cholangiocarcinoma remains controversial, and chemoradiation should be considered, particularly for R1 resection. Adjuvant gemcitabine and cisplatin remains a potential option, because the phase 3 trial with this combination was underpowered. The ongoing phase 3 ACTICCA-1 trial (NCT02170090) investigating gemcitabine and cisplatin versus capecitabine will be instructive in regard to future options.

Incidental Gallbladder Carcinoma

Better imaging techniques and assessment of risk factors have led to a higher rate of preoperative diagnosis of gallbladder carcinoma.[93] However, this cancer is often discovered incidentally during cholecystectomy for benign diseases such as polyps or cholecystitis[94–99]; the incidence of gallbladder carcinoma in all cholecystectomies is 0.2% to 3%.[100] In a retrospective analysis, 68% of patients underwent re-resection, with the most common surgical procedures being gallbladder BED resection, liver 4B/5 segmentectomy, and hepatoduodenal ligament lymphadenectomy. Resection with T2/T3 diseases significantly increased survival, whereas the resection of the common bile duct did not increase the R0 resection rate but increased postoperative complications, unless the cystic duct was involved by cancer.[95] The incidence of port-site metastases is about 10%, and routine resection of port sites has no effect on survival.[101] If gallbladder carcinoma is deemed unresectable perioperatively, systemic therapy is recommended. After surgical resection is completed for a resectable disease, adjuvant chemotherapy is recommended, with radiation reserved for margin-positive disease.

SYSTEMIC THERAPY FOR METASTATIC DISEASE

First-Line Chemotherapy

The standard-of-care frontline therapy for metastatic biliary tract cancer was established by the ABC-02 trial in 2010 which showed superiority of gemcitabine plus cisplatin compared with gemcitabine alone for advanced biliary cancers (Table 29–4).[76] In this phase 3 study, 410 patients with cholangiocarcinoma, gallbladder, or ampullary carcinoma were randomized in a 1:1 fashion to receive gemcitabine alone (1000 mg/m^2 on days 1, 8, and 15 of a 4-week cycle) or cisplatin (25 mg/m^2) followed by gemcitabine at above dose on day 1 and 8 of a 3-week cycle. At a follow-up of median 8.2 months, medial OS was 11.7 months in the gemcitabine plus cisplatin arm compared with 8.1 months with gemcitabine alone (HR 0.64, 95% CI 0.52–0.80; $P < .001$). Median PFS was 8.0 months in the doublet arm compared with 5.0 months with gemcitabine alone ($P < .001$). Rates of neutropenia were higher in the doublet arm (25.3% vs 16.6% grade 3/4); however, rates of infection were similar. Increased liver enzymes occurred with gemcitabine alone (27.1% vs 16.7%; $P = .01$), which the authors concluded may have been secondary to inferior control of the disease compared with the doublet.[76] Other toxicities were comparable. Gemcitabine and cisplatin compared with gemcitabine alone was also tested in a Japanese population with similar findings.[102]

A treatment regimen with better efficacy than gemcitabine and cisplatin has yet to be approved for clinical use, although several promising therapies are emerging. In a phase 2, open-label, single-arm study of gemcitabine, cisplatin, and nanoparticle albumin-bound (nab)-paclitaxel (NCT0239263), patients were treated with gemcitabine 1000 mg/m,^{2} cisplatin 25 mg/m,^{2} and nab-paclitaxel 125 mg/m^2 on days 1 and 8 of a three-week cycle.[34] Because of grade 3/4 hematologic toxicities, doses were reduced to 800 mg/m^2 of gemcitabine, 25 mg/m^2 of cisplatin, and 100 mg/m^2 of nab-paclitaxel ($n = 28$ in reduced-dose group). Of 60 patients, the majority had ICC (63%), followed by gallbladder carcinoma (22%), and ECC (15%). Patients who had prior chemotherapy were excluded (except in the adjuvant setting >6 months prior). A median PFS of 11.8 months (95% CI 6–15.6) and disease control rate of 84% was noted at 12.2 months follow-up. Twelve patients who had unresectable disease were converted to resectable and underwent surgery. Median OS of 19.2 months (95% CI 13.2–unable to estimate) was reported, which is an improvement compared with historical controls of gemcitabine and cisplatin.[34] Grade 3 or greater toxicity was seen in 58% (61% high-dose, 54% low-dose group). The most common grade 3 or higher toxicity was neutropenia (33%), followed by anemia (16%). Nonhematologic toxicities ranged from 2% to 6% for diarrhea, elevated alkaline phosphatase, vomiting, constipation, and transaminitis. A phase 3, randomized clinical trial to compare gemcitabine, cisplatin, and nab-paclitaxel with standard-of-care gemcitabine and cisplatin is currently underway (SWOG 1815 study; NCT03768414).

Other frontline studies have assessed the addition of agents such as S-1, an oral fluoropyrimidine derivative designed to enhance clinical use and reduce gastrointestinal toxicity (NCT02182778),[103,104] or derivatives such as NUC-1031 (a phosphoramidate transformation of gemcitabine) designed to overcome resistance mechanisms to gemcitabine (ABC-08 study, NCT02351765).[105,106] As described further below, there has been a paradigm shift toward targeted therapy in biliary tract cancers, and targeted agents alone or in combination with chemotherapy are also being evaluated in the frontline setting.

Second-Line Cytotoxic Chemotherapy

After progression on gemcitabine and cisplatin, standard-of-care second-line chemotherapy options are limited. In the ABC-06 study (NCT01926236), patients were randomly assigned 1:1 to modified (m) FOLFOX (folinic acid, fluorouracil, and oxaliplatin) with active symptom control (ASC) versus ASC alone after prior gemcitabine-cisplatin therapy.[107] Of 162 patients, the median OS was 6.2 versus 5.3 months for ASC with mFOLFOX compared with ASC alone; the 6- and 12-month OS rate was 50.6% and 25.9%, compared with 35.5% and 11.4%, respectively. Approximately 59% of patients experienced grade 3 or 4 toxicity in the chemo-ASC arm compared with 39% in the ASC-alone arm. Although survival was greater than expected with ASC alone, the findings indicate clinical benefit of mFOLFOX with ASC in the second-line setting.[107] Modified FOLFIRI (folinic acid, fluorouracil, and irinotecan) has been compared with mFOLFOX in the second-line setting via a 1:1 randomization after progression on gemcitabine/cisplatin, and mFOLFIRI was noted to be tolerable but not superior to mFOLFOX in the second line (NCT03464968).[108] Retrospective and meta-analyses of chemotherapy in the second or later line setting have shown a modest PFS of 2.4 to 3.2 months across studies, with an average median OS average of 7 months.[109–111]

Targeted Therapy: Molecular Profiling of Biliary Tract Cancers

The development of molecular profiling technologies has led to increased genomic-profiling studies of all cancers, including those of the biliary tract.[112–119] At

Table 29–4 Summary of pertinent systemic therapy trials in unresectable and metastatic biliary tract carcinoma

Trial Name (Clinical Trials Identifier)	Phase	Molecular Target	Treatment Regimen	Patients	Outcome	Adverse Events	Status[a] [reference]
ABC-02 (NCT00262769)	Randomized, phase 2 – first line	None – cytotoxic	Cisplatin (25 mg/m^2) + gemcitabine (1000 mg/m^2) D1, D8 (every 3 weeks) vs gemcitabine 1000 mg/m^2 D1, D8, D15 (every 4 weeks)	N = 410 randomized N = 204 assessed (gem/cis) N = 206 assessed (gem)	**mPFS:** 8.0 vs 5.0 mo ($P < .001$) **mOS:** 11.7 vs 8.1 mo (for gem/cis) **HR:** 0.64% (95% CI 0.52–0.80; $P < .001$)	**Gr 3/4: (gem/cis vs gem)** neutropenia (25.3 vs 16.6%), any hematologic (32.3 vs 23.6%); LFT abnormal (16.7 vs 27.1%); any infection (18.2 vs 19.1%)	Completed; standard of care first line[76]
Gemcitabine, cisplatin, and nab-paclitaxel for treatment of advanced biliary tract cancers (NCT02392637)	Open-label, single-arm, phase 2 – 1st line	None – cytotoxic	Gemcitabine 1000 mg/m,^{2} cisplatin 25 mg/m^2, and nab-paclitaxel 125 mg/m^2 D1, D8 (21-day cycle) After– N = 32, doses reduced: 800 mg/m,^{2} 25 mg/m,^{2} 100 mg/m,^{2} respectively	N = 60	**mPFS:** 11.8 mo (95% CI, 6.0–15.6) **mOS:** 19.2 mo (95% CI 13.2–not reached) **PRR:** 45% **DCR:** 84%	**Gr ≥3:** 58% total (61% in high dose; 54% dose reduced) **Gr3, Gr4:** neutropenia (30, 11%); diarrhea/ elevated ALP/ vomiting (4%)	Active, not recruiting[34]
ABC-06 (NCT01926236)	Randomized, multicenter, controlled, open-label – second line	None – cytotoxic	1:1 randomization: ACS + oxaliplatin/5-FU (mFOLFOX) vs ACS alone	N = 162 (81 per arm)	**ACS + mFOLFOX:** mOS: 6.2 mo; 6 mo and 12 mo OS rate: 50.6%, 25.9% vs **ACS alone:** mOS: 5.3; 6 mo and 12 mo OS rate: 35.5%, 11.4%.	**Gr 3/4:** 59% (ACS + mFOLFOX) vs 39% (ACS alone)	Completed[107]

(*Continued*)

Trial Name (Clinical Trials Identifier)	Phase	Molecular Target	Treatment Regimen	Patients	Outcome	Adverse Events	Status[a] [reference]
BGJ398 (Infigratinib; NCT02150967)	Open-label, phase 2 – 2nd line	*FGFR2* fusions or other *FGFR* alterations	Infigratinib PO 125 mg once daily for 21 days; 7 days off (28-day cycle)	N = 61 (FGFR2 fusions (48); mutations (8); amplifications (3)	**ORR:** 14.8% (18.8% for FGFR2 fusions) **DCR:** 75.4% (83.3% FGFR2 fusions) **mPFS:** 5.8 mo (95% CI 4.3–7.6)	**All Gr:** Hyperphos (72.1%); fatigue (36.1%); stomatitis (29.5%) **Gr 3/4:** hyperphos (16.4%); stomatitis (6.6%); HFS (4.9%)	Recruiting[128,129]
	Updated results: open-label, phase 2 – second line	*FGFR2* fusions/ translocations only	Infigratinib PO 125 mg once daily for 21 days; 7 days off (28-day cycle)	N = 71 (FGFR2 fusion/ translocation only)	**ORR:** 31.0% (95% CI 20.5–43.1) **cORR:** 26.9% (95% CI 16.8–39.1) **mPFS:** 6.8 mo (95% CI 5.3–76) **mOS:** 12.5 mo (95% CI 9.9–16.6)	**All Gr:** hyperphos (73.2%), fatigue (49.3%), stomatitis (45.1%), alopecia (38%) **Gr 3/4:** any (66.2%); hypophos (14.1%), hyperphos (12.7%)	
FLIGHT-202 Pemigatinib (NCT02924376)	Multicenter, open-label, single-arm, phase 2 – 2nd line	**COHORT:** (1) *FGFR2* fusions/ rearrangements; (2) other *FGFR* alterations (3) no *FGFR* alterations	Pemigatinib PO 13.5 mg daily for 14 days; 7 days off (21-day cycle)	N = 107 (FGFR2 fusion/ rearrangements) N = 20 *FGFR* alterations N = 18 no *FGFR* N = 1 unknown FGFR	**Cohort 1:** **ORR:** 35.5% (95% CI 26.5–45.4; 3 CR and 35 PR) **DCR:** 82% (74%–89%) **OS:** 21.1 (14.8–not reached) Cohort 2: **ORR:** 0%; **DCR:** 40%; **mOS:** 6.7mo (2.1–10.6) Cohort 3: **ORR:** 0%; **DCR:** 22%; **mOS:** 4.0 (2.3–6.5)	**Gr 1/2:** Hyperphos (55%); Alopecia (46%); Dysgeusia (34%); fatigue (31%) **Gr 3:** Hypophos (7%); stomatitis (5%); arthralgia and HFS (4%)	Active, not recruiting[132]

(*Continued*)

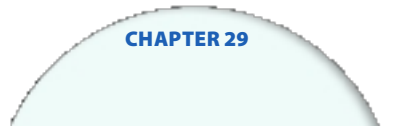
Table 29–4 Summary of pertinent systemic therapy trials in unresectable and metastatic biliary tract carcinoma *(Cont.)*

Trial Name (Clinical Trials Identifier)	Phase	Molecular Target	Treatment Regimen	Patients	Outcome	Adverse Events	Status[a] [reference]
FOENIX-CCA2 Futibatinib (TAS120) (NCT02052778)	Single-arm, multicenter, phase 2 – 2nd line	*FGFR2* gene fusions/ rearrangments	Futibatinib once daily oral dose continuous	N = 103 enrolled (interim analysis with n = 67; 82.1% with *FGFR2* fusions)	**ORR:** 34.3% (PR, n = 23) **DCR:** 76.1% **mTTR:** 1.6 mo (1.0–4.9) **mDOR:** 6.2 mo (2.1–14.2)	**All Grade:** Hyperphos (79.1%), Diarrhea (37.3%), dry mouth (32.8%) **Gr ≥3:** Any (73.1%); Hyperphos (25.4%)	Active, not recruiting[133,134]
ClarIDHy Ivosidenib (AG120) (NCT02989857)	Multicenter, randomized (2:1), double-blind, placebo-controlled, phase 3 – 2nd line (up to 2 prior lines)	*IDH1* mutations	Ivosidenib 500 mg once daily continuous (28-day cycle) vs matched placebo (crossover permitted)	N = 185 (n = 124 ivosidenib; n = 61 placebo)	**mPFS:** 2.7 mo (95% CI 1. 6–4.2) for ivosidenib vs 1.4 mo (1.4–1.6) placebo **HR:** 0.37 (95% CI 0.25–0.54; *P* < .0001) **mOS (ITT):** 10.8 mo (95% CI 7.7–17.6) vs 9.7 mo (4.8–12.1); HR 0.69 (95% CI 0.44–1.10; *P* = .06)	**Gr 1/2:** nausea (33% vs 24%); diarrhea (31% vs 15%); fatigue (23% vs 15%); cough (21% vs 8%). **Gr ≥3:** Any (30% treatment vs 22% placebo) Ascites (7% both arms); hyperbili (6% vs 2%); ALT elevation (5% vs 0%).	Active, not recruiting[142]
My Pathway (NCT02091141)	Open-label, multicenter, multi-basket, phase 2a – refractory	HER2 amplification/ overexpression or activating mutation	Pertuzumab + Trastuzumab	N = 11 (*HER2* amplified/ overexpressed) N = 8 (*HER2* mutated)	**Preliminary:** 4.2 mo follow-up: PR (n = 4); SD (n = 3)	No new signals	Recruiting[147]

(*Continued*)

Trial Name (Clinical Trials Identifier)	Phase	Molecular Target	Treatment Regimen	Patients	Outcome	Adverse Events	Status[a] [reference]
NCI-MATCH (EAY131) (NCT02465060)	Approximately 40 phase 2 molecularly targeted subprotocols – refractory (no prior trastuzumab/ pertuzumab/ T-DM1)	*HER2* amplification (CN >7)	T-DM1 3 .6 mg/kg IV every 3 weeks	N = 38 (n = 3 biliary tract)	PR rate: 5.6% (noncholangiocarcinoma) SD rate: 47% (noncholangiocarcinoma)	**Gr 1/2:** Anemia (34%), AST increase/ low platelets (26%), nausea/ vomiting (21%) **Gr 3:** Anemia (8); fatigue (5%); low platelets (5%)	Recruiting[148]
ROAR basket trial *BRAF V600E*-mutated biliary tract cohort (NCT02034110)	Open-label, phase 2 – second line or greater	*BRAFV600E* mutations	Dabrafenib 150 mg PO BID + trametinib 2 mg PO daily	N = 33 biliary tract cancer	**ORR** (investigator-assessed): 41% (95% CI 24–59). **mPFS:** 7.2 mo (95% CI 4.6–10.1) **mOS:** 11.3 mo (95% CI 7.3–17.6)	**Gr 3/4:** increased GGT (9%); leukopenia (9%)	Active, not recruiting[151]

[a]Clinicaltrials.gov status as of 6/27/2020.
ACS, active symptom control; ALT, alanine aminotransferase; BID, twice daily; BRAF, serine/threonine-protein kinase B-raf; Cis, cisplatin; DCR, disease control rate; FGFR, fibroblast growth factor receptor; Gem, gemcitabine; GGT, gamma-glutamyl transferase; HFS, hand-foot syndrome (palmar-plantar erythrodysesthesia); HR, hazard ratio; hyperbili, hyperbilirubinemia; hyperphos, hyperphosphatemia; hypophos, hypophosphatemia; IDH1, isocitrate dehydrogenase 1; ITT, intent to treat; LFT, liver function test; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; mTTR, median time to response; NCI-MATCH, National Cancer Institute-Molecular Analysis for Therapy Choice; PO, oral; PRR, partial response rate; ROAR, rare oncology agnostic research; T-DM1, ado-trastuzumab emtansine.



the chromosome level, initial studies of comparative genomic hybridization (CGH) shed light on chromosomal losses and gains and insight into the heterogeneity of biliary tract cancer.[113] A meta-analysis of five CGH studies encompassing a total of 98 ICCs showed frequent gains in chromosomes 1q, 5p, 7p, 8q, 17q, and 20q in three or more studies (>20% overall change).[113] Losses of copy number on chromosome 1q, 4p, 8p, 9p, 17p, and 18p were also reported. The aggregate data noted possible ethnic diversity between three Asian studies compared with a German study. Similarities were also noted to a previous CGH meta-analysis of HCC.

Comprehensive molecular profiling technologies and high-throughput genomic-profiling studies have shed light on commonly occurring alterations in biliary tract cancers.[114–119] Next-generation sequencing of 75 patients with cholangiocarcinoma that examined 236 cancer-related genes had shown tumor protein p53 (*TP53*) (35 and 45%) and *KRAS* (24 and 40%) as commonly occurring alterations in both ICC and ECC, respectively.[114] Other frequently altered genes in the intrahepatic subgroup include AT-rich interaction domain 1A (*ARID1A*), isocitrate dehydrogenase 1 (*IDH1*), myeloid cell leukemia 1 (*MCL1*), Erb-B2 receptor tyrosine kinase 2 (*ERBB2*), *SMAD4*, F0box, WD repeat domain containing 7 (*FBXW7*), and cyclin-dependent kinase inhibitor 2A (*CDKN2A*). In a larger study of patients (412 ICC, 57 ECC, and 85 gallbladder carcinoma), a similar profile was noted with commonly altered genes in *TP53*, *CDKN2A/B, KRAS, ARID1A, IDH1, SMAD4, ERBB2,* and fibroblast growth factor receptor (*FGFR*).[115] Of these, *FGFR* (11%) and *IDH* (20%) alterations were predominantly found in ICC and noted to be mutually exclusive. *KRAS* and *TP53* mutations were associated with poor prognosis, and *FGFR2* alterations were associated with better prognosis and OS (HR 0.478; $P = 0.03$), female gender, and younger age (<40 years). *IDH1/2* alterations were not found to be prognostic. *ERBB2* (16%) alterations were found predominantly in gallbladder carcinoma. Broadly, the functionally validated genes can be categorized into cell cycle–related (*TP53*, *CDKN2A* mutation/deletion, and *CCND1* amplification), receptor tyrosine kinases (*FGFR*), *MAPK* pathway (*KRAS, NRAS,* and *BRAF*), chromatin modifying (*ARID1A/B, BAP1, PBRM1*), and *IDH1/2* alterations.[116–121] *BAP1* alterations also appear to confer a more aggressive phenotype, associated with bone metastases, although case numbers have been limited.[114] A summary of commonly altered genes and their frequencies are found in Table 29–5.

Table 29–5 Frequency of Genetic Alterations in Biliary Tract Carcinomas

Genetic Alteration	Prevalence of Genetic Alterations		
	Intrahepatic Cholangiocarcinoma[a]	Extrahepatic Cholangiocarcinoma[a]	Gallbladder Carcinoma[a]
Total Genomic Alteration/Patient	**3.6**	**4.4**	**4.0**
TP53	25%–30%	40%	60%
RAS (KRAS/NRAS)	20%–25%	40%–45%	10%–15%
CDKN2A/B Loss	25%–30%	15%–20%	20%
ARID1A	15%–20%	10%–15%	10%–15%
BAP1	10%–15%	10%	6%
FGFR1-3	10%–15%	<5%	3%–5%
ERBB2 (HER2/neu) Amplification	3%–5%	15%	15%–20%
PBRM1	10%	5%	n/a[b]
IDH1/2	20%	0%	0%
SMAD4	4%–7%	20%–25%	30%
PTEN	5%	n/a[b]	Up to 4%
BRAF Substitution	5%	3%	1%
PIK3CA Substitution	5%–6%	7%	10%–15%
BRCA1	0.4%	2%	0.3%
BRCA2	2.7%	2%–3%	4%

[a]Rates of genetic alterations greater than 10 are rounded to the nearest 5 and provided in ranges.[114,115]
[b]Consensus on prevalence unclear.

The results of these and other molecular profiling studies have led to a paradigm shift in the treatment of advanced and metastatic biliary tract cancers with development and use of targetable agents. An estimated 35% to 40% of biliary tract cancers contain targetable genetic alterations.[122]

Targeted Therapies

FGFR Alterations

The *FGFR* signaling pathway is a family of proteins consisting of four receptors (FGFR1–4) and 22 ligands, which, when activated, results in downstream signaling via the mitogen-activated protein kinase, phosphoinositide 3-kinase (PI3K)/AKT, Janus kinase/signal transducers, and activators of transcription (JAK-STAT) pathways. This in turn leads to cell proliferation, growth, migration, and angiogenesis.[123,124]

FGFR alterations are found in approximately 15% of ICCs and tend to be driver mutations. *FGFR2* fusions or translocations are the most common type of alteration, and two common fusion partners identified have been the genes *AHCYL1* and *BICC1*.[125] These two fusions have been shown as mutually exclusive with *KRAS* and *BRAF* mutations and result in constitutive phosphorylation of mitogen-activated protein kinase in both in vitro and in vivo studies.[126,127]

Several FGFR inhibitors are currently under investigation. BGJ398, also known as infigratinib is an orally bioavailable FGFR1–3 inhibitor and was studied in a multicenter, open-label, phase 2 trial in the second-line setting for advanced or metastatic cholangiocarcinoma with *FGFR* alterations (NCT02150967).[128] Infigratinib was dosed at 125 mg once daily for 21 days of a 28-day cycle. Of the 61 patients reported at data cutoff, the majority (n = 48) had FGFR2 fusions, but mutations were found in eight patients and amplification in three patients. An ORR of 14.8% (18.8% for *FGFR2* fusion subset) and a median PFS of 5.8 months (95% CI 4.3–7.6), and a disease control rate (DCR) of 75.4% (83.3% in the FGFR2 fusion subset) was reported.[128] An update with 71 patients with *FGFR2* fusions showed an ORR of only 31.0% (95% CI 20.5–43.1) and disease control rate of 83.6% (95% CI 72.5–91.5). Median PFS was 6.8 months (95% CI 5.3–7.6) and median OS of 12.5 months (95% CI 9.9–16.6) was noted.[129] Overall the therapy was well tolerated, with hyperphosphatemia (73.2%), fatigue (49.3%), and stomatitis (45.1%) noted as the most common adverse events. Hyperphosphatemia is a common class effect of FGFR inhibitors secondary to the role of the FGFR pathway in renal phosphate metabolism and is considered an on-target effect.[130,131] As of this writing, hyperphosphatemia is managed with phosphate binders, low-phosphate diets, and diuretics.[131] Ocular toxicity is also a potential unique side effect of FGFR inhibitors.

Pemigatinib is another FGFR1–3 oral inhibitor investigated in a phase 2, multicenter, open-label study (FLIGHT-202; NCT02924376) for previously treated advanced or metastatic cholangiocarcinoma (89% ICC) patients with *FGFR* alterations.[132] The study included three cohorts: (1) those with FGFR2 fusions/rearrangements, (2) those with other FGF pathway alterations, and (3) patients without FGFR alterations. Patients were treated with 13.5 mg pemigatinib orally once daily for 14 consecutive days on a 21-day cycle until progression or toxicity. Of 146 patients enrolled in the study, the majority (n = 107) had FGFR2 fusions/rearrangements. At median follow-up of 17.8 months, an ORR of 38% (95% CI 26.5–45.4) was noted in the *FGFR2* fusion/rearrangement–containing subset. No responses were noted in the patients with other *FGFR* alterations or in those without *FGFR* alterations. A DCR of 82% (range 74%–89%) for fusion-containing patients was noted, compared with 40% (range 19%–64%) and 22% (range 6%–48%) in other and no *FGFR* alteration groups, respectively. Median OS was 21.1 months (range 14.8–not reached) in patients with *FGFR2* fusions. A similar side effect profile to infigratinib was noted with hyper- and hypophosphatemia, arthralgias, and stomatitis.[132] Based on these results, pemigatinib was given a FDA-accelerated approval for advanced or metastatic cholangiocarcinoma patients with *FGFR2* gene fusions or rearrangements after progression on at least one prior line of therapy pending verification in a confirmatory trial.

TAS120 or futibatinib is a highly selective FGFR1–4 irreversible inhibitor that has completed phase 1/2 trials in cholangiocarcinoma. In an initial phase 1 study of TAS120 in advanced solid tumors, an ORR of 25% was noted in cholangiocarcinoma patients with FGFR2 fusions (n = 28).[133] These initial results led to the FOENIX-CCA2 (NCT02052778) phase 2, single-arm, multicenter study in second-line or greater advanced or metastatic cholangiocarcinoma patients with *FGFR2* gene fusions/rearrangements.[134] Of 103 patients, an interim analysis of 67 patients with more than 6 months of follow-up showed an ORR of 34.3% and DCR of 76.1%. Median duration of response of was 6.2 months (range 2.1–14.2) with a 1.6-month (range 1.0–4.9) median time to response. Side effect profile was similar to the other FGFR inhibitors above.

Multiple other nonselective tyrosine kinase inhibitors with anti-FGFR activity are also under investigation in the second-line setting in patients with FGFR-altered cholangiocarcinoma.[124,135–139] All three of the agents above (infigratinib, pemigatinib, and futibatinib) are also under investigation in the first-line setting in phase 3, randomized clinical trials compared with standard-of-care gemcitabine-based chemotherapy in

this patient population (NCT03773302, NCT03656536, and NCT04093362).[140] The results of these studies can potentially lead to a chemotherapy-free option for patients with advanced or metastatic cholangiocarcinoma harboring *FGFR2* fusions/rearrangements.

IDH Inhibitors

Approximately 20% of cholangiocarcinomas (predominantly intrahepatic) contain *IDH1/2* mutations.[114,115,119] IDH1 and 2 are essential for production of metabolic enzymes that prevent cellular oxidative damage via conversion of isocitrate to alpha-ketoglutarate.[141] Mutations in these genes increase the production of D-2-hydroxyglutarate, an oncometabolite, and decreased α-ketoglutarate production, which in turn increases oncogenesis. The most common IDH1 mutation seen in cholangiocarcinoma is R132C.[141]

The phase 3, multicenter, randomized, double-blind study ClarIDHy (NCT02989857) investigated the efficacy of ivosidenib in *IDH1*-mutated cholangiocarcinoma after progression on prior therapy. Patients were randomly assigned 2:1 to receive ivosidenib 500 mg or placebo with the possibility for crossover on progression.[142] At 6.9 months, median PFS was 2.7 months for the ivosidenib group (95% CI 1.6–4.2) versus 1.4 months (95% CI 1.4–1.6) with a HR of 0.37 (95% CI 0.25–0.54; $P < .0001$). A significant difference in OS was not noted between the treatment and placebo groups (10.8 months in intent-to-treat [95% CI 7.7–17.6] vs 9.7 months [range 4.8–12.1], HR 0.69 [95% CI 0.44–1.10; $P = .06$]). Correcting via rank-preserving structural failure time method had noted a median OS of 6.0 months (HR 0.46 [range 0.28–0.75]; $P = .0008$). Objective response rates were low ($n = 3/124$ patients [2%]) with 51% achieving stable disease compared with 28% in the placebo group.[142] The 12-month OS rate of this study (48%) when compared with historic controls of regorafenib and mFOLFOX in second line (27% and 25.9%, respectively) show comparable results.[108,143,144] The most common grade 1/2 adverse events in the treatment group included nausea (33%), diarrhea (31%), and fatigue (23%). Grade 1/2 ascites was noted in 13% of the treatment group and 8% in the placebo group. Ascites was the most common grade 3 or greater adverse event, although rates were the same between the treatment and placebo groups (7%).[142]

HER2 Blockade

Overexpression of human epidermal growth factor receptor 2 (HER2) encoded by *ERBB2* is a well-established driver of oncogenesis in multiple cancer types and approved for use in breast and gastric/gastroesophageal carcinoma. In biliary tract cancer, genetic alterations (amplifications or mutations) in *ERBB2* are predominantly seen in gallbladder carcinoma (16%), followed by ECC (11%), and ICC (3%).[115,145]

A multihistology trial of ado-trastuzumab emtansine (T-DM1) at a dose of 3.6 mg/kg IV given once every 3 weeks in HER2-amplified solid cancers included 6 ($n = 58$) patients with biliary tract cancer (NCT02675829).[146] ORR was 26%, and 1 of 6 (17%) in biliary cancer. No significant correlation was found between the degree of HER2 amplification and response. MyPathway is an ongoing open-label, multicenter, phase 2a basket study (NCT02091141) aimed at evaluating safety and efficacy of targeted therapies across tumor types.[147] In a subset of 11 patients with advanced biliary tract cancer, with eight HER2 amplifications/overexpression and three mutations, four partial responses were seen at 12 months, with three others achieving disease stability. The National Cancer Institute–Molecular Analysis for Therapy Choice is a national study using genomic testing for matching patients with refractory disease to potential targeted therapies.[148] In a subprotocol evaluating T-DM1 in 36 patients with HER2-amplified nonbreast and nongastroesophageal cancers, three biliary adenocarcinoma patients were included. In this study, a trend toward increased tumor shrinkage was seen with higher levels of gene copy number. Although the above studies had small sample sizes and a small number of responders, basket trials are particularly useful for identification of signals to targeted therapy in rare tumors to warrant further investigation.[148,149]

BRAF Blockade

BRAF alterations are found in approximately 1% to 5% of biliary tract cancer. In the histology-independent, phase 2 basket study (NCT01524978) with *BRAF V600*–containing nonmelanomatous cancers, a total of 122 patients were enrolled.[150] Of these, eight patients with advanced cholangiocarcinoma were included. No CRs were noted; a partial response lasting more than 12 months was noted in one (12%) patient, and stable disease was achieved in four (50%) patients.[150] Combination BRAF + MEK inhibition (dabrafenib and trametinib) in *BRAFV600*-mutated rare tumors was studied in the phase 2, open-label "ROAR" basket trial, where 33 patients with biliary tract cancer were included (NCT02034110).[151] Of 32 evaluable patients, investigator-assessed ORR was 41% (95% CI 24–59). Median PFS of 7.2 months (95% CI 4.6–10.1 months) and median OS of 11.3 months (95% CI 7.3–17.6 months) was seen, warranting further clinical investigation in this patient population.

Other Targetable Pathways

Neurotrophic tropomyosin-related kinase gene fusions are present in approximately 3% to 5% of

cholangiocarcinomas, and larotrectinib tissue agnostic approval for all solid tumors in the refractory setting without known acquired mutation is also applicable to biliary tract cancers.[152] Anti–angiogenesis-directed therapies have also been highly studied in advanced biliary tract cancers, including vascular endothelial growth factor inhibitors and multi-tyrosine kinase inhibitors. Overall, results have not shown significant added benefit to the chemotherapy backbone in unselected patients with cholangiocarcinoma.[153–160]

Taken together, the identification of targeted genetic alterations in biliary tract cancer and the development of targeted agents have revolutionized therapy in the advanced and metastatic setting. Pertinent trial data have been summarized in Table 29–5. Sequencing of these agents and further studies into resistance mechanisms in terms of gatekeeper mutations and development of other secondary genetic alterations is an area of active research. In addition, with multiple FGFR inhibitors now being studied in the first-line setting compared with standard of care, a chemotherapy-free frontline option may soon become available in the metastatic setting for the FGFR-altered population (particularly those with *FGFR2* gene fusions).

Immunotherapy

Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of multiple cancer types; however, their role in biliary tract cancer is not well established. Certain genetic factors have shown to predict response to ICIs such as tumor mutation burden (TMB), program death-ligand/program cell death protein 1 (PD-L1/PD-1) expression, and mismatch repair (MMR) gene deficiency. These factors are indicative of high microsatellite instability (MSI-H) and an increased likelihood of tumor-specific neoantigen that can be recognized by the immune system.[161] The majority of biliary tract cancers have a low-to-intermediate TMB. Comprehensive genomic profiling of 3634 cholangiocarcinomas showed an approximately 1% rate of MSI-H.[119] Global loss of heterozygosity (gLOH) higher than 16% was seen in 11% of studied cases. Approximately 3.5% and 1.4% of evaluated cases had TMB higher than 10 and more than 20 mutations/megabase, respectively. PD-L1 positivity was seen in 9% of tested cases, and *PD-L1* amplification was present at a rate of 0.27%.[119,161] Stages of chronic inflammation and infectious/viral etiologies are associated with cholangiocarcinoma. Although other virally-associated cancer types have shown encouraging response rates to ICI therapies, it is unclear whether this pattern is evident in biliary tract cancer. The highly heterogeneous nature of these cancers and desmoplastic stroma may also be barriers of response to ICIs.[161] Key immunotherapy trials with dosing schedules and outcomes are summarized in Table 29–6 and highlighted below.

In the KEYNOTE-028 phase 1b study (NCT02054806) of pembrolizumab in advanced or metastatic biliary tract cancers in the second line or greater with at least 1% PD-L1 expression, an ORR of 13% (all PR, 95% CI 2.8–33.6) was seen among 23 patients at a median follow-up of 5.7 months (range 0.6–55.4). This translated to a median OS and PFS of 5.7 months (95% CI 3.8–9.8) and 1.8 months (95% CI 1.4–3.1), respectively. No grade 4 or 5 adverse events were noted, although 16.7% had grade 3 toxicities.[162,163] PD-L1 positivity was not a requirement for inclusion in KEYNOTE-158 (NCT02628067), a phase 2 study of 200 mg pembrolizumab given once every 3 weeks after progression on prior standard-of-care therapy. Of 104 patients included in this study, 61 were positive for PD-L1 expression. ORR was 5.8% (all PR, including 1 PD-L1–negative patient; 95% CI 2.1–12.1) in all patients (6.6% among PD-L1 expressors vs 2.9% among nonexpressors). Median duration of response had not been reached; however, an estimated 50% had duration of response at 24 months or longer. Median OS and PFS were 7.4 months (95% CI 5.5–9.6) and 2.0 months (95% CI 1.9–2.1), respectively. One patient had grade 5 renal failure, and grade 3 or higher adverse events were reported in 13.5%. Taken together, these data suggest modest activity of pembrolizumab monotherapy without new safety signals noted[162,163]

A multicenter, phase 2 study of nivolumab in 54 patients with biliary tract cancer who had received between one and three prior lines (NCT02829918) showed a 22% investigator-assessed ORR had been noted with a DCR of 59% (central independent review; ORR 11%, DCR 50%). All responses were in patients with proficient MMR. Median PFS was 3.68 months (95% CI 2.3–5.69) and median OS was 14.24 (95% CI 5.98–not reached). PD-L1 expression was significantly associated with prolonged PFS ($P < .001$). Grade 3/4 toxicities included hyponatremia (6%) and elevated alkaline phosphatase (4%).[164]

Preliminary data from a randomized, phase 2, multicenter study (BilT-01; NCT03101566) of nivolumab with gemcitabine-cisplatin (Arm A) or nivolumab with anticytotoxic T-lymphocyte–associated protein 4 (CTLA-4) agent ipilimumab (Arm B) in untreated advanced or metastatic biliary tract cancer was reported.[165] Of 71 eligible patients (n = 35 Arm A; n = 36 Arm B), the 6-month PFS rate was 70% in arm A and 18.6% in Arm B. This translated to a median PFS of 8.8 months (95% CI 6.1–11.3) and median PFS of 4.1 months (95% CI 2.4–5.2)), respectively.[165] Although the combination immunotherapy arm appears to be inferior to the nivolumab with chemotherapy arm, the preliminary data are comparable with historical

Table 29–6 Summary of Pertinent Immunotherapy Therapy Trials in Unresectable and Metastatic Biliary Tract Carcinoma

Trial Name (Clinical Trials Identifier)	Phase	Molecular Target	Treatment Regimen	Patients	Outcome	Adverse Events	Statusa [reference]
KEYNOTE-028 (NCT02054806)	Phase 1b, basket study	PD-L1 positive	Pembrolizumab 10 mg/kg IV every 2 weeks	N = 24	**ORR:** 13.0% (95% CI 2.8–33.6) **mDOR:** not reached **mOS:** 5.7 mo (3.1–9.8) **mPFS:** 1.8 mo (1.4–3.1)	**Gr 3–5:** 16.7% **Any Gr:** pyrexia (16.7%), nausea/pruritis (12.5%), hypothyroid (8.3%), severe skin reaction/colitis (4.2%)	Active, not recruiting[162]
KEYNOTE-158 (NCT02628067)	Phase 2, multicohort	Unselected for PD-L1	Pembrolizumab 200 mg IV every 3 weeks	N = 104 (PD-L1 expressor, n = 61; PD-L1 nonexpressor, n = 24)	**ORR:** 5.8% (95% CI 2.1–12.1); (6.6% PD-L1 pos; 2.9% (PD-L1 neg) **mDOR:** not reached **mOS:** 7.4 mo (95% CI 5.5–9.6) **mPFS:** 2.0 mo (95% CI 1.9–2.1)	**Gr 3–5:** 13.5% **Any Gr:** fatigue (14.4%), rash (11.5%), hypothyroidism (7.7%), pneumonitis (5.8%)	Recruiting[163]
Nivolumab for patients with advanced/refractory biliary tract cancer (NCT02829918)	Multicenter, phase 2	PD-L1 positivity not required	Nivolumab 240 mg IV every 2 weeks (16 weeks), then 480 mg IV every 4 weeks	N = 54 (n = 46 assessed) • PD-L1+: n = 18	**ORR:** 22% (investigator-assessed); 11% (central review) • PD-L1 + investigator assessed: 50% **DCR:** 59% **mPFS:** 3.68 mo (95% CI 2.3–5.69) **mOS:** 14.24 mo (95% CI 5.98–not reached)	**Any Gr:** increased ALP (24.1%), lymphopenia (22.2%), AST increase/fatigue (20.4%), anemia (18.5%) **Gr 3:** hypoNa (5.6%), HTN/ALP increase (3.7%)	Active, not recruiting[164]

(*Continued*)

Trial Name (Clinical Trials Identifier)	Phase	Molecular Target	Treatment Regimen	Patients	Outcome	Adverse Events	Statusa [reference]
BilT-01 (NCT03101566)	Multicenter, randomized, phase 2	Unselected	**Arm A:** gemcitabine 1000 mg/m^2 + cisplatin 25 mg/m^2 D1, D8 every 3 weeks + nivolumab 360 mg D1 every 3 weeks (6 mo and 240 mg every 2 weeks) **Arm B:** Nivolumab 240 mg every 2 weeks + 1 mg/kg every 6 weeks (6 mo and then nivolumab 240 mg every 3 weeks)	N = 71 (35 Arm A, 36 Arm B)	**PFS rate, 6 mo:** 70% (A); 18.6% (B). **mPFS (A):** 8.8 mo (95% CI 6.1–12.3) **mPFS (B):** 4.1 mo (95% CI 2.4–5.2) **mOS (A):** 10.6 mo (6.8–not reached) **mOS (B):** 8.3 mo (5.9–16.9)	Pending	Active, not recruiting [165]
Durvalumab +/- tremelimumab biliary tract cancer expansion cohort (NCT01938612)	Phase 1, open-label, multicenter	Unselected	**Cohort 1:** Durvalumab 0 mg/kg every 2 weeks **Cohort 2:** Durvalumab 20 mg/kg + tremelimumab 1 mg/kg every 4 weeks	N = 42 (Durvalumab) N = 65 (Durvalumab + tremelimumab)	**PR** (D): n = 2 **PR** (D+T): n = 7 **DCR** (D): 16.7% **DCR** (D+T): 32.2% **mOS** (D): 8.1 mo (95% CI 5.6–10.1) **mOS** (D+T): 10.1 (95% CI 6.2–11.4)	Any Gr: 64% (D); 82% (D+T)	Active, not recruiting [166]

(*Continued*)

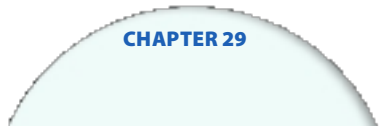


Table 29–6 Summary of Pertinent Immunotherapy Therapy Trials in Unresectable and Metastatic Biliary Tract Carcinoma *(Cont.)*

Trial Name (Clinical Trials Identifier)	Phase	Molecular Target	Treatment Regimen	Patients	Outcome	Adverse Events	Statusa [reference]
Durvalumab with gemcitabine-cisplatin +/– tremelimumab (NCT03046862)	Phase 2, open-label, first line	Unselected	**Cohort 1:** (**Biomarker**) gem 1000 mg/m^2 + cisplatin 25 mg/m^2 D1, D8, → gem/cis + durvalumab (1120 mg) + tremelimumab (75 mg) every 3 weeks **Cohort 2:** gem/cis + durvalumab **Cohort 3:** gem/cis + durvalumab + tremelimumab	Cohort 1: N = 30 Cohort 2: N = 45 Cohort 3: N = 46	**ORR (95% CI):** Biomarker: 50% (31.1–67.9) Cohort 2: 73.4% (60.5–86.3) Cohort 3: 73.3% (60.4–86.2) **DCR:** Biomarker: 96.7% Cohort 1: 100% Cohort 2: 97.8%	**Any Gr:** neutropenia (54.5%), nausea (59.5%), pruritus (55.4%) **Gr 3/4:** neutropenia (50.4%), anemia (35.5%), thrombocytopenia (16.5%)	Recruiting [167]

[a]Clinicaltrials.gov status as of 6/27/2020.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; D, durvalumab; DCR, disease control rate; HTN, hypertension; HypoNa, hyponatremia; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate; PD-L1, program death-ligand 1; PR, partial response; T, tremelimumab.

controls of PFS for gemcitabine-cisplatin alone, suggesting unclear survival benefit of nivolumab to standard-of-care chemotherapy at this time. Response rates, safety profiles, and survival data are pending maturity, which will shed further light on the clinical benefit and utility of the above combinations.

Durvalumab with or without tremelimumab has also been studied in the phase 1 setting (NCT01938612) in an Asian population.[166] A DCR and median OS of 16.7% and 8.1 months, and 32.2% and 10.1 months in the durvalumab (n = 42) arm compared with the durvalumab and tremelimumab (n = 65) arm, respectively, was reported at 12 weeks. Both the monotherapy and combination therapy arms were noted to show encouraging clinical benefit warranting further investigation.

Preliminary data from a phase 2 study of durvalumab and gemcitabine-cisplatin with or without tremelimumab in patients naïve to prior chemotherapy (NCT03046862)[167] has also been reported. Patients were enrolled in three cohorts as detailed in Table 29–6. Initial biomarker analyses noted frequent mutations in ataxia telangiectasia–mutated (*ATM*), *BRCA2*, DNA polymerase epsilon, mutS homolog 2 (*MSH2*), and *CDKN2A* genes with distinct somatic variants in responders compared with nonresponders. TMB had not correlated with survival outcomes (PFS or OS); however, interestingly, early reductions in cell-free circulating tumor (ct) DNA allele frequencies on cycle 3 on day 1 were significantly associated with ORR ($P < .015$). Response rates (73.4% and 73.3%) were similar in the three- and four-combination cohorts, and the triple combination (gemcitabine-cisplatin and durvalumab) has moved forward to phase 3 testing compared with gemcitabine-cisplatin alone in the first line (TOPAZ-1; NCT03875235).

In summary, the treatment of biliary tract cancer has evolved rapidly in the last decade. An understanding of the diversity of these cancers and their molecular underpinnings, and access to novel therapies have led to transformative changes for patients with this cancer.

MD ANDERSON APPROACH TO BILIARY TRACT CARCINOMA

Our approach to biliary tract cancer is guided by its clinical and molecular diversity and focuses on multidisciplinary management. Given the guarded prognosis of these cancers, clinical trials are encouraged in all clinical settings. The majority of cases of biliary tract cancer treated at our center are ICC, a trend that is commonly seen in all cancer centers in the United States. The diagnosis of ICC is established by a core-needle biopsy and includes an immunohistochemical analysis to exclude other sites of primary invasion. Routine endoscopies to rule out other primary sites are not performed in the absence of symptoms. High-quality liver protocol imaging is mandated for all patients, and PET/CT is used to examine ambiguous findings. Surgical resection with nodal dissection, followed by adjuvant capecitabine or gemcitabine and cisplatin is offered for patients with early-stage disease. Neoadjuvant chemotherapy with gemcitabine and cisplatin or gemcitabine, cisplatin, and nab-paclitaxel is considered for high-risk cases such as multifocal and radiologic node-positive diseases. Postoperative radiotherapy is usually reserved for margin-positive ICC.

Extrahepatic biliary tract cancers, particularly hilar cholangiocarcinoma (Klatskin tumor) requires a complex, multispecialty approach that includes endoscopy; interventional radiology; and medical, surgical, and radiation oncology teams. Complications from this cancer include biliary obstructions and cholangitis with sepsis, and therefore, establishment and maintenance of biliary drainage is critical. Specialized imaging to detect a hilar mass, vascular approximation, and nodal spread is required, and specific CT/MRI protocols have been established. A tissue diagnosis for these cancers is established with brush cytology or biopsy using endoscopic ultrasound. Core biopsy of the hilar stricture carries a risk of peritoneal dissemination and is therefore discouraged. A minority of patients are candidates for surgery and adjuvant therapy. Given the relatively limited benefit with adjuvant capecitabine for hilar cholangiocarcinoma, chemotherapy with gemcitabine and capecitabine, followed by chemoradiation with capecitabine as per prior phase 2 data (SWOG 0809) are encouraged. Select patients with hilar tumors larger than 3 cm and fitting the Mayo Clinic criteria are offered orthotopic liver transplantation. Gallbladder cancer in the early stages is often detected incidentally during cholecystectomy. For these cases and for surgically resectable tumors, radical cholecystectomy is performed, followed by adjuvant chemotherapy. Perioperative chemotherapy is often considered for a high-risk disease, such as with nodal disease, T3 tumors, and regional spread.

All patients with biliary tract cancer, regardless of stage or histology, are offered molecular profiling using next-generation sequencing. Furthermore, patients receiving targeted therapies are also offered serial liquid biopsies. Given the timeline for these analyses, targeted therapy is typically offered in the second or subsequent lines of treatment. Typical first-line regimens for biliary tract cancers include gemcitabine-cisplatin and gemcitabine-cisplatin-nab-paclitaxel, or clinical trials such as currently with a first-line FGFR inhibitor versus chemotherapy. Sequencing of therapies based on clinical outcomes, such as systemic chemotherapy followed by consolidative IMRT or SBRT, is commonly used in cholangiocarcinoma at MDACC.

Continuous chemotherapy until progression is not encouraged because this affects quality of life.

The choice of systemic therapy in the second-line setting is guided largely by molecular profiling results. ICC, in particular, is enriched with *FGFR, IDH1*, *BRAF*, and other actionable targets and has many options available as clinical trials; pemigatinib was recently FDA approved in this setting for ICC with *FGFR2* fusions. Biliary tract cancers without actionable mutations are usually treated with FOLFOX as per the ABC-06 clinical trial. The role of immunotherapy with checkpoint inhibitors is considered as experimental for biliary tract cancers, other than those tumors with MSI-H. However, several clinical trials are currently investigating the role of checkpoint inhibitors combined with systemic chemotherapy or radiotherapy.

MD ANDERSON PRACTICE TIPS

- Treatment is guided by clinical and molecular diversity and uses a multidisciplinary approach.
- In early-stage ICC, surgical resection with nodal dissection is followed by adjuvant capecitabine or gemcitabine-cisplatin; radiation therapy is given postoperatively for positive margins.
- Neoadjuvant chemotherapy is considered for disease with high-risk features, including presence of a multifocal disease or radiographic node positivity.
- Select patients meeting the Mayo Clinic criteria with hilar tumors smaller than 3 cm are candidates for orthotopic liver transplantation.
- All patients with biliary tract cancer are offered molecular profiling using next-generation sequencing.
- The choice of systemic therapy in the second-line metastatic setting is guided largely by molecular profiling results and actionable targets. *FGFR, IDH1, HER2*, and *BRAF* alterations are among the most enriched and numerous clinical trial options available for these patients.

REFERENCES

1. Uenishi T, Ariizumi S, Aoki T, et al. Proposal of a new staging system for mass-forming intrahepatic cholangiocarcinoma: a multicenter analysis by the Study Group for Hepatic Surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. *J Hepatobiliary Pancreat Sci.* 2014;21(7):499-508.
2. Vijgen S, Terris B, Rubbia-Brandt L. Pathology of intrahepatic cholangiocarcinoma. *Hepatobiliary Surg Nutr*. 2017;6(1):22-34.
3. Balitzer D, Joseph NM, Ferrell L, et al. Immunohistochemical and molecular features of cholangiolocellular carcinoma are similar to well-differentiated intrahepatic cholangiocarcinoma. *Mod Pathol.* 2019;32(10):1486-1494.
4. Bertram S, Padden J, Kalsch J, et al. Novel immunohistochemical markers differentiate intrahepatic cholangiocarcinoma from benign bile duct lesions. *J Clin Pathol.* 2016;69(7):619-626.
5. Adachi T, Haraguchi M, Irie J, et al. Gallbladder small cell carcinoma: a case report and literature review. *Surg Case Rep*. 2016;2(1):71.
6. Bahadur S, Shaukat A, Gibbs J, et al. Cisplatin and gemcitabine for small cell carcinoma of the gall bladder. *Am J Clin Oncol.* 2005;28(4):425-426.
7. Florio AA, Ferlay J, Znaor A, et al. Global trends in intrahepatic and extrahepatic cholangiocarcinoma incidence from 1993 to 2012. *Cancer.* 2020;126(11):2666-2678.
8. Khan SA, Tavolari S, Brandi G. Cholangiocarcinoma: Epidemiology and risk factors. *Liver Int.* 2019;39(suppl 1):19-31.
9. Saha SK, Zhu AX, Fuchs CS, Brooks GA. Forty-year trends in cholangiocarcinoma incidence in the U.S.: intrahepatic disease on the rise. *Oncologist.* 2016;21(5):594-599.
10. Lazcano-Ponce EC, Miquel JF, Munoz N, et al. Epidemiology and molecular pathology of gallbladder cancer. *CA Cancer J Clin.* 2001;51(6):349-364.
11. Rawla P, Sunkara T, Thandra KC, Barsouk A. Epidemiology of gallbladder cancer. *Clin Exp Hepatol*. 2019;5(2):93-102.
12. Schmidt MA, Marcano-Bonilla L, Roberts LR. Gallbladder cancer: epidemiology and genetic risk associations. *Chin Clin Oncol*. 2019;8(4):31.
13. Diehl AK. Gallstone size and the risk of gallbladder cancer. *JAMA.* 1983;250(17):2323-2326.
14. Aloia TA, Jarufe N, Javle M, et al. Gallbladder cancer: expert consensus statement. *HPB (Oxford).* 2015;17(8):681-690.
15. Shaib Y, El-Serag HB. The epidemiology of cholangiocarcinoma. *Semin Liver Dis.* 2004;24(2):115-125.
16. Khan SA, Toledano MB, Taylor-Robinson SD. Epidemiology, risk factors, and pathogenesis of cholangiocarcinoma. *HPB (Oxford).* 2008;10(2):77-82.
17. Burak K, Angulo P, Pasha TM, Egan K, Petz J, Lindor KD. Incidence and risk factors for cholangiocarcinoma in primary sclerosing cholangitis. *Am J Gastroenterol.* 2004;99(3):523-526.
18. Barr Fritcher EG, Kipp BR, Voss JS, et al. Primary sclerosing cholangitis patients with serial polysomy fluorescence in situ hybridization results are at increased risk of cholangiocarcinoma. *Am J Gastroenterol.* 2011;106(11):2023-2028.
19. Mhatre S, Wang Z, Nagrani R, et al. Common genetic variation and risk of gallbladder cancer in India: a case-control genome-wide association study. *Lancet Oncol.* 2017;18(4):535-544.
20. Cha PC, Zembutsu H, Takahashi A, Kubo M, Kamatani N, Nakamura Y. A genome-wide association study identifies SNP in DCC is associated with gallbladder cancer in the Japanese population. *J Hum Genet.* 2012;57(4):235-237.
21. Tsuchiya Y, Sato T, Kiyohara C, et al. Genetic polymorphisms of cytochrome P450 1A1 and risk of gallbladder cancer. *J Exp Clin Cancer Res*. 2002;21(1):119-124.
22. Sharma KL, Rai R, Srivastava A, et al. A multigenic approach to evaluate genetic variants of PLCE1, LXRs, MMPs, TIMP, and CYP genes in gallbladder cancer predisposition. *Tumour Biol.* 2014;35(9):8597-8606.
23. Castro FA, Koshiol J, Hsing AW, et al. Inflammatory gene variants and the risk of biliary tract cancers and stones: a population-based study in China. *BMC Cancer.* 2012;12:468.
24. Davidson JTt, Jin LX, Krasnick B, et al. Staging laparoscopy among three subtypes of extra-hepatic biliary malignancy: a 15-year experience from 10 institutions. *J Surg Oncol.* 2019;119(3):288-294.
25. Amin MB, Edge SB, Greene F, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. Springer; 2017.
26. Heimbach JK, Sanchez W, Rosen CB, Gores GJ. Transperitoneal fine needle aspiration biopsy of hilar cholangiocarcinoma is associated with disease dissemination. *HPB (Oxford).* 2011;13(5):356-360.
27. Ghazale A, Chari ST, Zhang L, et al. Immunoglobulin G4-associated cholangitis: clinical profile and response to therapy. *Gastroenterology.* 2008;134(3):706-715.
28. Zheng Y, Elsayes KM, Waranch C, et al. IgG4-related disease in the abdomen and pelvis: atypical findings, pitfalls, and mimics. *Abdom Radiol (NY)*. 2020;5(8):2485-2499.
29. Creasy JM, Goldman DA, Gonen M, et al. Evolution of surgical management of gallbladder carcinoma and impact on outcome: results from two decades at a single-institution. *HPB (Oxford).* 2019;21(11):1541-1551.
30. Bridgewater J, Galle PR, Khan SA, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *J Hepatol.* 2014;60(6):1268-1289.
31. Komaya K, Ebata T, Yokoyama Y, et al. Recurrence after curative-intent resection of perihilar cholangiocarcinoma: analysis of a large cohort with a close postoperative follow-up approach. *Surgery.* 2018;163(4):732-738.
32. Chua TC, Mittal A, Arena J, Sheen A, Gill AJ, Samra JS. Resection margin influences survival after pancreatoduodenectomy for distal cholangiocarcinoma. *Am J Surg.* 2017;213(6):1072-1076.
33. Creasy JM, Goldman DA, Dudeja V, et al. Systemic chemotherapy combined with resection for locally advanced gallbladder carcinoma: surgical and survival outcomes. *J Am Coll Surg.* 2017;224(5):906-916.
34. Shroff RT, Javle MM, Xiao L, et al. Gemcitabine, cisplatin, and nab-paclitaxel for the treatment of advanced biliary tract cancers: a phase 2 clinical trial. *JAMA Oncol.* 2019;5(6):824-830.
35. Maker AV, Butte JM, Oxenberg J, et al. Is port site resection necessary in the surgical management of gallbladder cancer? *Ann Surg Oncol.* 2012;19(2):409-417.
36. Charnsangavej C, Clary B, Fong Y, Grothey A, Pawlik TM, Choti MA. Selection of patients for resection of hepatic colorectal metastases: expert consensus statement. *Ann Surg Oncol.* 2006;13(10):1261-1268.
37. Ribero D, Zimmitti G, Aloia TA, et al. Preoperative cholangitis and future liver remnant volume determine the risk of liver failure in patients undergoing resection for hilar cholangiocarcinoma. *J Am Coll Surg.* 2016;223(1):87-97.
38. Komaya K, Ebata T, Fukami Y, et al. Percutaneous biliary drainage is oncologically inferior to endoscopic drainage: a propensity score matching analysis in resectable distal cholangiocarcinoma. *J Gastroenterol.* 2016;51(6):608-619.
39. Darwish Murad S, Kim WR, Harnois DM, et al. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. *Gastroenterology.* 2012;143(1):88-98 e83; quiz e14.
40. Schreuder AM, Engelsman AF, van Roessel S, et al. Treatment of mid-bile duct carcinoma: local resection or pancreatoduodenectomy? *Eur J Surg Oncol.* 2019;45(11):2180-2187.
41. Tao R, Krishnan S, Bhosale PR, et al. Ablative radiotherapy doses lead to a substantial prolongation of survival in patients with inoperable intrahepatic cholangiocarcinoma: a retrospective dose response analysis. *J Clin Oncol.* 2016;34(3):219-226.

42. Elganainy D, Holliday EB, Taniguchi CM, et al. Dose escalation of radiotherapy in unresectable extrahepatic cholangiocarcinoma. *Cancer Med.* 2018;7(10):4880-4892.
43. Yamashita S, Koay EJ, Passot G, et al. Local therapy reduces the risk of liver failure and improves survival in patients with intrahepatic cholangiocarcinoma: a comprehensive analysis of 362 consecutive patients. *Cancer.* 2017;123(8):1354-1362.
44. Potters L, Kavanagh B, Galvin JM, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) Practice Guideline for the Performance of Stereotactic Body Radiation Therapy. *Int J Radiat Oncol Biol Phys*. 2010;76(2):326-332.
45. Phillips JG, Wolfgang JA, Hong TS. Emerging techniques in image-guided radiation therapy and stereotactic body radiation therapy. In: Herman JM, Pawlik TM, Thomas JCR, eds. *Biliary Tract and Gallbladder Cancer: A Multidisciplinary Approach*. Springer–Berlin Heidelberg; 2014:311-320.
46. Kalbasi A, Ben-Josef E. External beam radiation therapy: 3D-conformal, intensity-modulated, and proton beam. In: Herman JM, Pawlik TM, Thomas JCR, eds. *Biliary Tract and Gallbladder Cancer: A Multidisciplinary Approach*. Springer–Berlin Heidelberg; 2014:283-293.
47. Crane CH, Koay EJ. Solutions that enable ablative radiotherapy for large liver tumors: Fractionated dose painting, simultaneous integrated protection, motion management, and computed tomography image guidance. *Cancer.* 2016;122(13):1974-1986.
48. Kavanagh BD, Schefter TE, Cardenes HR, et al. Interim analysis of a prospective phase I/II trial of SBRT for liver metastases. *Acta Oncol.* 2006;45(7):848-855.
49. Osmundson EC, Wu Y, Luxton G, Bazan JG, Koong AC, Chang DT. Predictors of toxicity associated with stereotactic body radiation therapy to the central hepatobiliary tract. *Int J Radiat Oncol Biol Phys.* 2015;91(5):986-994.
50. Andratschke NH, Nieder C, Heppt F, Molls M, Zimmermann F. Stereotactic radiation therapy for liver metastases: factors affecting local control and survival. *Radiat Oncol (London, England)*. 2015;10:69.
51. Mahadevan A, Dagoglu N, Mancias J, et al. Stereotactic body radiotherapy (SBRT) for intrahepatic and hilar cholangiocarcinoma. *J Cancer.* 2015;6(11):1099-1104.
52. Ben-Josef E, Normolle D, Ensminger WD, et al. Phase II trial of high-dose conformal radiation therapy with concurrent hepatic artery floxuridine for unresectable intrahepatic malignancies. *J Clin Oncol.* 2005;23(34):8739-8747.
53. Hong TS, Wo JY, Yeap BY, et al. Multi-institutional phase II study of high-dose hypofractionated proton beam therapy in patients with localized, unresectable hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Clin Oncol.* 2016;34(5):460-468.
54. Gonzalez Gonzalez D, Gerard JP, Maners AW, et al. Results of radiation therapy in carcinoma of the proximal bile duct (Klatskin tumor). *Semin Liver Dis.* 1990;10(2):131-141.
55. Crane CH, Macdonald KO, Vauthey JN, et al. Limitations of conventional doses of chemoradiation for unresectable biliary cancer. *Int J Radiat Oncol Biol Phys.* 2002;53(4):969-974.
56. Grossman SA, Ellsworth S, Campian J, et al. Survival in patients with severe lymphopenia following treatment with radiation and chemotherapy for newly diagnosed solid tumors. *J Natl Compr Canc Netw.* 2015;13(10):1225-1231.
57. Ben-Josef E, Guthrie KA, El-Khoueiry AB, et al. SWOG S0809: a phase II intergroup trial of adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine in extrahepatic cholangiocarcinoma and gallbladder carcinoma. *J Clin Oncol.* 2015;33(24):2617-2622.
58. Kato A, Shimizu H, Ohtsuka M, et al. Surgical resection after downsizing chemotherapy for initially unresectable locally advanced biliary tract cancer: a retrospective single-center study. *Ann Surg Oncol.* 2013;20(1):318-324.
59. Kuriyama N, Usui M, Gyoten K, et al. Neoadjuvant chemotherapy followed by curative-intent surgery for perihilar cholangiocarcinoma based on its anatomical resectability classification and lymph node status. *BMC Cancer.* 2020;20(1):405.
60. Le Roy B, Gelli M, Pittau G, et al. Neoadjuvant chemotherapy for initially unresectable intrahepatic cholangiocarcinoma. *Br J Surg.* 2018;105(7):839-847.
61. DeOliveira ML, Cunningham SC, Cameron JL, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg.* 2007;245(5):755-762.
62. Frosio F, Mocchegiani F, Conte G, et al. Neoadjuvant therapy in the treatment of hilar cholangiocarcinoma: review of the literature. *World J Gastrointest Surg*. 2019;11(6):279-286.
63. Lang H, Sotiropoulos GC, Sgourakis G, et al. Operations for intrahepatic cholangiocarcinoma: single-institution experience of 158 patients. *J Am Coll Surg.* 2009;208(2):218-228.
64. McMasters KM, Tuttle TM, Leach SD, et al. Neoadjuvant chemoradiation for extrahepatic cholangiocarcinoma. *Am J Surg.* 1997;174(6):605-608; discussion 608-609.
65. Poultsides GA, Zhu AX, Choti MA, et al. Intrahepatic cholangiocarcinoma. *Surg Clin North Am.* 2010;90(4):817-837.
66. Spolverato G, Vitale A, Cucchetti A, et al. Can hepatic resection provide a long-term cure for patients with intrahepatic cholangiocarcinoma? *Cancer.* 2015;121(22):3998-4006.
67. Nelson JW, Ghafoori AP, Willett CG, et al. Concurrent chemoradiotherapy in resected extrahepatic cholangiocarcinoma. *Int J Radiat Oncol Biol Phys.* 2009;73(1):148-153.
68. Hyder O, Hatzaras I, Sotiropoulos GC, et al. Recurrence after operative management of intrahepatic cholangiocarcinoma. *Surgery.* 2013;153(6):811-818.
69. Hasegawa S, Ikai I, Fujii H, et al. Surgical resection of hilar cholangiocarcinoma: analysis of survival and postoperative complications. *World J Surg.* 2007;31(6):1256-1263.
70. Jarnagin WR, Ruo L, Little SA, et al. Patterns of initial disease recurrence after resection of gallbladder carcinoma and hilar cholangiocarcinoma: implications for adjuvant therapeutic strategies. *Cancer.* 2003;98(8):1689-1700.
71. Komaya K, Ebata T, Yokoyama Y, et al. Recurrence after curative-intent resection of perihilar cholangiocarcinoma: analysis of a large cohort with a close postoperative follow-up approach. *Surgery.* 2018;163(4):732-738.
72. Hadjis NS, Blenkharn JI, Alexander N, et al. Outcome of radical surgery in hilar cholangiocarcinoma. *Surgery.* 1990;107(6):597-604.
73. Pichlmayr R, Weimann A, Klempnauer J, et al. Surgical treatment in proximal bile duct cancer. A single-center experience. *Ann Surg.* 1996;224(5):628-638.
74. Su CH, Tsay SH, Wu CC, et al. Factors influencing postoperative morbidity, mortality, and survival after resection for hilar cholangiocarcinoma. *Ann Surg.* 1996;223(4):384-394.
75. Wakai T, Shirai Y, Moroda T, et al. Impact of ductal resection margin status on long-term survival in patients undergoing resection for extrahepatic cholangiocarcinoma. *Cancer.* 2005;103(6):1210-1216.
76. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med.* 2010;362(14):1273-1281.
77. Ulusakarya A, Karray W, Abdou J, et al. FOLFIRINOX as a first-line chemotherapy for patients (pts) with advanced biliary tract cancer (BTC). *Ann Oncol.* 2018;29:viii260.
78. Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. *J Clin Oncol.* 2012;30(16):1934-1940.
79. Takada T, Amano H, Yasuda H, et al. Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase

III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. *Cancer.* 2002;95(8):1685-1695.
80. Ma KW, Cheung TT, Leung B, et al. Adjuvant chemotherapy improves oncological outcomes of resectable intrahepatic cholangiocarcinoma: a meta-analysis. *Medicine (Baltimore).* 2019; 98(5):e14013.
81. Sur MD, In H, Sharpe SM, et al. Defining the benefit of adjuvant therapy following resection for intrahepatic cholangiocarcinoma. *Ann Surg Oncol.* 2015;22(7):2209-2217.
82.. Edeline J, Benabdelghani M, Bertaut A, et al. Gemcitabine and Oxaliplatin Chemotherapy or Surveillance in Resected Biliary Tract Cancer (PRODIGE 12-ACCORD 18-UNICANCER GI): a randomized phase III study. *J Clin Oncol.* 2019;37:658-667.
83. Neoptolemos JP, Moore MJ, Cox TF, et al. Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs observation on survival in patients with resected periampullary adenocarcinoma: the ESPAC-3 periampullary cancer randomized trial. *JAMA.* 2012;308(2):147-156.
84. Primrose JN, Fox RP, Palmer DH, et al. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. *Lancet Oncol.* 2019;20(5):663-673.
85. Kelley ST, Bloomston M, Serafini F, et al. Cholangiocarcinoma: advocate an aggressive operative approach with adjuvant chemotherapy. *Am Surg.* 2004;70(9):743-748; discussion 748-749.
86. Kraybill WG, Lee H, et al. Multidisciplinary treatment of biliary tract cancers. *J Surg Oncol.* 1994;55(4):239-245.
87. Todoroki T, Ohara K, Kawamoto T, et al. Benefits of adjuvant radiotherapy after radical resection of locally advanced main hepatic duct carcinoma. *Int J Radiat Oncol Biol Phys.* 2000;46(3):581-587.
88. Lin YK, Hsieh MC, Wang WW, et al. Outcomes of adjuvant treatments for resectable intrahepatic cholangiocarcinoma: chemotherapy alone, sequential chemoradiotherapy, or concurrent chemoradiotherapy. *Radiother Oncol.* 2018;128(3):575-583.
89. Abrams MJ, Huber KE, Knisely JP, et al. Capecitabine as a radiosensitizer in adjuvant chemoradiotherapy for pancreatic cancer: a retrospective study. *Anticancer Res.* 2015;35(12):6901-6907.
90. Hofheinz RD, Wenz F, Post S, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. *Lancet Oncol.* 2012;13(6):579-588.
91. Blanquicett C, Saif MW, Buchsbaum DJ, et al. Antitumor efficacy of capecitabine and celecoxib in irradiated and lead-shielded, contralateral human BxPC-3 pancreatic cancer xenografts: clinical implications of abscopal effects. *Clin Cancer Res.* 2005;11(24 pt 1):8773-8781.
92. Chu E, Haller D, Cartwright T, et al. Epidemiology and natural history of central venous access device use and infusion pump function in the NO16966 trial. *Br J Cancer.* 2014;110(6):1438-1445.
93. Chijiiwa K, Sumiyoshi K, Nakayama F. Impact of recent advances in hepatobiliary imaging techniques on the preoperative diagnosis of carcinoma of the gallbladder. *World J Surg.* 1991;15(3):322-327.
94. Box JC, Edge SB. Laparoscopic cholecystectomy and unsuspected gallbladder carcinoma. *Semin Surg Oncol.* 1999;16(4):327-331.
95. Fuks D, Regimbeau JM, Le Treut Y-P, et al. Incidental Gallbladder Cancer by the AFC-GBC-2009 Study Group. *World J Surg.* 2011;35(8):1887-1897.
96. Goetze TO, Paolucci V. Adequate extent in radical re-resection of incidental gallbladder carcinoma: analysis of the German Registry. *Surg Endosc.* 2010;24(9):2156-2164.
97. Pawlik TM, Gleisner AL, Vigano L, et al. Incidence of finding residual disease for incidental gallbladder carcinoma: implications for re-resection. *J Gastrointest Surg.* 2007;11(11):1478-1486; discussion 1486-1477.
98. Varshney S, Butturini G, Gupta R. Incidental carcinoma of the gallbladder. *Eur J Surg Oncol.* 2002;28(1):4-10.
99. Wullstein C, Woeste G, Barkhausen S, Gross E, Hopt UT. Do complications related to laparoscopic cholecystectomy influence the prognosis of gallbladder cancer? *Surg Endosc.* 2002;16(5):828-832.
100. Romano F, Franciosi C, Caprotti R, et al. Laparoscopic cholecystectomy and unsuspected gallbladder cancer. *Eur J Surg Oncol.* 2001;27(3):225-228.
101. Søreide K, Guest RV, Harrison EM, et al. Systematic review of management of incidental gallbladder cancer after cholecystectomy. *Br J Surg.* 2019;106(1):32-45.
102. Okusaka T, Nakachi K, Fukutomi A, et al. Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. *Br J Cancer.* 2010;103(4):469-474.
103. Chhetri P, Giri A, Shakya S, Shakya S, Sapkota B, Pramod KC. Current development of anti-cancer drug S-1. *J Clin Diagn Res.* 2016;10(11):XE01-XE05.
104. Sakai D, Kanai M, Kobayashi S, et al. Randomized phase III study of gemcitabine, cisplatin plus S-1 (GCS) versus gemcitabine, cisplatin (GC) for advanced biliary tract cancer (KHBO1401-MITSUBA). ESMO 2018 abstract 6150. *Ann Oncol.* 2018;29(suppl 8):viii205.
105. McNamara MG, Bridgewater J, Palmer D, et al. A new ProTide, NUC-1031, combined with cisplatin for the first-line treatment of advanced biliary tract cancer (ABC-08). ESMO 2018 abstract 5616. *Ann Oncol.* 2018;29(suppl 8):viii205-viii270.
106. McNamara MG, Bridgewater JA, Palmer DH, et al. ABC-08: a phase Ib, multi-centre, open-label study of a first-in-class nucleotide analogue NUC-1031 in combination with cisplatin in patients with locally advanced/metastatic biliary tract cancers. 2019 ASCO Annual Meeting: digital program. *J Clin Oncol.* 2019;36(suppl 4):abstract TPS544.
107. Lamarka A, Palmer DH, Wasan HS, et al. ABC-06 | A randomised phase III, multi- centre, open-label study of active symptom control (ASC) alone or ASC with oxaliplatin / 5-FU chemotherapy (ASC+mFOLFOX) for patients (pts) with locally advanced / metastatic biliary tract cancers (ABC) previously-treated with cisplatin/gemcitabine (CisGem) chemotherapy. 2019 ASCO Annual Meeting: digital program. *J Clin Oncol.* 2019;37(suppl 15):abstract 4003.
108. Kim JW, Suh KJ, Kim JW, et al. A randomized phase II study of oxaliplatin/5-FU (mFOLFOX) versus irinotecan/5-FU (mFOLFIRI) chemotherapy in locally advanced or metastatic biliary tract cancer refractory to first-line gemcitabine/cisplatin chemotherapy. 2020 ASCO Annual Meeting: digital program. *J Clin Oncol.* 2020;38(suppl 15):abstract 4063.
109. Rogers JE, Law L, Nguyen VD, et al. Second-line systemic treatment for advanced cholangiocarcinoma. *J Gastrointest Oncol.* 2014;5(6):408-413.
110. Mizrahi JD, Gunchick V, Mody K, et al. Multi-institutional retrospective analysis of FOLFIRI in patients with advanced biliary tract cancers. *World J Gastrointest Oncol.* 2020;12(1):83-91.
111. Lamarca A, Hubner RA, David Ryder W, Valle JW. Second-line chemotherapy in advanced biliary cancer: a systematic review. *Ann Oncol.* 2014;25(12):2328-2338.
112. Kendall T, Verheij J, Gaudio E, et al. Anatomical, histomorphological and molecular classification of cholangiocarcinoma. *Liver Int.* 2019;39:7-18.
113. Andersen JB, Thorgeirsson SS. Genetic profiling of intrahepatic cholangiocarcinoma. *Curr Opin Gastroenterol.* 2012;28(3):266-272.
114. Churi CR, Shroff R, Wang Y, et al. Mutation profiling in cholangiocarcinoma: prognostic and therapeutic implications. *PLoS One.* 2014;9(12):e115383.

115. Javle M, Bekaii-Saab T, Jain A, et al. Biliary cancer: Utility of next-generation sequencing for clinical management. *Cancer.* 2016;122(24):3838-3847.
116. Lowery MA, Ptashkin R, Jordan E, et al. Comprehensive molecular profiling of intrahepatic and extrahepatic cholangiocarcinomas: potential targets for intervention. *Clin Cancer Res.* 2018;24:4154-4161.
117. Jain A, Kwong LN, Javle M. Genomic profiling of biliary tract cancers and implications for clinical practice. *Curr Treat Options Oncol.* 2016;17:58.
118. Jain A, Javle M. Molecular profiling of biliary tract cancer: a target rich disease. *Gastrointest Oncol*. 2016;7:797-803.
119. Javle M, Murugesan K, Shroff RT, et al. Profiling of 3,634 cholangiocarcinomas (CCA) to identify genomic alterations (GA), tumor mutational burden (TMB), and genomic loss of heterozygosity (gLOH). 2019 ASCO Annual Meeting: digital program. *J Clin Oncol*. 2019;37(suppl 15):abstract 4987.
120. Xue R, Chen L, Zhang C, et al. Genomic and transcriptomic profiling of combined hepatocellular and intrahepatic cholangiocarcinoma reveals distinct molecular subtypes. *Cancer Cell.* 2019;35:932-947.
121. Farshidfar F, Zheng S, Gingras MC, et al. Integrative genomic analysis of cholangiocarcinoma identifies distinct IDH-mutant molecular profiles. *Cell Rep.* 2017;19:2878-2880.
122. Pellino A, Loupakis F, Cadamuro M, et al. Precision medicine in cholangiocarcinoma. *Transl Gastroenterol Hepatol*. 2018;3:40.
123. Babina IS, Turner NC. Advances and challenges in targeting FGFR signalling in cancer. *Nat Rev Cancer.* 2017;17(5):318-332.
124. Touat M, Ileana E, Postel-Vinay S, et al. Targeting FGFR signaling in cancer. *Clin Cancer Res.* 2015;21(12):2684-2694.
125. Wu YM, Su F, Kalyana-Sundaram S, et al. Identification of targetable FGFR gene fusions in diverse cancers. *Cancer Discov.* 2013;3:636-647.
126. Arai Y, Totoko Y, Hosoda F, et al. Fibroblast growth factor receptor 2 tyrosine kinase fusions define a unique molecular sybtype of cholangiocarcinoma. *Hepatology.* 2014;59:1427-1434.
127. Bahleda R, Dienstmann R, Adamo B, et al. Phase I study of JNJ-42756493, a panfibroflast growth factor receptor (FGFR) inhibitor, in patients with advanced solid tumors. 2014 ASCO Annual Meeting: digital program. *J Clin Oncol.* 2014;32:5s(abstract 2501).
128. Javle M, Lowery M, Shroff RT, et al. Phase II study of BGJ398 in patients with FGFR-altered advanced cholangiocarcinoma. *J Clin Oncol.* 2018;36(3):276-282.
129. Javle M, Kelley RK, Roychowdhury S, *et al.* LBA28-Updated results from a phase II study of infigratinib (BGJ398), a selective pan-FGFR kinase inhibitor, in patients with previously treated advanced cholangiocarcinoma containing FGFR2 fusions. Presented at the ESMO 2018 Congress, October 19-23, 2018; Munich, Germany.
130. Wöhrle S, Henninger C, Bonny O, et al. Pharmacological inhibition of fibroblast growth factor (FGF) receptor signaling ameliorates FGF23-mediated hypophosphatemic rickets. *J Bone Miner Res.* 2013;28(4):899-911.
131. Chae YK, Ranganath K, Hammerman PS, et al. Inhibition of the fibroblast growth factor receptor (FGFR) pathway: the current landscape and barriers to clinical application. *Oncotarget.* 2017;8(9):16052-16074.
132. Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. *Lancet Oncol.* 2020;21(5):671-684.
133. Meric-Bernstam F, Arkenau H, Tran B, et al. Efficacy of TAS-120, an irreversible fibroblast growth factor receptor (FGFR) inhibitor, in cholangiocarcinoma patients with FGFR pathway alterations who were previously treated with chemotherapy and other FGFR inhibitors. ESMO 2018 abstract O-001. *Ann Oncol.* 2018;29(suppl 5).
134. Goyal L, Meric-Bernstam F, Hollebecque A, et al. FOENIX-CCA2: A phase II, open-label, multicenter study of futibatinib in patients (pts) with intrahepatic cholangiocarcinoma (iCCA) harboring FGFR2 gene fusions or other rearrangements. 2020 ASCO Annual Meeting: digital program. *J Clin Oncol.* 2020;38(suppl 15):abstract 108.
135. Bahleda R, Italiano A, Hierro C et al. Multicenter phase I study of erdafitinib (JNJ-42756493), oral pan-fibroblast growth factor receptor inhibitor, in patients with advanced or refractory solid tumors. *Clin Cancer Res.* 2019;25(16):4888-4897.
136. Porta R, Borea R, Coelho A, et al. FGFR a promising druggable target in cancer: molecular biology and new drugs. *Crit Rev Oncol Hematol.* 2017;113:256-267.
137. Soria JC, DeBraud F, Bahleda R. et al. Phase I/IIa study evaluating the safety, efficacy, pharmacokinetics, and pharmacodynamics of lucitanib in advanced solid tumors. *Ann Oncol.* 2014;25(11):2244-2251.
138. Smyth EC, Turner NC, Peckitt C, et al. Phase II multicenter proof of concept study of AZD4547 in FGFR amplified tumours. 2015 ASCO Annual Meeting: digital program. *J Clin Oncol.* 2015;33(suppl 15):abstract 2508.
139. Cleary JM, Iyer G, Oh DY, et al. Final results from the phase I study expansion cohort of the selective FGFR inhibitor Debio 1347 in patients with solid tumors harboring an FGFR gene fusion. 2020 ASCO Annual Meeting: digital program. *J Clin Oncol.* 2020;38(suppl):abstract 3603.
140. Makawita S, Abou-Alfa G, Roychowdhury S, et al. Infigratinib in patients with advanced cholangiocarcinoma with FGFR2 gene fusions/translocations: the PROOF 301 trial. *Future Oncol*. 2020;16(30):2375-2384.
141. Lowery MA, Burris HA 3rd, Janku F, et al. Safety and activity of ivosidenib in patients with IDH1-mutant advanced cholangiocarcinoma: a phase 1 study. *Lancet Gastroenterol Hepatol*. 2019;4(9):711-720.
142. Abou-Alfa GK, Macarulla T, Javle MM, et al. Ivosidenib in IDH1-mutant, chemotherapy- refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol.* 2020;21(6):796-807.
143. de la Fouchardiere C. Towards greater clarity in the treatment of cholangiocarcinoma. *Lancet Oncol.* 2020;21(6):738-739.
144. Demols A, Borbath I, Van den Eynde M, et al. Exploratory analysis based on tumor location of REACHIN, a randomized, double-blinded, placebo controlled phase 2 trial of regorafenib after failure of gemcitabine and platinum-based chemotherapy for advanced/metastatic biliary tract tumors. *Ann Oncol.* 2019;30(suppl 4):iv127.
145. Javle M, Churi C, Kang HC, et al. HER2/neu-directed therapy for biliary tract cancer. *J Hematol Oncol.* 2015;8:58.
146. Li BT VM, Buonocore DJ, Offin MD, et al. A multi-histology basket trial of ado-trastuzumab emtansine in patients with HER2 amplified cancers. 2019 ASCO Annual Meeting: digital program. *J Clin Oncol.* 2018;36(suppl):abstract 2502.
147. Javle MM, Hainsworth JD, Swanton C, et al. Pertuzumab + trastuzumab for HER2-positive metastatic biliary cancer: preliminary data from MyPathway. *J Clin Oncol.* 2017;35:402.
148. Jhaveri KL, Wang XV, Makker V, et al. Ado-trastuzumab emtansine (T-DM1) in patients with HER2-amplified tumors excluding breast and gastric/gastroesophageal junction (GEJ) adenocarcinomas: results from the NCI-MATCH trial (EAY131) subprotocol Q. *Ann Oncol.* 2019;30(11):1821-1830.
149. Meric-Bernstam F, Johnson AM, Dumbrava EEI, et al. Advances in HER2-targeted therapy: novel agents and opportunities beyond breast and gastric cancer. *Clin Cancer Res.* 2019;25(7):2033-2041.
150. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. *N Engl J Med.* 2015;373(8):726-736.

151. Wainberg, ZA, Lassen UN, Elez E, et al. Efficacy and safety of dabrafenib (D) and trametinib (T) in patients (pts) with BRAF V600E–mutated biliary tract cancer (BTC): A cohort of the ROAR basket trial. 2019 ASCO Annual Meeting: digital program. *J Clin Oncol.* 2019;37:(suppl 4):abstract 187.
152. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N Engl J Med.* 2018;378(8):731-739.
153. Simone V, Brunetti O, Lupo L, et al. Targeting angiogenesis in biliary tract cancers: an open option. *Int J Mol Sci.* 2017;18(2):418.
154. Kabbinavar F, Hurwitz HI, Fehrenbacher L. et al. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. *J Clin Oncol.* 2003;21(1):60-65.
155. Spratlin J. Ramucirumab (IMC-1121B): monoclonal antibody inhibition of vascular endothelial growth factor receptor-2. *Curr Oncol Rep.* 2011;13(2):97-102.
156. Guion-Dusserre JF, Lorgis V, Vincent J, Bengrine L, Ghiringhelli F. FOLFIRI plus bevacizumab as a second-line therapy for metastatic intrahepatic cholangiocarcinoma. *World J Gastroenterol.* 2015;21(7):2096-2101.
157. Mizrahi J, Javle M, Xiao L et al. A phase II study of ramucirumab for advanced, pre-treated biliary cancers. 2018 ASCO Annual Meeting: digital program. *J Clin Oncol.* 2018;36(suppl 15):abstract 4081.
158. Valle JW, Li-Yuan B, Orlova R, et al. Ramucirumab (RAM) or merestinib (MER) or placebo (PL) plus gemcitabine (GEM) and cisplatin (CIS) as first-line treatment for advanced or metastatic biliary tract cancer (BTC): a randomized, double-blind, phase II study. 2020 GI ASCO Symposium: digital program. *J Clin Oncol.* 2020;38(4 suppl 477).
159. Arkenau HT, Martin-Liberal J, Calvo E, et al. Ramucirumab plus pembrolizumab in patients with previously treated advanced or metastatic biliary tract cancer: nonrandomized, open-label, phase I trial (JVDF). *Oncologist.* 2018;23(12):1407-e1136.
160. Goyal L, Zheng H, Yurgelun MB, et al. A phase 2 and biomarker study of cabozantinib in patients with advanced cholangiocarcinoma. *Cancer.* 2017;123(11):1979-1988.
161. Kelley RK, Bridgewater J, Gores GJ, Zhu AX. Systemic therapies for intrahepatic cholangiocarcinoma. *J Hepatol.* 2020;72(2):353-363.
162. Bang Y, Ueno M, Malka D, et al. Pembrolizumab (pembro) for advanced biliary adenocarcinoma: results from the KEYNOTE-028 (KN028) and KEYNOTE-158 (KN158) basket studies. *J Clin Oncol.* 2019;37:4079.
163. Piha-Paul SA, Oh DY, Ueno M, et al. Efficacy and safety of pembrolizumab for the treatment of advanced biliary cancer: results from the KEYNOTE-158 and KEYNOTE-028 studies. *Int J Cancer.* 2020;147(8):2190-2198.
164. Kim RD, Chung V, Alese OB, et al. A phase 2 multi-institutional study of nivolumab for patients with advanced refractory biliary tract cancer. *JAMA Oncol.* 2020;6(6):1-8.
165. Sahai V, Griffith KA, Beg MS, et al. A multicenter randomized phase II study of nivolumab in combination with gemcitabine/cisplatin or ipilimumab as first-line therapy for patients with advanced unresectable biliary tract cancer (BilT-01). 2020 ASCO Annual Meeting: digital program. *J Clin Oncol.* 2020;38(suppl):abstract 4582.
166. Tatsuya Ioka, Makoto Ueno, Do-Youn Oh, et al. Evaluation of safety and tolerability of durvalumab (D) with or without tremelimumab (T) in patients (pts) with biliary tract cancer (BTC). *J Clin Oncol*. 2019;37:387.
167. Oh DY, Lee KH, Lee KW, et al. Phase II study assessing tolerability, efficacy, and biomarkers for durvalumab (D) ± tremelimumab (T) and gemcitabine/cisplatin (GemCis) in chemo-naïve advanced biliary tract cancer (aBTC). 2020 ASCO Annual Meeting: digital program. *J Clin Oncol.* 2020;38(suppl):abstract 4520.

This page intentionally left blank

30 Hepatocellular Carcinoma

Sunyoung S. Lee
Hao Chi Zhang
Hop S. Tran Cao
Sudha Kodali
Joshua D. Kuban
Eugene J. Koay
Rony Avritscher
Ahmed O. Kaseb

KEY CONCEPTS

- Risk factors for liver cirrhosis and hepatocellular carcinoma (HCC) include chronic hepatitis B and C infections, metabolic syndrome, and alcohol abuse. Hepatology management of risk factors reduces the risk of cancer recurrence.
- Treatment for HCC is multidisciplinary and involves hepatology; interventional radiology; and medical, surgical, and radiation oncology.
- Surgical resection is considered for patients who have small-volume disease without portal hypertension. Those with portal hypertension receive locoregional and/or radiation therapy, and liver transplantation is considered.
- Systemic therapy is recommended for patients with advanced or metastatic HCC, and locoregional and radiation therapy are combined in eligible patients.
- Targeted therapy (anti-vascular endothelial growth factor and tyrosine kinase inhibitors) and immune checkpoint inhibitors are two main backbones of systemic therapy. These include sorafenib, lenvatinib, atezolizumab with bevacizumab, nivolumab with and without ipilimumab, pembrolizumab, cabozantinib, regorafenib, and ramucirumab.
- There are no established guidelines for fibrolamellar HCC (FLHCC) and combined HCC-cholangiocarcinoma (cHCC-CC). Systemic therapy such as 5-fluorouracil plus interferon-α2b for FLHCC and platinum-based chemotherapy for cHCC-CC is combined with surgical resection and locoregional and radiation therapy.

Hepatocellular carcinoma (HCC) is a malignancy of worldwide significance and has become increasingly important in the United States (US). It is the most common primary liver malignancy, the sixth most common cancer, and the third most common cause of cancer-related deaths worldwide.[1] Eighty percent of new cases occur in developing countries, but the incidence is rising in economically developed regions, including Japan, Western Europe, and the US.[2–5] Liver cirrhosis is the seventh leading cause of death in the world, the tenth most common cause of death in the US, and is acknowledged as a premalignant condition for developing HCC.[6,7]

In the US, hepatitis C virus (HCV), alcohol use, and nonalcoholic fatty liver disease (NAFLD) are the most common causes of cirrhosis.[8] The incidence of HCC doubled between the years 1975 to 1995 and continued to rise through 1998.[9,10] This trend was previously expected to continue because of the estimated 4 million US individuals who are HCV-seropositive and the known latency of HCC development from the initial HCV infection, which may take two to three decades.[10] However, given the improved treatment regimens now available for patients with chronic HCV, HCV-related HCC incidence may decrease in the next few years.[11] It is also known that NAFLD-associated cirrhosis is on the rise in the US.[12–14] A majority of patients diagnosed with HCC present with advanced disease that is not amenable to curative procedures.

EPIDEMIOLOGY

Hepatocellular carcinoma represents approximately 85% of all primary liver cancers.[15] The distribution of HCC varies significantly by geography; it is endemic in parts of the world where hepatitis B virus (HBV) is also endemic. In Western countries, HCV infection

and alcoholic cirrhosis are the principal risk factors for HCC. Because of the rising incidence of HCV infection in American subpopulations, the incidence has increased.[10] Moreover, HCC incidence increases with age, with the age of peak incidence varying somewhat with the population. The median age group for development of HCC is between the fifth and sixth decades of life. The disease is also seen in children and young adults in areas where HBV is endemic, and most of these infections occur perinatally. In all populations worldwide, there is a strong male predominance in HCC incidence. In the US, the male-to-female ratio is 2.7:1, and HCC incidence rates are higher among Blacks than Whites (6.1 vs 2.8 per 100,000 in men). Hispanics, Asians, Pacific Islanders, and Native Americans have a higher HCC frequency. Independent of HBV status, a family history of HCC in first-degree relatives carries a relative risk of 2.4 and overall risk (OR) of 2.9.[16] Hepatoblastoma is the most common type of childhood liver cancer, and Beckwith-Wiedemann syndrome is known to be associated with this.[17] Familial aggregation and germline mutations of the *APC* (adenomatous polyposis coli) gene have also been reported in hepatoblastoma.[18] Hereditary tyrosinemia, type 1 glycogen storage disease, Alagille syndrome, Fanconi anemia, and ataxia-telangiectasia increase the risk of HCC.[19–25]

ETIOLOGY AND RISK FACTORS

HCC develops commonly, but not exclusively, in a setting of liver cell injury, which leads to inflammation, hepatocyte regeneration, liver matrix remodeling, fibrosis, and ultimately cirrhosis. The major etiologies of liver cirrhosis are diverse and include chronic hepatitis B and chronic hepatitis C infections, chronic alcohol consumption, certain medications or toxic exposures, and genetic metabolic diseases. Nonalcoholic fatty liver disease, especially in association with obesity and diabetes, is emerging as a recognized risk factor for HCC, even in patients without cirrhosis. The mechanisms by which these varied etiologies lead to HCC are not fully elucidated. The principal risk factors that have been associated with cirrhosis and HCC are listed in Table 30–1. As such, the populations deemed to bear a significant risk for HCC generally reflect the same population for which routine screening is targeted (Table 30–2). The recommendations for the target population are also deemed to be cost-effective.[26] The ability of the clinician to identify at-risk patients eligible for HCC screening should be emphasized because utilization of HCC screening is revealed to be suboptimal, even among patients with a gastroenterology subspecialist.[27,28] This has significant implications for early detection of HCC and treatment options.

Chronic Hepatitis B Infection

Chronic infection HBV remains common and well recognized as a strong risk factor for HCC. An important mechanism in HBV is the integration of HBV DNA into the cellular DNA of hepatocytes.[29,30] Effects on transcription factors, JAK/STAT pathways, and DNA repair, even in the absence of fibrosis, may be a culprit in the pathogenesis.[29,31] In vitro studies suggest that the X protein encoded by HBV plays a role in the pathogenesis of HCC through the mechanism of HBV binding to and inhibiting p53-mediated transcriptional activity and downregulating DNA repair ability.[32] It is hypothesized that this mechanism is related to potential carcinogenesis, augmented by HBV replication in the case of active chronic HBV.

The estimated 5-year cumulative frequency of progression to cirrhosis ranges from 8% to 20% without treatment for HBV, at higher frequencies in HBV e-antigen (HBeAg)-negative patients relative to HBeAg-positive patients.[29] The incidence of HCC in patients with chronic HBV without cirrhosis is estimated to be 0.1 to 0.8 per 100 person-years, in contrast to 2.2 to 4.3 per 100 person-years in the context of cirrhosis.[33] Based on the examination of ethnicity, geographic origin, and medical history, certain high-risk groups have been identified in the recommendations to implement HCC screening.[26,29,33]

Hepatitis B virus replication also correlates with HCC risk.[34] Patients with active chronic HBV with ongoing viremia should also be screened, although chronic HBV treatment is available and considered safe. However, achieving viral suppression may not reduce the risk of HCC to nil, and this population continues to be screened. Inactive carriers who are HBeAg-negative also bear a higher risk for HCC compared with controls who are HBsAg-negative.[34,35] Although not tested for routinely, genotype C in Asians, genotype F in Alaskans, and mutations in precore or basal core promoter regions have been implicated in increased HCC risk.[31,34]

The at-risk population in chronic HBV with or without cirrhosis should undergo routine HCC screening.[29,30,33] Screening also applies to patients who have achieved viral suppression (ie, undetectable HBV DNA levels, normal serum alanine aminotransferase level) who are HBsAg-positive because ongoing treatment does not entirely eliminate the risk for HCC. The REACH-B scoring system allows the clinician to readily input data including gender, age, serum alanine aminotransferase level, HBeAg status, and HBV DNA levels to generate a 3-, 5-, and 10-year estimates for the risk of development of HCC.[36,37]

Chronic Hepatitis C Infection

Hepatocellular carcinoma in the context of chronic HCV is diagnosed more frequently in the cirrhotic liver

Table 30–1 Etiologic Factors Associated with an Increased Risk of Cirrhosis and Hepatocellular Carcinoma

Category	Specific Etiology	Comment
Infectious (77% of cases of HCC worldwide attributed to viral hepatitis)	Chronic hepatitis B virus infection	Underlying etiology in a significant majority of HCC cases worldwide, primarily in Asia, sub-Saharan Africa; patients without cirrhosis are at increased risk of HCC
	Chronic hepatitis C virus infection	Principal underlying etiology in Japan, the United States, Western Europe, Mediterranean basin countries; may account for 20%–25% HCC cases worldwide
Metabolic disorders deficiency	Hereditary hemochromatosis	Phlebotomy in patients whose disease has progressed to cirrhosis does not alter or improve the HCC risk
	Wilson disease	
	α-1 antitrypsin deficiency	
	Porphyria cutanea tarda	
	Glycogen storage disease (GSD)	HCC risk is best described in GSD type I via adenoma transformation
	Citrullinemia	
	Familial intrahepatic cholestasis	
Other	Alcohol	Significant cause of cirrhosis; synergistic cofactor with HCV
	Aflatoxin B_1	Cofactor with HBV that increases risk of developing HCC; relative risk varies from 2- to 4-fold in nonendemic regions
	Androgenic steroids	Some association reported, primarily case reports and small series
	Oral contraceptives	
	Autoimmune hepatitis	
	Primary biliary cholangitis (PBC)	Elevated HCC risk is pertinent when disease progresses to cirrhosis or in male patients with PBC
	Nonalcoholic fatty liver disease (NAFLD)/ nonalcoholic steatohepatitis (NASH)	Increasing evidence for association with HCC with or without cirrhosis; incidence of NAFLD is rising in the United States
	Tobacco	Weak association suggested that it is independent of HBV infection, alcohol

than in the non-cirrhotic liver.[38] Unlike HBV, HCV does not integrate into the host DNA. The exact mechanism of carcinogenesis is not well understood. The risk of developing HCC further increases with concomitant alcohol use, which may act in synergy.[39]

Pertinent risk factors for acquiring HCV include but are not limited to intravenous drug use, sexual exposure, chronic hemodialysis, blood transfusions before year the 1992, perinatal transmission, and acquiring tattoos/piercings at unregulated establishments.[40,41] In the US, the birth cohort of patients born between 1945 and 1965 directed prior screening recommendations.[41,42] In 2020, the US Services Preventative Task Force updated the screening recommendation to include general screening of patients ages 18 to 79 years for HCV infection.[43] Expanding the screening cohort allows for identification of the undiagnosed population. As such, eligible patients can be promptly treated to achieve sustained viral remission (SVR), preferably before cirrhosis develops, thereby curtailing the progression to cirrhosis and, subsequently, the risk for developing HCC.

With interferon (IFN)-based therapies, the annual incidence of HCC could be reduced from 1% to 8% to 0.07% to 1.2%.[31,44] The motivation for treatment is further driven by the advent and efficacy of direct-acting antivirals (DAAs) used to treat chronic HCV.[33] DAAs have become the standard for chronic HCV treatment since 2014, supplanting IFN-based treatment, which was fraught with limitations including genotype coverage and adverse effects. DAAs have better tolerance and improved adverse effect profiles

Table 30–2 Patients at Highest Risk for HCC with Recommendations for Screening

Population Group	Threshold Incidence for Efficacy of Surveillance (>0.25 LYG; % per year)	Incidence of HCC (% range per year)
Surveillance Benefit		
Asian male hepatitis B carriers over age 40 y	0.2	0.4–0.6
Asian female hepatitis B carriers over age 50 y	0.2	0.3–0.6
Hepatitis B carrier with family history of HCC	0.2	Incidence higher than without family history
African and/or North American Blacks with hepatitis B	0.2	HCC occurs at a younger age
Hepatitis B carriers with cirrhosis	0.2–1.5	3–8
Hepatitis C cirrhosis	1.5	3–5
Stage 4 PBC	1.5	3–5
Genetic hemochromatosis and cirrhosis	1.5	Unknown, but probably >1.5
Alpha-1 antitrypsin deficiency and cirrhosis	1.5	Unknown, but probably >1.5
Other cirrhosis	1.5	Unknown
Surveillance Benefit		
Hepatitis B carriers younger than 40 y (males) or 50 y (females)	0.2	<0.2
Hepatitis C and stage 3 fibrosis	1.5	<1.5
NAFLD without cirrhosis	1.5	<1.5%

LYG, life-years gained; PBC, primary biliary cholangitis.
Reproduced with permission from Marrero JA, Kulik LM, Sirlin CB, et al: Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases, Hepatology 2018 Aug;68(2):723-750.

to allow for achieving SVR after 8 to 12 weeks of treatment. Effective pan-genotypic coverage by glecaprevir/pibrentasvir and sofosbuvir/velpatasvir has overcome the challenges of treating some patients with HCV, such as those with genotype 3. Several DAAs, including these two medications, have also been approved for treatment in patients with compensated cirrhosis. In non-cirrhotic patients, SVR may curtail the risk of progression to cirrhosis and even potentially reduce the extent of fibrosis. In cirrhotic patients, SVR reduces but does not eliminate the risk of HCC.[44]

Once SVR is achieved, the risk of HCC persists. In a Veterans Affairs study, SVR led to a reduced risk of HCC to an annual incidence of 0.90%, in contrast to a higher annual incidence of 3.45% in those who did not achieve SVR.[45] In comparison, in patients who achieved SVR after receiving IFN-based therapies, the annual incidence was estimated to be 0.33%.[45,46] Direct-acting antiviral treatment was not without controversy in the field of HCC. One study was concerned that SVR with DAA still led to a 3.16% rate of developing de novo HCC; for the patients already treated for HCC, the study reported recurrence in 28.81% of patients.[47] Another study reported recurrence of HCC in 27.6% of the examined cohort.[48] Additional studies, however, did not support the aforementioned concern.[49,50] Nonetheless, after achieving SVR, these patients continue to undergo HCC screening or surveillance.[30,33]

Although some data have suggested that HCC can potentially arise in the non-cirrhotic liver, a formal recommendation about routine screening in this population is not established.[51,52] Specifically, there is risk observed in patients with bridging fibrosis without frank cirrhosis.[52] The American Association for the Study of Liver Diseases (AASLD) recognizes chronic HCV with advanced fibrosis (stage 3) without cirrhosis as being at an increased risk.[33] The decision of whether to screen this population is also predicated on the clinician's ability to reliably ascertain the fibrosis stage. Several noninvasive methods (such as the NAFLD fibrosis score, serologic fibrosis tests, and elastography) are available.

Some of the principal differences between hepatitis B- and hepatitis C-associated HCC are listed in Table 30–3.

Table 30–3 Comparison Between Hepatitis B Viral Infection and Hepatitis C Infection and Hepatocellular Carcinoma

Factor	HBV	HCV
Mean age (y) of HCC presentation (range)	55 (31–76)	66 (38–83)
Highest incidence	400 million carriers in Asia and Africa	170 million infected worldwide; accounts for 50% of HCC cases in Japan, the United States, and Western Europe
Cirrhosis	Cirrhosis presents in 88% of HBV infection	Cirrhosis presents in 93% of HCV infection
Morphology	Solitary lesions	Multifocal lesions, more severe inflammation
Rate of progression to HCC (y)	10–30	>30
Percentage likely to develop HCC	4% per year	1–7% per year

Metabolic Factors

Diabetes

The association of diabetes with the increased risk of HCC has been previously described, although with limitations inherent in the published studies, including confounding factors such as viral hepatitis C.[31,53] A study of VA patients comparing diabetic and nondiabetic patients, the majority comprised of men, demonstrated a doubling of the risk (HR 2.16), independent of alcoholic history, viral hepatitis, or demographics features.[53] Despite achieving SVR in HCV, diabetes is still a risk factor for HCC.[46]

Obesity

The high prevalence of obesity in the US has real clinical implications on liver health. Body mass index (BMI) alone, however, does not adequately account for the increased risk in developing HCC. One systematic review showed a positive association in 7 of 10 cohort studies, no associations in two studies, and even one study suggesting an inverse relationship.[54] The association between BMI and HCC may instead be clarified by identification of intermediary factors known as "proximal" associations, including abdominal fat (instead of BMI, which is considered a "distal" association), humoral mechanisms, and steatohepatitis.[55] Abdominal visceral fat, for instance, correlates with the waist-to-hip ratio. An elevated waist-to-hip ratio may confer up to about a 3.5-fold higher risk for development of HCC, implying that abdominal visceral fat plays a major role.[56,57] Because patients with obesity and/or metabolic syndrome are also at risk for NAFLD, careful evaluation for NAFLD should be made in conjunction.

Nonalcoholic Fatty Liver Disease

The widespread prevalence of NAFLD has prompted concern for its implications in patients whose disease evolves into a state of steatohepatitis and transforms to cirrhosis. These considerations have garnered particular interest in defining the degree of HCC risk in this population.

Certain genetic factors have been implicated in the pathophysiology of NAFLD/nonalcoholic steatohepatitis (NASH). Genetic variants of the *PNPLA3* (patatin-like phospholipase domain–containing 3) gene are hypothesized to play a role in the progression of NAFLD.[58–60] For instance, the *PNPLA3* polymorphism rs738409[G] (genotype GG), encoding I148M, is linked to increased hepatic fat levels and hepatic inflammation.[59] The prevalence of *PNPLA3* genotype CC (wild-type) is decreased in cases of NAFLD-related HCC.[61] In patients with NAFLD or alcoholic liver disease, wherein 11.5% of patients with NAFLD had HCC, the *KCNQ1* genotype TT was found to be significant in patients with HCC.[61]

NAFLD is increasingly recognized as a common etiology of cirrhosis. Some patients diagnosed with "cryptogenic" cirrhosis are also felt to have potentially undiagnosed NASH as an underlying etiology.[62] In these cases, HCC tended to present as a single nodule and with lower rates of portal vein thrombosis, compared with the other three underlying conditions.[62] Consequently, delineating the potential risks in the NAFLD population without cirrhosis is important. Broadly, the absolute risk in this population is not known; small studies indicate an estimated annual incidence less than 1% versus 2.6% in cirrhosis related to NASH.[33,63–65] The AASLD recognizes NAFLD without cirrhosis as bearing increased risk.[33]

The observation that HCC could arise in non-cirrhotic NAFLD has generated newfound vigilance.[64–66] The prevalence of HCC in patients with non-cirrhotic NASH was 38% (odds ratio [OR] of 2.61 vs the non-cirrhotic control).[67] From the national Veterans Affairs database, for those diagnosed with HCC in the absence of cirrhosis, both NAFLD and metabolic syndrome conferred increased risk with odds ratios of 5.4 and 5.0, respectively, when compared with HCV-related HCC.[68] Male gender, alcohol consumption, and the FIB-4 index (fibrosis score) are recognized risk factors.[69] One study suggested cumulative HCC mortality of potentially 0% to 3% over 20 years in patients without cirrhosis, and that NASH-related cirrhosis bore a cumulative risk of 2.4% over 7 years to 12.8% over 3 years; yet, the risk remained lower than that of cirrhosis related to hepatitis C.[70]

Even if the risk is perceived to be relatively lower than some other risk factors for HCC, the population-attributable fraction may argue for NAFLD being a more salient risk factor, especially when viewed in conjunction with metabolic syndrome.[33,55] The observation of an apparently increased HCC risk in patients with non-cirrhotic NAFLD emphasizes the importance of estimating fibrosis, identification of other concurrent HCC risk factors, and ongoing follow-up to continuously reassess risk and candidacy for undergoing an HCC screening program. These patients would benefit from engaging in related conversations with a hepatologist. Liver fibrosis estimation tools allow for a noninvasive way of risk-stratifying these patients in those clinical discussions.[71] Weight loss efforts remain the first-line recommendation for patients to potentially reduce steatosis, improve steatohepatitis, and in some cases reverse fibrosis, to secondarily reduce the risk of developing cirrhosis and HCC.

Glycogen Storage Diseases

Glycogen storage diseases (GSDs) represent disorders of inborn errors related to glucose or glycogen metabolism. Cases of HCC have been described in GSD type I, a rare autosomal recessive genetic disease. The association between GSD subtype Ia (related to deficiency in the glucose-6-phosphatase enzyme) and HCC is most commonly recognized. Hepatic malignancy in the context of GSD type I is hypothesized to arise from an adenoma-to-HCC transformation sequence.[72–74] The prevalence of hepatic adenomas is estimated to be up to 75% of adults with GSD type I and further increases with age.[72,75,76] The pathogenesis of these hepatic adenomas are thought to be related to inadequate metabolic control; improved metabolic control could lead to some degree of regression of the adenomas.[72,75] With hepatic adenomas, the risk is estimated to be about 10% for malignant transformation.[75] However, tumor markers such as serum α-fetoprotein (AFP) may be normal despite the presence of HCC, and ultrasonography may not always be sensitive enough to detect small hepatic adenomas, which presents a challenge in screening or surveillance.[72] Recommendations for screening in patients with GSDs is initially abdominal ultrasonography every 12 to 24 months in the pediatric population, with transition to interval surveillance with contrast-enhanced magnetic resonance imaging (MRI) or computed tomography (CT) of the abdomen in older patients (starting at age 18 years).[72,76,77]

Alcoholic Liver Disease

Excessive alcohol consumption can lead to cirrhosis and thus is a risk factor for development of HCC. The autopsies of patients with alcoholic cirrhosis have reported up to 10% undiagnosed HCC. In the US, alcoholic cirrhosis is associated with about 15% of HCC and cholangiocarcinoma.[78,79] One meta-analysis suggested that there was a dose-dependent effect of alcohol on the risk of HCC, where drinkers of three or more alcoholic beverages per day bore a 16% increased risk compared with nondrinkers.[80] A recent review compares the epidemiology and reported incidences of HCC in alcoholic and nonalcoholic liver disease.[81] As in studies of NAFLD, genetic factors have also been studied in alcoholic liver disease. Like NAFLD-associated HCC, the *KCNQ1* genotype TT was also observed to be significant.[61]

As previously introduced, alcohol use appears to have an adverse synergistic effect in patients with concurrent chronic HCV, such that alcohol increases circulating HCV viral titer and HCC risk.[39] Similar effects could be said in the context of metabolic syndrome. Other types of cirrhosis and parenchymal liver diseases—such as primary biliary cholangitis (PBC), hemochromatosis, Wilson disease, α-1 antitrypsin deficiency, and GSD—significantly increase HCC risk when alcohol is a cofactor.

Cirrhosis

The status of cirrhosis alone, regardless of etiology, is recognized as an inherent predisposition for increased risk of developing HCC. However, as previously suggested, differences in the magnitude of that risk depend on the etiology. For instance, chronic HBV or chronic HCV appears to pose a higher risk than NAFLD/NASH. In general, societies recommend routine screening for HCC every 6 months if the patient has a diagnosis of cirrhosis.[30,33,82]

The clinician should be attentive to specific conditions affecting the liver that may progress to severe fibrosis and cirrhosis, including PBC, hereditary hemochromatosis, Wilson disease, and α-1 antitrypsin

deficiency. In Wilson disease, copper accumulation in the liver is thought to induce oxidative stress, which is likely complicit in malignant transformation, as suggested in animal studies.[29,83] In patients with PBC, the increased risk of HCC is felt to be pertinent when cirrhosis develops, at which point routine HCC screening is recommended.[33] The AASLD also recommends HCC screening in men with PBC even outside the context of cirrhosis.[84]

Aflatoxin B_1

Food contaminated with aflatoxin, a mycotoxin found in grains, can induce HCC in animals. Peanuts, corn, and soybeans stored in damp environments increase the risk of exposure to aflatoxin. Exposure to *Aspergillus flavus* and *Aspergillus parasiticus* are important risk factors, especially in Asia and Africa.[29] Moreover, a strong synergistic association exists between aflatoxin exposure and HBV carrier status.[29] Relative risks of HCC are three-fold for aflatoxin, nine-fold for chronic HBV infection, and 59-fold for concurrent aflatoxin and chronic HBV infection. The underlying mechanism is polymorphism variants of glutathione *S*-transferase M1 and epoxide hydrolase genes and G-to-T point mutation of the *p53* gene.[85–87]

Other Environmental Factors

The use of oral contraceptive pills significantly increases the incidence of benign hepatic adenomas. There is some evidence that they also increase HCC risk. Multiple studies of tobacco smoking and HCC risk have yielded mixed conclusions. Occupational exposure to arsenic or vinyl chloride significantly increases the risk of liver angiosarcoma. Exposure to the radiograph contrast medium thorium dioxide from the years 1930 to 1955 is associated with a very high risk of hemangiosarcoma, cholangiocarcinoma, and HCC.[88]

CLINICAL PRESENTATION

Most cases of HCC are identified incidentally or through screening programs of high-risk individuals. It is common for patients to be asymptomatic until their disease is very far advanced. The only potentially curative modalities for HCC include liver resection (partial hepatectomy) and transplantation. Unfortunately, the actual number of patients who qualify for these modalities is small (~10%–30%) because most patients present with locally advanced and metastatic disease or have significant liver dysfunction that precludes curative options. Many patients present with symptoms of advanced liver dysfunction from both cirrhosis and HCC. The most common initial symptom is right upper quadrant abdominal pain. Anorexia or early satiety with weight loss is the second most common symptom. HCC may present with various paraneoplastic symptoms through the secretion of numerous hormones. Late-stage symptoms include jaundice, tumor fever, bone pain caused by metastatic lesions, and complications from portal venous hypertension, such as esophageal varices, hypoalbuminemia, ascites, thrombocytopenia, and coagulopathy.

On physical examination, hepatomegaly is present in more than 90% of patients. A hepatic arterial bruit or a friction rub, ascites, splenomegaly, and jaundice are found in up to 50% of patients. Muscle wasting, fever, and dilated abdominal veins are also common. The Budd-Chiari syndrome is caused by malignant invasion and occlusion of the hepatic veins. AFP is often elevated to above 400 ng/mL.

PATHOLOGY

Based on the growth pattern, HCC is classified into four major gross anatomic types: spreading, multifocal, encapsulated, and combined patterns.[89] Normal liver parenchyma is shown in Fig. 30–1. The spreading type of HCC grows in nodular, pseudolobular, or invasive patterns with poorly defined margins, occurs in the setting of hepatic cirrhosis, and accounts for nearly 50% of cases in the US. The multifocal type has numerous tumors of similar size that make it difficult to determine whether the lesions are intrahepatic metastases or second primary tumors (Fig. 30–2A, B). The encapsulated type of tumor grows by expanding, compressing, and distorting the surrounding liver tissue. Satellite or metastatic lesions are seen in late-stage disease. This type is most common in Asia and Africa but seen in only 13% of cases in the US. The combined patterns of the three are seen in up to 25% of cases. Figure 30–3 shows an HCC histopathology specimen.

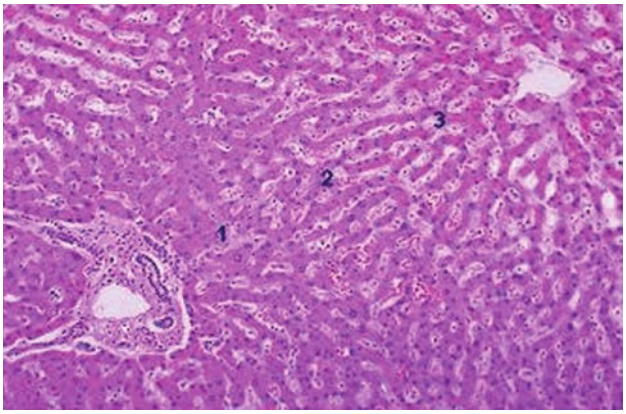


FIGURE 30–1 Photomicrograph of normal parenchyma.



FIGURE 30–2 **A. Gross pathologic specimens of multifocal HCC. B. Gross appearance of HCC. (Reproduced with permission from Cooke RA, Stewart B: Colour Atlas of Anatomical Pathology, 3rd ed. Edinburgh, Churchill Livingstone; 2004. Photo contributor: Dr RA Cooke, Brisbane, Australia.).**

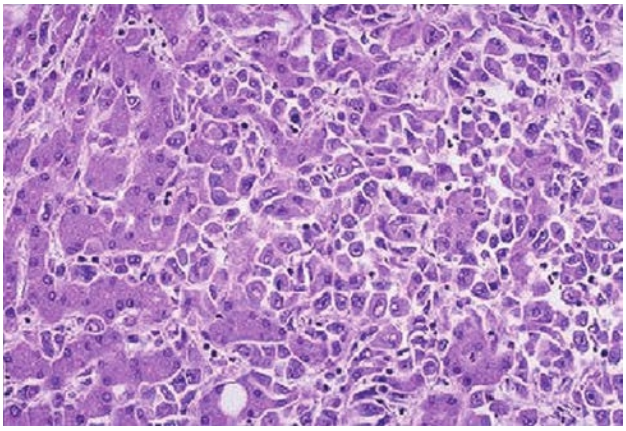


FIGURE 30–3 **Photomicrograph with standard hematoxylin and eosin stain of hepatocellular carcinoma cells in hepatic parenchyma.**

Approximately 60% to 70% and 80% to 90% of HCC in Whites and Asians, respectively, show elevated AFP, which is the most useful marker for HCC. Originally, AFP is produced by the fetal liver and yolk sac but falls to below 10 ng/mL in adult serum. A transient elevation of AFP to 20 to 400 ng/mL may occur when there is hepatocyte regeneration, as in cirrhosis, active hepatitis, or partial hepatectomy. The HCC positive predictive value of an AFP level of 400 ng/mL is over 95%, and normal AFP levels may exist in patients with low tumor burden. The lectin-reactive isoenzyme of AFP (AFP-L3) has shown increased sensitivity. As of this writing, serum AFP level and ultrasonography are the "gold standard" for HCC screening in high-risk populations.[90]

Variants of Hepatocellular Carcinoma

Hepatocellular carcinoma variants with differential molecular and prognostic significance include combined HCC and cholangiocarcinoma (cHCC-CC) and fibrolamellar HCC (FLHCC). cHCC-CC is a rare combination of cholangiocarcinoma and HCC and staged as intrahepatic cholangiocarcinoma, not HCC. This was believed to behave in a fashion similar to cholangiocarcinoma, but growing evidence suggests that cHCC-CC has intermediate clinical features and prognosis between HCC and CC.[91,92] A comprehensive molecular characterization of cHCC-CC demonstrates three main subclasses[93]: (1) a subtype sharing the molecular characteristics of both HCC and intrahepatic cholangiocarcinoma arising from a common clonal origin; (2) cholangiolocellular carcinoma representing a distinct biliary-derived entity, with significant upregulation of transforming growth factor-β signaling and enrichment of inflammation-related and immune response signatures; and (3) stem cell–like features with enrichment of progenitor-like signatures, leading to more aggressive tumor behavior and poor clinical outcome.

FLHCC is predominantly seen in the right hepatic lobe, accounts for 2% to 4% of HCC and occurs equally in men and women. It typically occurs in adolescents and young adults; the etiology is unknown. Histologically, it is characterized by fibrosis arranged in lamellar fashion around HCC cells, consisting of large polygonal tumor cells with eosinophilic granular cytoplasm, large vesicular nuclei, and prominent nucleoli. Immunohistochemistry profiles are similar to that of HCC and shows positive staining for hepatocyte paraffin 1 (HepPar1), glypican-3 (GPC3), arginase-1, polyclonal

carcinoembryonic antigen (pCEA), and CD10 positivity. CD68 and epithelial membrane antigen are specific for FLHCC.[94–96] It is associated with *DNAJB1-PRKACA* fusion, mainly seen in younger patients, and BAP1 mutation is commonly seen in older patient groups.[97,98]

Rare primary liver neoplasms include hepatoblastoma, sarcoma, angiosarcoma, rhabdomyosarcoma, and epithelioid hemangioendothelioma. Patients may present with fatigue, anorexia, weight loss, and abdominal pain. Hemorrhagic ascites is common, and AFP level is usually normal. Angiography and contrast-enhanced CT of the liver are the best diagnostic tools. Open or percutaneous liver biopsy is needed for diagnosis. Surgical resection is still the principal means of therapy if tumors are diagnosed at relatively early stages. They are often resistant to chemotherapy and radiotherapy (RT), and the overall prognosis is poor.

Benign Liver Tumors

Hemangiomas are the most common benign tumors of the liver. Their size ranges from a few millimeters to 25 cm. They appear as calcified solitary lesions in up to 7% of the general population. Magnetic resonance imaging is better than CT at distinguishing HCC from hemangioma on heavily T2-weighted images. Surgical resection is used for symptomatic lesions or when malignancy cannot be excluded. Hepatic artery ligation is an alternative for large, cavernous hemangiomas.[99] Hepatic adenoma is another common benign solitary tumor seen in women who have used estrogen-containing medications such as oral contraceptive pills for more than 10 years. It is composed of sinusoids, central veins, and arteries without well-defined portal tracts or bile ducts. Hepatic angiography is the most valuable diagnostic tool. Small adenomas usually regress when contraceptive pills are discontinued. Symptomatic lesions are treated with resection.[100,101] Focal nodular hyperplasia (FNH) occurs predominantly in young women. Liver function studies and the serum AFP level are normal. A technetium sulfur colloid radioisotope scan of the liver shows increased radioisotope uptake in FNH compared with hepatic adenomas or carcinomas. The prognosis is excellent. Female sex hormones such as oral contraceptive pills are not associated with FNH.[102,103]

DIAGNOSTIC EVALUATION, STAGING, AND PROGNOSIS

In addition to performing a complete medical history and physical examination, the diagnostic workup for a patient suspected of having HCC should include serum for complete blood cell count, electrolytes, liver function tests, albumin level, prothrombin time, hepatitis B and C serologies, and tumor markers (AFP and CA 19-9). The medical history should include a thorough review of potential HCC risk factors: transfusions, tattoos, intravenous drug abuse, high-risk sexual practices, familial syndromes, oral contraceptive pills or hormone replacement use, androgenic steroid use, and chemical exposures.

Several radiographic imaging modalities are useful in evaluating a patient with HCC. Ultrasonography often serves as the initial screening modality, followed by triple-phase CT scan or MRI. Randomized studies have shown that hepatic ultrasonography has 78% sensitivity and 93% specificity to detect HCC in high-risk populations, especially for patients with normal AFP levels.[104] Color-flow Doppler can assist preoperative assessment and planning.

Abdominal CT has relatively higher sensitivity and specificity than ultrasonography. With special arterial- and venous-phase scans, CT also makes it possible to evaluate the blood supply of the normal liver parenchyma (portal vein) and neoplastic lesions (hepatic artery). MRI is useful in distinguishing benign lesions from malignant tumors by the combination of T2-weighted phase-contrast and spin-echo sequences. MRI can also demonstrate fatty degeneration of tumor and vascular invasion.[105]

Hepatic radionuclide imaging has low spatial resolution and is only about 70% sensitive in demonstrating neoplasms. Using the glucose metabolic difference between neoplastic and normal cells, positron emission tomography differentiates benign lesions from malignant tumors, detects extrahepatic metastasis, and evaluates response to therapy.

In summary, ultrasonography is the most cost-effective HCC screening test in high-risk populations. Abdominal CT with liver protocol (with and without contrast) is the most helpful in accurately staging patients before surgery. No single diagnostic modality has greater than 50% to 60% sensitivity in detecting lesions less than 1 cm in size. The combination of AFP level, ultrasonography, and CT provides the best hope of early diagnosis.

A variety of staging and prognostic systems has been developed to evaluate patients with HCC. Four staging systems (Okuda; CLIP, Cancer of the Liver Italian Program; CUPI, Chinese University Prognostic Index; BCLC, Barcelona Clinic Liver Cancer Stage; and AJCC, American Joint Committee on Cancer TNM) have evolved since the 1980s. Currently, we use the AJCC-TNM and BCLC at MDACC (Table 30–4).[106] The Child-Pugh Classification System provides an estimate of a patient's functional liver reserve and is used principally to assist in evaluating a patient's suitability for hepatic resection.

Table 30–4 TNM Staging System for Hepatocellular Carcinoma

Stage Group	TNM	Scheme
Stage IA	T1aN0M0	Single tumor ≤2 cm
Stage IB	T1bN0M0	Single tumor >2 cm without vascular invasion
Stage II	T2N0M0	Single tumor >2 cm with vascular invasion, or multiple tumors, none >5 cm
Stage IIIA	T3N0M0	Multiple tumors, at least one of which is >5 cm
Stage IIIB	T4N0M0	Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein or tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum
Stage IVA	T1–4NN1M0	Regional lymph node metastasis
Stage IVB	T1–T4N0–N1M1	Distant metastasis
Fibrosis score		0–4, none to moderate; 5–6, severe fibrosis/cirrhosis

TNM, tumor, node, metastasis; UICC, Union for International Cancer Control.
Data from Edge SB, Byrd DR, Byrd DR, et al: AJCC Cancer Staging Manual, 8th ed. New York, NY: Springer; 2017

TREATMENT

HCC is treated in the multidisciplinary fashion. There are five options: surgical resection, liver transplant, locoregional therapy, radiation, and systemic therapy. They are summarized in Table 30–5.

Surgical Resection

After liver transplantation, surgical resection offers the next best chance at long-term survival, with 5-year survival exceeding 50% in well-selected patients.[107] However, recurrence is common, with more than 70% of patients experiencing tumor recurrence at 5 years.[26] In considering surgery for patients with HCC, several factors must be balanced, including patient performance status, the condition of the underlying liver parenchyma, tumor characteristics, and the future liver remnant (FLR). When properly selected, surgery for HCC is safe, with modern series demonstrating perioperative mortality below 5% compared with rates of 20% in the 1980s.[108]

Patients with poor performance status, especially in the setting of severe uncontrolled comorbidities, and those with advanced, uncompensated cirrhosis (Child-Pugh class C) are not suitable candidates for hepatectomy and are best served with nonsurgical options. Instead, surgery is reserved for patients with preserved liver function. As a general rule, patients with Child-Pugh class A cirrhosis may be candidates for major hepatectomy, whereas those with class B cirrhosis should only be considered for more limited resections. Yet, because the Child-Pugh score does not fully account for portal hypertension, it is important to carefully review the patient's chart for evidence thereof, including the presence of varices, splenomegaly, ascites, recanalization of the umbilical vein, enlarged portal vein diameter, and thrombocytopenia. Additional investigational tools may include upper endoscopy to rule out esophageal varices and measurement of portal venous pressure. This heightened focus on portal hypertension is based on the fact that this condition is associated with increased risk of both long- and short-term mortality and postoperative decompensation and liver failure.[109] As such, patients with Child-Pugh class A cirrhosis with portal hypertension are often treated in the same fashion as those with class B disease.

In addition to the condition of the underlying liver disease, tumor characteristics must also be considered. Under the BCLC system, surgical resection is only recommended for single tumors without evidence of vascular invasion in the setting of normal liver function.[110] Additional factors associated with greater risk of disease recurrence and worse outcomes include tumor size larger than 5 cm and elevated AFP levels.[108] Thus, in our group's experience, no firm limits on either tumor size or AFP exist to contraindicate resection, because survival for these patients is improved compared with alternative approaches. Instead, these high-risk factors are taken into account during treatment planning, which may then consider preoperative adjunctive treatments for disease control and assessment of tumor biology. Likewise, multifocality and limited vascular invasion, although strongly associated with risk of disease recurrence, do not represent strict contraindications to hepatectomy, which must be considered with extreme care and should only be offered selectively in this patient population.

A final, but critical, element to consider when planning any liver resection is liver volumetry. In particular, the standardized FLR is predictive of the risk of postoperative liver failure. In the case of HCC, because of the presence of cirrhosis of the background liver, a standardized FLR of at least 40% is required for safe resection.[111]

Table 30–5 Treatment Options for Management of Hepatocellular Carcinoma

Treatment Option	Comments
Liver transplantation	Historically low survival rates (20%–36%)
	Recent improvement (75%–80% 5-year survival), likely related to adoption of Milan criteria at US transplant centers
	Currently HCC represents 25% or more of liver transplants performed annually in the United States.
Surgical resection	Historic 5-year survival rates 30%-40%
	Recent series indicated 5-year progression-free survival as high as 48%. A majority of patients develop recurrence or second primary tumors.
	Resection in cirrhotic patients carries high morbidity and mortality and is reserved for those with compensated disease: major hepatectomy is an option for Child-Pugh class A without portal hypertension; only minor hepatectomy for Child-Pugh class B or Child-Pugh class A with portal hypertension.
Transarterial chemoembolization (TACE)	Modest survival benefit demonstrated for repeated TACE (82% 1-year survival) vs supportive care (63%) in patients with preserved liver function, PS 0, small tumor burden
	Improvement in 1-year survival from 32% in control (supportive care) to 57% for TACE shown in randomized study of 279 primarily HBV patients with tumors <7 cm
Locoregional therapy and radiation therapy	Improvement in time-to-progression (26 months) with Y-90 compared with conventional TACE (6.8 months). Phase 3 clinical trials have shown mixed data on survival benefit from Y-90 combined with sorafenib. Ongoing trials will provide more information about a role of Y-90.
Percutaneous treatments (RFA, MWA, ethanol injection)	RFA similar recurrence rates to resection for small tumors. Higher recurrence rate than resection in tumors > 3cm. Ethanol injection has high rate of recurrence.
External beam radiation therapy	It can be delivered with stereotactic radiation therapy (3–5 fractions) to achieve 80%–90% local control at 1 year or with hypofractionated radiation therapy (10–15 fractions) to achieve 95% local control at 2 years. Ongoing phase 3 trials (RTOG1112 and NRG GI003) will help define a role of radiation therapy.
Molecular targeted therapy	Sorafenib, lenvatinib, cabozantinib, regorafenib, bevacizumab (combined with atezolizumab), and ramucirumab (for patients with AFP ≥ 400)
Immune checkpoint inhibitors	Nivolumab, nivolumab with ipilimumab, pembrolizumab, and atezolizumab (combined with bevacizumab)

MWA, microwave ablation; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; Y-90, Yttrium-90.

Portal vein embolization (PVE) can be used to induce hypertrophy of the FLR if it falls below this threshold and improve postoperative outcomes.[112] The procedure has been shown to be safe and well tolerated, and response to PVE, especially in cirrhosis, is reflective of the regenerative potential and physiologic reserve of the liver. Indeed, degree of hypertrophy below 5% after PVE is associated with increased mortality and poor outcomes.[113] In the event of inadequate liver growth, although attempts at further augmenting the FLR may be considered with the addition of hepatic vein embolization and/or Yttrium-90 (Y-90) radioembolization, these patients may be better served with nonoperative treatment.

Liver Transplantation

With the increase in number of cases of HCC, the number of patients listed for liver transplantation (LT) is also increasing.[114,115] A large retrospective study using the United Network of Organ Sharing showed that among 109,018 registrants between January 2004 and December 2015, 18.5% were registered for LT because of HCC. In 2015, HCC was the leading diagnosis among registrants (23.9% of registrations) and recipients (27.2% of recipients).[114] LT is the treatment of choice for patients with advanced cirrhosis and clinically significant portal hypertension and decompensated liver disease where surgical resection is not possible, if the tumors are within Milan criteria (one tumor up to 5 cm, or two to three tumors with the largest being <3 cm).[116,117] Before universal acceptance of the Milan criteria for listing, the lack of good selection criteria led to poor outcomes, high recurrence rates (32%–54%), and low survival at 5 years.[118] Patients with small, unresectable HCC within the Milan criteria have excellent long-term survival, and hence LT is an effective

and efficient therapy.[33,116] Patients who are listed with tumors within Milan Criteria (T2HCC) have exception points, and patients with larger tumors (T3HCC) can be successfully downstaged and are eligible for exception (see https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf).

In the last two decades, multiple studies have shown good survival with larger tumors, based on the University of California–San Francisco criteria (a solid tumor <6.5 cm in size or up to three tumors with <4.5 cm as the largest diameter and a total tumor burden of 8 cm) with similar survival results.[119,120] Tumor markers including AFP, AFP-L3, and des-gamma-carboxy prothrombin have shown a predictive value along with an AFP cutoff value of 300 ng/mL for delisting patients to improve outcomes and reduce risk of recurrence post-LT.[121–124] A recent large series of LT for patients beyond University of California–San Francisco criteria showed overall survival (OS) and recurrence-free survival (RFS) to be comparable with that of patients transplanted within the Milan criteria.[125] A waitlist time of more than 9 months with aggressive locoregional therapies while waiting for transplant was used as a bridge for these patients.[125] Recurrence rates of 11% to 18% have been reported post-LT in patients with HCC, and recurrence rates are higher in patients with bigger tumors that were downstaged.[125–128] Based on explant liver pathology, the risk of recurrence is higher with vascular invasion, poorly differentiated tumors, history of hepatectomy, AFP at the time of transplant, and viable tumors.[125,127,129] A multicenter risk stratification scoring system (RETREAT) has been validated and takes into account AFP at the time of transplant, microvascular invasion, and largest viable tumor size with a score of 0–5, where a score of 0 had 3% and a score of 5 had a more than 75% risk of recurrence. This has been used to determine surveillance protocols for patients post-LT,[129] like frequent CT scans of the chest and abdomen every 6 months for the first 3 years post-LT.[33] Given the highest rates of recurrence in the first 2 to 3 years of transplant, avoiding calcineurin inhibitors that are known to be tumorigenic and instead selecting mammalian target of rapamycin (mTOR) inhibitors having antiproliferative properties against HCC is recommended.[130–132] Sirolimus is a mTOR inhibitor, has an anti-angiogenic activity that decreases the production of vascular endothelial growth factor (VEGF), and inhibits a response of vascular endothelial cells to stimulation by VEGF.[133,134] Sirolimus has been shown to reduce the risk of HCC recurrence after LT: in a large prospective, randomized, open-labeled, international trial, there was an improvement in RFS in the first 3 to 5 years.[135] In the case of recurrence post-LT, surgical resection, ablation, liver-directed therapy, stereotactic radiation, or therapy tailored to the site of recurrence can be considered.[128,136]

In the era of DAAs, two important factors that need to be considered in deciding timing of treatment for HCV include anticipated waitlist time and whether the patient has compensated or decompensated cirrhosis. Initiation of DAA may be withheld until after LT if LT is imminent (ie, <3–6 months), whereas treatment pre-LT may be considered for patients who may be on the waitlist longer than 6 months. Patients with decompensated cirrhosis should be treated and monitored at a transplant center. Recommendations guiding HCV treatment decisions in different scenarios are outlined in a review by Terrault et al.[137]

In summary, LT can be considered as the first-line treatment option for unresectable HCC with acceptable perioperative mortality and one-year mortality of 3% and less than 10%, respectively.[33,117] Locoregional therapies can be used for treating tumors within the Milan criteria and for downstaging larger tumors for listing. Aggressive post-LT surveillance scans and immunosuppression with mTOR inhibitors is recommended for patients who are at a higher risk of recurrence based on explant pathology.

Locoregional Therapy

Hepatocellular carcinoma derives its blood supply almost exclusively from the hepatic artery. This important anatomic feature offers unique advantages for catheter-based therapies, because arterial embolization interrupts blood flow to the tumor while preserving the portal vein and normal liver parenchyma. Transarterial therapies for HCC include transarterial chemoembolization (TACE), bland hepatic artery embolization (HAE) and selective internal radiation therapy (SIRT) using Y-90.

The combination of tissue ischemia with highly concentrated chemotherapy delivered into the hepatic artery enhances tumor necrosis. TACE was first described by Yamada et al and incorporates these concepts.[138] It has since become one of the most commonly used procedures in interventional radiology practice. Landmark, prospective, randomized clinical trials published in 2002 validated the use of chemoembolization for unresectable advanced HCC. In the multicenter study including 112 patients, when compared with bland embolization or best supportive therapy, patients who underwent TACE with a combination of doxorubicin and iodized oil followed by gelatin sponge demonstrated a clear survival advantage, leading to premature stoppage of the trial.[139] Survival in the chemoembolization group at 1 and 2 years was 82% and 63%, respectively. Survival in the bland embolization group was 75% and 50%, respectively; in the best supportive care group, survival was 63% and 27%, respectively, and reached statistical significance.

A single-center study compared 80 patients with unresectable HCC randomly assigned to undergo TACE with cisplatin and iodized oil followed by gelatin sponge or best supportive care.[140] Survival in the chemoembolization group at 1 and 2 years was 57% and 31%, respectively. Survival for the patients randomly assigned to the supportive care group was 32% and 11%, respectively, also reaching statistical significance. The difference in survival rates between the Llovet and Lo studies can be attributed to the inclusion of a larger proportion of patients with more advanced stages of underlying chronic liver disease in the latter study. Besides iodized oil used in those seminal studies, TACE using drug-eluting beads that enable controlled and sustained release of chemotherapeutic agents into the surrounding tumor was made available.[141] This device enables delivery of a higher concentration of drugs with low systemic toxicity.[142–144]

Bland HAE is similar to TACE in its embolic effect but is done without mixed or suspended chemotherapeutic. A small, randomized clinical trial comparing embolization with microspheres alone versus drug-eluting beads loaded with doxorubicin 150 mg in 101 patients with HCC did not show significant differences in progression-free survival (PFS) or OS between the groups.[145]

Selective interval radiation therapy with Y-90 has been in clinical use since 1999 when Y-90–impregnated glass microspheres (Therasphere, BTG) were given a humanitarian device exception from the FDA owing to studies showing safety and efficacy of glass microspheres in patients with HCC.[146] Y-90 had first been used in patients with portal vein thrombosis because of the nonembolic nature of glass microspheres compared with TACE and HAE. A long-term outcomes study of 291 patients with HCC who were treated with Y-90 showed the objective response rate of 57%, time-to-progression (TTP) of 7.9 months, and median OS of 17.2 months (Child-Pugh class A) and 7.7 months (Child-Pugh class B).[147] Y-90 has also been used in patients with more advanced disease who were not eligible for TACE or other local therapies. Hilgard et al demonstrated safety and efficacy of Y-90 in patients with advanced HCC, with TTP of 10 months and median OS of 16.4 months without lung or visceral toxicity.[148] Multiple comparison trials have been performed between Y-90 and TACE[149,150] and sorafenib.[151,152] Cohort OS with Y-90 therapy has not been significantly different from TACE or sorafenib in these trials, but has offered the advantages of improved response rates, lower rates of adverse events, and improved quality-of-life measurements. In addition, Y-90 has shown survival benefits in some subgroups (age <65 years, nonalcoholic cirrhosis, and noncirrhotic liver disease).[153] Y-90 has been shown to be an effective tool to downstage to transplant. Mohamed at el reviewed 60 patients treated with radiofrequency ablation (RFA), TACE, Y-90, and stereotactic body radiation therapy (SBRT), showing pathologic CR rates of 28.5% in SBRT, 41% in TACE, 60% in RFA, and 75% in Y-90.[154] A recent study published long-term results of 207 patients with HCC who had effective bridging or downstaging therapy with Y-90 before liver transplant.[155] Notably, most studies on Y-90 have not measured the dose delivered to the tumor, but only the administered dose. The dose delivered to the tumor has been shown to predict treatment response, and further advances in Y-90 dosimetry have the potential to further increase the efficacy and safety profile of Y-90.

Percutaneous therapy for patients with HCC includes heat-based thermal ablation (microwave ablation [MWA], radiofrequency ablation [RFA], cryoablation, ethanol injection, and irreversible electroporation [IRE]). Heat-based thermal ablation with RFA and MWA is the contemporary, preferred approach, owing to improved efficacy and safety. RFA and MWA both cause tissue necrosis by the controlled deposition of thermal energy and are traditionally used for nonresectable disease for lesions smaller than 5 cm, or three lesions smaller than 3 cm. These techniques are highly effective in the treatment of small and early HCC, with outcomes similar to surgical resection.[156] Recurrences after RFA are usually attributable to a microsatellite disease and the limitation of ablation size that can be obtained with RFA. MWA is an alternative hyperthermic ablative technique that has recently become the favored ablative modality for HCC. The main reason for this is that MWA does not rely on heat conduction through the tissue and similarly is not limited by the "heat sink" effect that surrounding vessels may impart,[157] allowing for the creation of larger ablation zones. Furthermore, combination therapy consisting of hyperthermic ablation with arterial HAE/TACE can improve cell death because an occlusion of blood flow leads to larger ablation zones.[158,159] Both RFA and MWA are limited by lesion proximity to adjacent critical structures, such as lung, gallbladder, colon, and central bile ducts. However, with the exception of lesions adjacent to a central bile duct, utilization of advanced organ displacement techniques allows most lesions to be treated with MWA or RFA.

At MDACC, for nonsurgical patients, ablation is the preferred strategy for lesions less than 3 cm. TACE is routinely used for patients with HCC with more than three lesions measuring up to 3 cm each, or a single lesion greater than 5 cm. In patients with portal vein thrombosis, infiltrative diseases, or more than four lesions, Y-90 SIRT is preferred. SIRT is also used to treat patients with single lesions up to 7 cm who do not have significant extrahepatic arterial supply.

Radiation Therapy

Technological advances in RT delivery have enabled the safe escalation of radiation doses to focal parts of the liver. Specifically, these technologies include image guidance, respiratory motion management, and highly conformal radiation delivery techniques. Retrospective and prospective data demonstrate that the combination of these technologies results in high rates of local control and promising rates of survival in several different settings of HCC management. Collectively, these promising clinical data from multiple studies demonstrate that HCCs are radiosensitive. Sustained local control rates ranging from 71% to 100% have been reported after 30 to 90 Gy delivered over 1 to 8 weeks.[160,161]

Historically, investigators from Michigan used conformal RT (1.5 Gy twice daily over 6–8 weeks) with concurrent hepatic arterial 5-fluorodeoxyuridine to treat HCC safely to doses as high as 90 Gy and achieved a median survival duration of 15.2 months.[162] Analysis of these data suggested that doses greater than 75 Gy resulted in more durable in-field local control than lower doses.

A prospective French phase 2 trial administered 66 Gy in 33 fractions to HCC in patients ineligible for curative therapies and noted 92% tumor responses and 78% one-year local control rates.[163] Using higher doses and fewer fractions (hypofractionated RT), Canadian researchers have noted excellent local control rates ranging from 70% to 90% when the radiation beam can be directed from multiple planes (stereotactic body RT, SBRT) converging on the tumor. Often with SBRT, the majority of the liver can be spared from irradiation using image guidance and respiratory motion management.[160,164,165] The ongoing RTOG 1112 randomized study of sorafenib versus sorafenib with SBRT for patients with HCC is ongoing and has OS as the primary end point.

In contrast to photon irradiation, for which the dose delivered to the tumor is limited by the entrance and exit doses that can potentially harm normal tissues, accelerated proton beams deposit a dose within the tumor without exiting through normal tissues beyond the tumor.[166] Japanese investigators have reported mature results of the treatment of 162 patients with 192 unresectable HCCs with 72 Gy in 16 fractions of proton beam therapy.[167] The 5-year local control rate of 87% and OS rate of 23.5% in the absence of significant toxicity are clinically noteworthy. Furthermore, an impressive 5-year survival rate of 53.5% was achieved in a subset of 50 patients with solitary tumors and Child-Pugh class A cirrhosis. A prospective multicenter phase 2 trial of hypofractionated radiation therapy (58.05–67.5 Gy in 15 fractions) for HCC and intrahepatic cholangiocarcinoma demonstrated similar results.[168] In this study, the median maximum dimension for patients with HCC was 5.0 cm, and 27.3% of patients had multiple tumors; 29.5% of patients had portal vein tumor thrombus, and the majority of the patients were treatment naïve (30/44). For the HCC group (n = 44), the 2-year local control rate was 94.8%, and the 2-year OS rate was 63.2%.

Our own MDACC experience reflects these observations that higher doses are associated with better overall, in-field progression-free and biochemical PFS.[169,170] Across all partial liver radiation paradigms, the most common site of first recurrence is intrahepatic but outside the high-dose irradiated volume, and toxicities are more common in Child-Pugh class B patients.

Given the excellent local control rate as noted with RT alone, RT has been combined with TACE to overcome treatment resistance. Korean researchers initially noted more than 60% response rates and a significant drop in tumor marker levels using this combination treatment strategy.[171,172] It was reported that TACE followed by RT improved OS over TACE alone in a retrospective analysis of this experience. Similar results have been reported by other groups as well.[173–175]

For the treatment of unfavorable tumors, multiple groups have reported favorable outcomes in patients with portal venous tumor thrombus (PVTT) treated with RT.[176–185] Response rates from these older studies ranged from 37.5% to 100%, and median survival durations ranged from 3.8 months to 10.7 months. Our retrospective data from MDACC indicate that patients with PVTT who received higher doses of RT had better rates of local control and longer survival compared with those who received lower doses.[186] Most recently, neoadjuvant 3D conformal RT before hepatectomy for patients with limited PVTT and resectable HCC demonstrated an OS advantage with strong effect compared with hepatectomy alone in a multicenter, randomized controlled trial in Japan.[187] On multivariable Cox regression analyses, the hazard ratio was 0.35 (range 0.23–0.54), favoring the preoperative RT regimen.

Future directions for RT with photons and protons will include use of functional imaging or biomarkers to personalize therapy for patients. Proof of concept has been demonstrated in a phase 2 study of SBRT for patients with advanced cirrhosis or impaired liver function.[188] The investigators used indocyanine green as a readout of liver function during SBRT to decide whether it was safe to deliver the full five-fraction course of SBRT or stop after three fractions. Sixty-two of 90 enrolled patients completed all five fractions using this personalized strategy. Six of the patients (7%) experienced a 2-point decline in Child-Pugh score within 6 months, which was lower than historical data that used a nonadaptive approach. The 2-year local control rate was 95%.

Taken together, these advances have permitted the escalation of radiation dose to unresectable HCCs without causing undue toxicity in multiple clinical scenarios from resectable to unresectable disease, as well as in the context of patients with limited hepatic reserve. Strategies that combine RT with other therapies merit continued evaluation to maximize the relative benefits of each approach.

Systemic Therapy

A majority (>80%) of patients diagnosed with HCC have advanced disease at presentation and—based on the number, size, location of lesions, and the severity of the underlying cirrhosis—are not candidates for transplantation, surgical resection, or locoregional therapies. Systemic therapy is recommended for patients with adequate liver function as demonstrated by Child-Pugh class A or B cirrhosis. Those with Child-Pugh class C cirrhosis have insufficient liver function to tolerate medication treatment, locoregional therapy, radiation therapy, or surgical intervention.[189,190] Therefore, best supportive care is recommended for this patient population.

Since the approval of sorafenib in 2007, several medications have been investigated, approved by the FDA, or recommended by the National Comprehensive Cancer Network guideline. Sorafenib, lenvatinib, atezolizumab plus bevacizumab, and nivolumab monotherapy (for patients considered ineligible or intolerant to other frontline medications) are recommended in the first-line setting; nivolumab monotherapy, nivolumab plus ipilimumab, pembrolizumab, cabozantinib, regorafenib, and ramucirumab (patients with AFP >400) are recommended in the subsequent-line therapy. Systemic therapy is recommended for patients with Child-Pugh class A except for nivolumab (Child-Pugh class A/B) and sorafenib (Child-Pugh class A/B7) by the National Comprehensive Cancer Network.

Hepatocellular carcinoma is inherently chemotherapy resistant[191] and known to express the multidrug-resistance gene *MDR-1*.[192,193] 5-fluorouracil plus oxaliplatin versus doxorubicin as palliative chemotherapy was navigated, and it showed the median OS and PFS of 6.4 versus 5.0 months and 2.9 versus 1.8 months, respectively.[194] Other chemotherapeutic medications showed similar results, and chemotherapy is rarely considered outside a setting of a clinical trial.

Sorafenib

Sorafenib is a tyrosine kinase inhibitor of VEGFR 1, 2, and 3 and platelet-derived growth factor receptor–β (PDGFR-β). It was approved by the FDA for patients with renal cell carcinoma.[195,196] Sorafenib was later tested in patients with advanced HCC in a phase 3, double-blind, placebo-controlled trial.[197] The median OS was 10.7 months in the sorafenib group (vs 7.9 months in the placebo group) with a HR of 0.69 (range 0.55–0.87). The median time-to-radiologic progression was 5.5 months (vs 2.8 months). The ORR was 2%, and the disease control rate (DCR) was 43%. The most common grade 3–4 adverse events were diarrhea, palmar-plantar erythrodysesthesia, and fatigue. Based on this study, sorafenib was approved in November 2007 for patients with unresectable HCC. Sorafenib was the only option for advanced HCC until April 2017, when regorafenib was approved for the second-line therapy and the only frontline medication, until lenvatinib was approved in August 2018.

Lenvatinib

Lenvatinib is a tyrosine kinase inhibitor of VEGFR 1, 2, 3; fibroblast growth factor receptor (FGFR) 1, 2, 3, and 4; and PDGFRα, KIT, and RET. It has been approved for patients with endometrial cancer, renal cell carcinoma, and thyroid cancer.[198–200] It was initially investigated in a phase 2 clinical trial for patients with advanced HCC, and safety and efficacy were validated.[201] This study demonstrated that lenvatinib had an ORR and DCR of 37% and 78%, respectively. Median OS and TTP were 18.7 and 7.8 months, respectively. The efficacy of lenvatinib was further investigated in a phase 3, randomized, noninferiority study to compare the efficacy versus sorafenib as a frontline treatment.[202] Patients were Child-Pugh class A only and BCLC stage B/C. Patients with portal vein tumor thrombosis and 50% or higher liver occupation were excluded from the study. Lenvatinib dose was 12 mg for patients with a body weight of 60 kg or more and 8 mg for those weighing less than 60 kg. The primary end point, the medial OS, was 13.6 months (range 12.1–14.9), and it was noninferior to sorafenib (12.3 months, range 10.4–13.9). The median PFS was 7.4 months (range 6.9–8.8), and ORR and DCR were 24% (1% complete response) and 75%. Based on this promising result, the FDA approved lenvatinib 12 mg daily in patients with 60 kg or greater body weight or 8 mg in those less than 60 kg in August 2018. Lenvatinib was the first frontline systemic therapy approved by the FDA after sorafenib in 2007.

Atezolizumab and Bevacizumab Combination

Atezolizumab is a fully humanized, monoclonal antibody of IgG1 isotype against the programmed cell death-ligand 1 (PD-L1). Atezolizumab has a proven efficacy in patients with triple-negative breast cancer, non–small cell lung cancer, small cell lung cancer, and urothelial carcinoma.[203–210] Bevacizumab is a humanized antibody binding to VEGF and prevents

angiogenesis. It has shown antitumor efficacy in multiple tumors including cervical cancer, colorectal cancer, glioblastoma, non–small cell lung cancer, ovarian cancer, renal cell carcinoma, and endometrial cancer.[209,211–215] A phase 1b study of atezolizumab and bevacizumab in patients with unresectable HCC showed an ORR of 36% and a median PFS of 7 months.[216] This combination was recently validated in a global, phase 3 clinical trial, and patients were randomized to this combination or sorafenib in patients with unresectable HCC.[217] Patients were Child-Pugh class A5 or A6, and 82% of patients were BCLC stage C. Primary end points were OS and PFS. The median OS of patients in the combination arm could not be evaluated at the time of data collection (over 17 months), and that of those who received sorafenib was 13.2 months (range 10.4–NE). HR for death was 0.58 (range 0.42–0.79). The median PFS was 6.8 months (range 5.7–8.3) versus 4.3 months (range 4.0–5.6) in the respective groups, with a HR of 0.59 (range 0.47–0.76). The ORR was 33.3% (10.2% and 23.1%, complete and partial response rates, respectively) versus 13.3% (range 1.9% and 11.4%), and the DCR was 72.3% and 55.1%, respectively. The most common grade 3–4 adverse events included hypertension (15.2%), increased aspartate aminotransferase (7%), thrombocytopenia (3.3%), and proteinuria (3%) in the combination arm. Of note, atezolizumab monotherapy and bevacizumab monotherapy also showed antitumor activity for advanced HCC, with an ORR of 17% and 13% to 14%, respectively.[216,218–220] This combination is the first regimen in HCC showing better survival than sorafenib as all other FDA-approved medications showed similar outcomes when compared with sorafenib.

Nivolumab

Nivolumab is a fully human IgG4 antibody inhibiting programmed cell death-1 (PD-1) from binding to the ligands PD-L1 and PD-L2. It is an immune checkpoint inhibitor with known activities in multiple cancer types including microsatellite unstable colorectal cancer, head and neck squamous cell carcinoma, Hodgkin lymphoma, melanoma, non–small cell lung cancer, small cell carcinoma, renal cell carcinoma, and urothelial carcinoma.[221–231] It was tested in a phase 1/2, open-label trial (CheckMate 040).[232] Forty-eight patients and 214 patients were treated in the dose-escalation phase and the dose-expansion phase for patients with Child-Pugh class A cirrhosis. Nivolumab 3 mg/kg was chosen for dose expansion. The ORR was 20% (range 15%–26%) in the dose-expansion phase and 15% (range 6%–28%) in the dose-escalation phase. A total of 154 patients received sorafenib and progressed on or were intolerant to it. The confirmed ORR in this patient group was 14.3% (range 9.2%–20.8%) with 3 complete responses and 19 partial responses. The DCR was 64%. The median OS and PFS were 15.0 and 4.0 months, respectively. The duration of response ranged from 3.2 to 38.2+ months; 91% of responders had responses lasting 6 months or longer, and 55% had responses lasting 12 months or longer. The most common grade 3–4 adverse events were increased lipase, aspartate aminotransferase, and alanine aminotransferase, as well as fatigue. The FDA approved nivolumab 240 mg every 2 weeks in the second-line setting in September 2017. It is also recommended in the frontline setting if patients are considered ineligible or intolerant to other frontline medications.

Pembrolizumab

Pembrolizumab is a humanized monoclonal antibody binding to PD-1 and inhibiting the binding of PD-1 to its ligand PD-L1 and PD-L2. Its clinical activities have been proven in several different cancers that include triple-negative breast cancer, cervical cancer, endometrial cancer, esophageal and gastric cancers, head and neck squamous cell carcinoma, Hodgkin lymphoma, melanoma, Merkel cell carcinoma, mycosis fungoides and Sézary syndrome, non–small cell lung cancer, primary mediastinal large B-cell lymphoma, renal cell carcinoma, small-cell lung cancer, urothelial carcinoma, and microsatellite unstable cancers.[198,233–250] Pembrolizumab was investigated in Keynote 224, a single-arm trial for patients with Child-Pugh class A and disease progression on or intolerance to sorafenib.[251] The median PFS and OS were 4.9 (range 3.4–7.2) and 12.9 months (range 9.7–15.5), respectively. The ORR and DCR were 17% (range 11%–26%) and 67%. The duration of response ranged from 3.1 to 16.7 months. Fatigue (4%) and increased aspartate aminotransferase (7%) and alanine aminotransferase (4%) were the most common grade 3–4 adverse events. Pembrolizumab 200 mg every 3 weeks was approved for advanced HCC in the second-line setting by the FDA in November 2018.

Nivolumab and Ipilimumab Combination

Nivolumab was tested in combination with ipilimumab, a recombinant human IgG1 antibody binding to the cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) for advanced HCC. Ipilimumab showed clinical efficacy in microsatellite unstable colorectal adenocarcinoma, melanoma, renal cell carcinoma, and small-cell lung cancer.[117,222,227,252,253] This combination was investigated in cohort 4 of CheckMate 040.[254] A total of 50 and 49 patients received nivolumab 1 mg/kg plus ipilimumab 3 mg/kg and nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks followed by nivolumab 240 mg

every 2 weeks. Most patients had advanced HCC at baseline: 88% of patients had vascular invasion or extrahepatic spread, and 91% had BCLC stage C. This combination showed the ORR of 32% and 31%, and DCR of 54% and 43% in respective arms. The median OS was 23 months and 12 months, respectively. Response duration ranged from 4.6 to 30.5+ months, with 31% of responses lasting at least 24 months. As discussed above, the ORR and median OS of nivolumab monotherapy demonstrated in CheckMate 040 were 14% and 16 months, and the combination of nivolumab and ipilimumab clearly showed clinical benefit. The combination showed that 37% of patients had grade 3–4 adverse events, with the most common being pruritus and rash, as well as other known immune-related adverse events reported in clinical studies for other cancers. Based on this result, nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg every 3 weeks for four doses, followed by single-agent nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks was approved by the FDA in March 2020 in the second-line setting.

Cabozantinib

Cabozantinib is an inhibitor of VEGFR 1, 2, and 3; MET; and AXL. It has shown its clinical efficacy in renal cell carcinoma and thyroid cancer.[255–257] It was initially tested in a phase 2 trial for patients with advanced HCC, regardless of previous treatment with sorafenib.[258] Patients with Child-Pugh class B/C were excluded. This showed a median OS of 11.5 months and a median PFS of 5.2 months. This was validated in a randomized phase 3 trial, and a total of 707 patients were assigned in a 2:1 ratio to receive cabozantinib 60 mg daily or placebo.[259] The primary end point was OS, and the secondary end points were PFS and ORR. A median OS was 10.2 months versus 8.0 months in the cabozantinib and placebo arms, with a HR of 0.76 (range 0.63–0.92). Median PFS and ORR were 5.2 months with a HR of 0.44 (range 0.36–0.52) and 4% (P = .009). The DCR was 64%. The most common grade 3–4 adverse events were palmar-plantar erythrodysesthesia (17%), hypertension (16%), and increased aspartate aminotransferase (12%). Based on this trial, cabozantinib was approved by the FDA in January 2019 in the second-line setting.

Regorafenib

Regorafenib is a multikinase inhibitor of multiple targets including VEGFR 1, 2, and 3; KIT; and PDGFRα and β. It had been approved for patients with metastatic colon cancer and gastrointestinal stromal tumor.[260–262] It was investigated in a randomized, double-blind, placebo-controlled trial for patients with advanced HCC.[263] Patients were Child-Pugh class A and BCLC stage B/C. Patients in the regorafenib arm had a median OS of 10.6 months (vs 7.8 months in the placebo arm; range 9.1–12.1) with a HR of 0.63 (range 0.5–0.79) and a PFS of 3.1 months (vs 1.5 months in the placebo arm) with a HR of 0.46 (range 0.37–0.56). The ORR and DCR were 11% and 65%, respectively. The most common grade 3–4 adverse events were hypertension (15%), palmar-plantar erythrodysesthesia (13%), fatigue (9%), and diarrhea (3%). The FDA approved regorafenib 160 mg once a day after a low-fat meal for 21 days on and 7 days off of each 28-day cycle for patients with advanced HCC in the second-line setting in April 2017.

Ramucirumab

Ramucirumab is a recombinant monoclonal antibody inhibiting VEGFR2 and blocking ligand-receptor interaction with VEGF-A, -C, and -D. It causes reduced cancer vascularity and growth.[264] It has been used in metastatic non–small cell lung cancer, esophageal and gastric cancers, and colorectal cancer.[264–267] Ramucirumab was investigated in a randomized, double-blind, placebo-controlled, phase 3 trial for HCC patients with Child-Pugh class A, BCLC stage B/C, and AFP >400 ng/mL.[268] The medication was used for patients who had received sorafenib. The median OS was 8.5 months (vs 7.3 months in the placebo arm; range 7.0–10.6) with a HR of 0.71 (range 0.53–0.95). The PFS was 2.8 months (range 2.8–4.1) versus 1.6 months with a HR of 0.45 (range 0.34–0.60). The ORR and DCR were 5% and 59.9%, respectively. Grade 3–4 adverse events included hypertension (13%), hyponatremia (6%), and increased aspartate aminotransferase (3%). Ramucirumab 8 mg/kg once every 2 weeks was approved by the FDA in May 2019 for patients with AFP of ≥400 ng/mL in the second-line setting.

Neoadjuvant Systemic Therapy

The only potentially curative modalities for HCC include liver resection and transplantation. However, the actual number of patients who qualify for these modalities is small (~10%–30%) because most patients present with locally advanced or metastatic disease or have significant liver dysfunction that precludes curative options. In addition, for those who undergo resection, tumor recurrence is common, with a 5-year recurrence rate of more than 70%,[26,269] and the 5-year survival rate for patients with resected HCC has been reported to be 30% to 70%.[270–272] The potential reasons for recurrence after surgical resection involve the presence of micrometastases not

seen on conventional imaging or the dissemination of tumor cells during surgery. Patients who initially are surgical candidates at diagnosis could have significant progression during the time between initial diagnosis and surgery and do not quality for surgery at a later time.

In this regard, preoperative therapy has been proposed and has theoretical benefits including tumor downsizing and reduction in micrometastases. Recently, sorafenib was tested in the neoadjuvant setting. In the open-label, phase 2 study reported at the Gastrointestinal American Society of Clinical Oncology (GI ASCO) in 2016, four weeks of sorafenib given before surgical resection resulted in 50% or higher tumor necrosis in 24% of surgical specimens.[273] In addition, this small study yielded a 32% ORR by mRECIST.

Immune checkpoint inhibitors can be safely administered in the preoperative setting as demonstrated by preoperative trials of an anti–CTLA-4 antibody before curative surgery in bladder cancer and other cancers.[274,275] In addition, immune checkpoint inhibitors investigated in the preoperative setting at MDACC indicated an impressive signal of activity in patients with resectable HCC.[276] In this pilot, randomized trial of perioperative immunotherapy with nivolumab with and without ipilimumab for resectable HCC, five of 21 resected cases (two treated with nivolumab and three with nivolumab and ipilimumab) demonstrated the complete pathologic response. However, there are no standard, systemic preoperative therapies for resectable HCC as of this writing. Ongoing trials with tyrosine kinase inhibitors or immune checkpoint inhibitors will provide more information in the neoadjuvant setting.

Adjuvant Systemic Therapy

Early studies of adjuvant chemotherapy published in the late 1990s to early 2000s demonstrated mixed results. For example, randomized studies of adjuvant capecitabine and 5-fluorouracil showed the improved time-to-recurrence and 5-year OS rate[277,278]; other studies of adjuvant epirubicin, tegafur, or carmofur did not show survival benefit or decrease in the recurrence rate.[279,280] More recently, sorafenib was tested as adjuvant treatment in a phase 3, randomized clinical trial.[281] This study included more than 500 patients in the sorafenib and placebo groups. The investigators did not find a difference in the median RFS (33.3 vs 33.7 months; HR 0.94, range 0.78–1.13), whereas patients in the sorafenib arm showed increased adverse events including palmar-plantar erythrodysesthesia and elevated liver enzymes. Adjuvant immunotherapy platforms including lymphocyte infusion, tumor-directed vaccines, cytokine-induced killer cells, and autologous cytokine-induced killer cells have been investigated with mixed results.[282–285] As of this writing, multiple clinical trials of tyrosine kinase inhibitors and immune checkpoint inhibitors are underway, but no systemic therapy is considered a standard of care in the adjuvant setting.[286]

Combined Hepatocellular Carcinoma and Cholangiocarcinoma (cHCC-CC)

Surgical resection is the only curative option in cHCC-CC, similar to intrahepatic cholangiocarcinoma and HCC. There are limited data on the role of LT. For example, two of three patients with cHCC-CC underwent LT, and two patients survived at 25 and 35 months[287,288]; another report shows that 8 of 14 patients had tumor recurrence at a median follow-up of 32 months, with a median DFS of 8 months status post-LT.[289] For unresectable tumors, systemic therapy is the main backbone of treatment. However, there is no consensus of opinions about chemotherapy or molecular targeted therapy. A retrospective analysis of patients with unresectable cHCC-CC who received systemic treatment including gemcitabine monotherapy, gemcitabine with platinum with or without bevacizumab, and sorafenib showed poor responses, with 71% having disease progression on the first radiographic scan.[290] The median OS and the tumor control rate were 8.3 months and 21%. Another retrospective analysis revealed the median OS for gemcitabine plus cisplatin, 5-fluorouracil plus cisplatin, and sorafenib of 11.9, 10.2, and 3.5 months, respectively,[291] whereas another case report of sorafenib monotherapy showed patients achieved remission after progression on chemotherapy.[292] Overall, gemcitabine plus platinum (cisplatin or oxaliplatin) with and without bevacizumab or molecular targeted therapy including sorafenib is considered the main backbone of systemic therapy.[293] Locoregional therapy or external beam radiation can also be considered in a similar fashion to the treatment in HCC or intrahepatic cholangiocarcinoma.

Fibrolamellar Hepatocellular Carcinoma (FLHCC)

In our recent publications[294,295] with the largest single-institution sample of 94 patients, the patients who received neoadjuvant (n = 34) or adjuvant therapy (n = 10) had the longest median OS—60 and 110.5 months, respectively—in the entire cohort.

The median age was 23 years (range 14–75), the median OS was 57.2 months (range 36.4–77.9), and the median RFS was 13.9 months (range 8.8–18.9). White race, female gender, early tumor stage, and tumor resection (including metastasectomy) were positively associated with a longer OS, whereas female gender was the only significant positive predictor of longer RFS. The 5-fluorouracil plus IFN-α2b combination was the most frequently used systemic therapy.[294]

Surgical resection remains the standard of care in patients with resectable and locally advanced FLHCC. In a systematic review that evaluated data from 575 patients with FLHCC, the authors noted that patients who underwent surgical resection had a 5-year survival rate of 70% compared with 0% among patients who did not undergo resection.[296] However, recurrence could be as high as 100% after surgical resection; moreover, chemotherapy options in neoadjuvant and adjuvant settings are not well defined.[295,297] None of the presently used chemotherapy regimens are based on randomized clinical data because of the limited number of patients with FLHCC. For patients with an unresectable disease, LT can be considered, and 3-year survival approaches 75% to 80% after transplantation,[298] whereas transplantation is much more commonly indicated for patients with HCC than for those with FLHCC. This is likely because HCC is more common than FLHCC, and a regional lymph node metastasis, a relative contraindication to transplant, is more common in FLHCC (42.2%) compared with patients with HCC (22.2%).[299]

Although not well studied, radiation therapy has been used to treat recurrent FLHCC in case reports and small case series[300,301]: in one case report, Peacock et al demonstrated an 85% decrease in tumor volume of FLHCC metastases after treatment with 40 Gy in 10 fractions over a 13-day period. In a retrospective study of 10 patients with metastatic FLHCC treated with external beam radiation in addition to chemotherapy, three patients had partial responses, six patients had stable disease, and one patient had early progression. The use of liver-directed therapies (eg, chemoembolization, Y-90, and ablation) in FLHCC remains poorly defined. Recently, Mafeld et al reported a patient with successful downstaging of an initially unresectable FLHCC with TACE followed by Y-90. The tumor decreased in volume from 350 to 20 cm^3, allowing curative or microscopically margin-negative (R0) resection with an extended left hepatectomy and reconstruction of the inferior vena cava.[302]

FLHCC is not typically responsive to chemotherapy.[294,303] Although there is no consensus regarding the ideal chemotherapeutic regimen for FLHCC, platinum-based chemotherapy regimens, as well as combination regimens including IFN-α2b have been used with some success.[304–306] A phase 2 trial reported complete or partial responses in 5 of 8 patients treated with 5-fluorouracil and IFN-α2b.[306] In this trial, patients received 5-fluorouracil at a dose of 200 mg/m^2 infused continuously over 21 days with IFN-α2b at a dose of 4 million U/m^2 three times weekly during 5-fluorouracil infusion on a 28-day cycle. The median OS was 23.1 months (range 10.3–35.9). Approximately 9% of patients had grade 3–4 neutropenia, thrombocytopenia, or anemia. Nonhematologic toxicities were mostly grade 1–2 mucositis (39.5%), diarrhea (13.9%), nausea and vomiting (13.9%), fatigue (34.9%), and skin reaction (23.3%). Since that publication, the 5-fluorouracil plus IFN-α2b combination has been established as the most frequently used systemic therapy.[294] There is limited and conflicting evidence demonstrating the efficacy of immune checkpoint inhibitors.[307,308] However, the addition of an immune checkpoint inhibitor to 5-fluorouracil plus IFN-α2b, which is known to augment immune cell infiltration, increases PD-L1 expression and restores the INF-γ–producing capacity of CD8+ T cells and may prolong survival.[309,310] As of this writing, there is a clinical trial for patients with FLHCC at MDACC: a phase 1/2 study of atezolizumab plus bevacizumab with 5-fluorouracil and IFN-α2b for unresectable FLHCC.

MD ANDERSON APPROACH TO HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma and other primary liver tumors require multidisciplinary input, and patients benefit from clinical care that integrates the expertise of surgical oncology, LT, diagnostic and interventional radiology, gastroenterology and hepatology, radiation oncology, and medical oncology. New cases of HCC are reviewed at a weekly multidisciplinary liver tumor conference to develop a consensus approach to each patient's case. Careful attention is paid to precise tumor staging, histopathologic diagnosis, and each patient's performance status. Figure 30–4 depicts the general approach followed by the multidisciplinary hepatobiliary team in treating patients with HCC. MDACC has multiple clinical trials of combined approaches with systemic therapy, radiation therapy, and locoregional therapy, and clinical trials are offered at different levels of treatment.

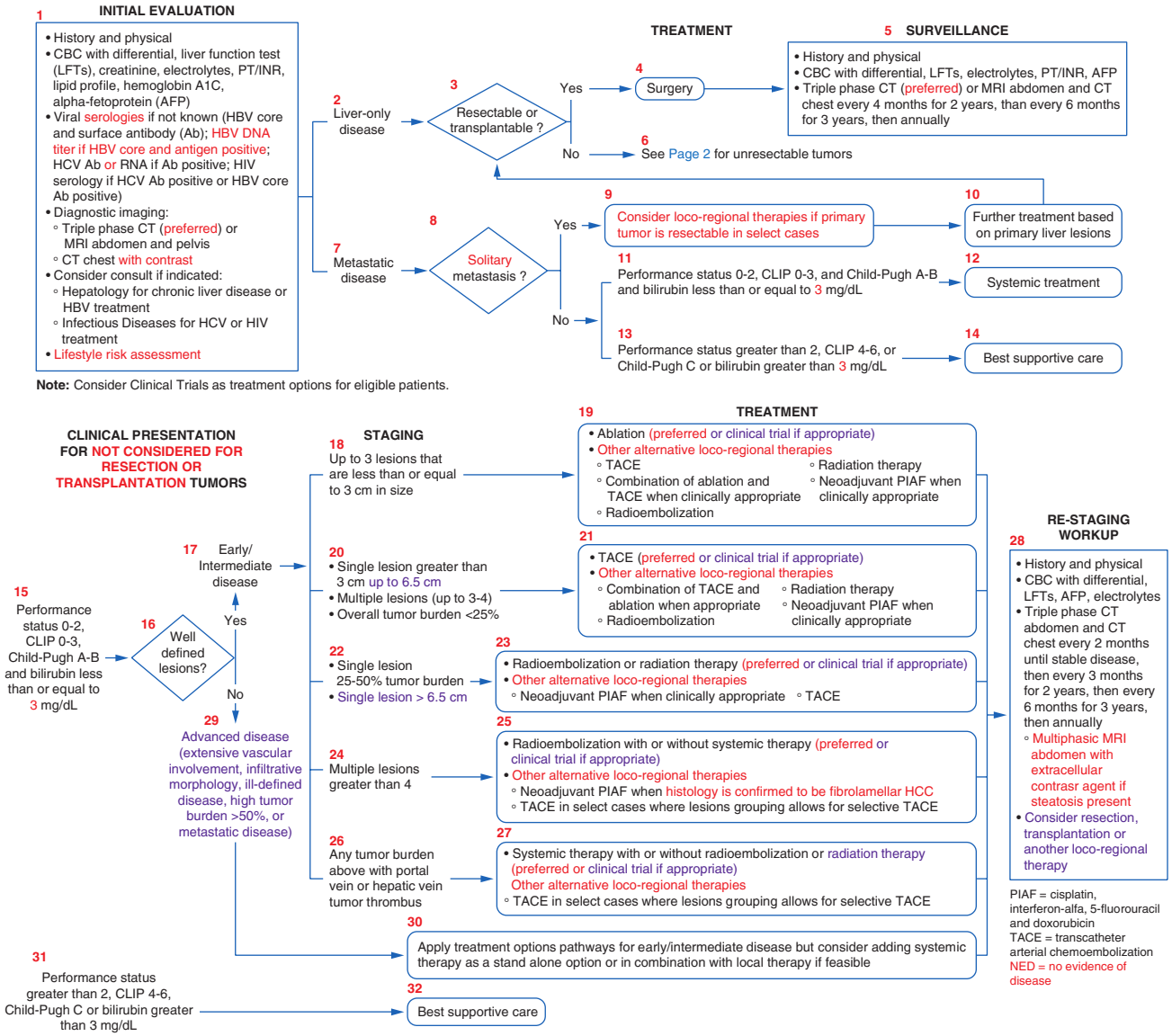


FIGURE 30–4 MDACC approach to HCC treatment. (Adapted with permission from the University of Texas MD Anderson Cancer Center.)

MD ANDERSON PRACTICE TIPS

- Patients with HCC are co-managed by a multidisciplinary approach with hepatology, medical oncology, surgical oncology, radiation oncology, and interventional radiology.
- MDACC collaborates with transplant hepatology at Houston Methodist and Baylor College of Medicine for transplant-eligible patients.
- Liver function (eg, Child-Pugh score for liver cirrhosis) and portal hypertension, as well as the stage of liver cancer, are assessed before a treatment decision is made.
- For patients with early-stage liver cancer, locoregional therapy, radiation therapy, surgical resection, and LT are considered. Clinical trials of neoadjuvant and adjuvant therapy are offered.
- Systemic therapy is the main backbone of cancer treatment for patients with advanced or metastatic HCC. Clinical trials are offered for eligible patients, and locoregional and radiation therapy are combined.
- All patients with HCC are offered pathologic and molecular profiling using next-generation sequencing.

REFERENCES

1. World Health Organization . WHO Mortality Database. WHO Statistical Information System. Accessed April 25, 2021. https://www.who.int/data/data-collection-tools/who-mortality-database.
2. Davis GL, Albright JE, Cook SF, Rosenberg DM. Projecting future complications of chronic hepatitis C in the United States. *Liver Transpl.* 2003;9(4):331-338.
3. Deuffic S, Poynard T, Buffat L, Valleron AJ. Trends in primary liver cancer. *Lancet.* 1998;351(9097):214-215.
4. Parkin DM, Bray FI, Devesa SS. Cancer burden in the year 2000. The global picture. *Eur J Cancer.* 2001;37(suppl 8):S4-S66.
5. Taylor-Robinson SD, Foster GR, Arora S, Hargreaves S, Thomas HC. Increase in primary liver cancer in the UK, 1979-94. *Lancet.* 1997;350(9085):1142-1143.
6. Smart RG, Mann RE, Suurvali H. Changes in liver cirrhosis death rates in different countries in relation to per capita alcohol consumption and Alcoholics Anonymous membership. *J Stud Alcohol.* 1998;59(3):245-249.
7. Wong JB, McQuillan GM, McHutchison JG, Poynard T. Estimating future hepatitis C morbidity, mortality, and costs in the United States. *Am J Public Health.* 2000;90(10):1562-1569.
8. Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. *Gastroenterology.* 2015;148(3):547-555.
9. El-Serag HB, Davila JA, Petersen NJ, McGlynn KA. The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. *Ann Intern Med.* 2003;139(10):817-823.
10. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med.* 1999;340(10):745-750.
11. Kohli A, Shaffer A, Sherman A, Kottilil S. Treatment of hepatitis C: a systematic review. *JAMA.* 2014;312(6):631-640.
12. Loguercio C, De Simone T, D'Auria MV, et al. Non-alcoholic fatty liver disease: a multicentre clinical study by the Italian Association for the Study of the Liver. *Dig Liver Dis.* 2004;36(6):398-405.
13. McCullough AJ. The clinical features, diagnosis and natural history of nonalcoholic fatty liver disease. *Clin Liver Dis.* 2004;8(3):521-533, viii.
14. Ruhl CE, Everhart JE. Epidemiology of nonalcoholic fatty liver. *Clin Liver Dis.* 2004;8(3):501-519, vii.
15. Parkin DM. The global burden of cancer. *Semin Cancer Biol.* 1998;8(4):219-235.
16. Shen FM, Lee MK, Gong HM, Cai XQ, King MC. Complex segregation analysis of primary hepatocellular carcinoma in Chinese families: interaction of inherited susceptibility and hepatitis B viral infection. *Am J Hum Genet.* 1991;49(1):88-93.
17. DeBaun MR, Tucker MA. Risk of cancer during the first four years of life in children from The Beckwith-Wiedemann Syndrome Registry. *J Pediatr.* 1998;132(3 Pt 1):398-400.
18. Giardiello FM, Petersen GM, Brensinger JD, et al. Hepatoblastoma and APC gene mutation in familial adenomatous polyposis. *Gut.* 1996;39(6):867-869.
19. Esquivel CO, Mieles L, Marino IR, et al. Liver transplantation for hereditary tyrosinemia in the presence of hepatocellular carcinoma. *Transplant Proc.* 1989;21(1 Pt 2):2445-2446.
20. Franco LM, Krishnamurthy V, Bali D, et al. Hepatocellular carcinoma in glycogen storage disease type Ia: a case series. *J Inherit Metab Dis.* 2005;28(2):153-162.
21. Kim B, Park SH, Yang HR, Seo JK, Kim WS, Chi JG. Hepatocellular carcinoma occurring in alagille syndrome. *Pathol Res Pract.* 2005;201(1):55-60.
22. Litten JB, Tomlinson GE. Liver tumors in children. *Oncologist.* 2008;13(7):812-820.
23. Patil MM, Patil SV. Ataxia telangiectasia with hepatocellular carcinoma. *Indian Pediatr.* 2009;46(6):546.
24. Rosenberg PS, Alter BP, Ebell W. Cancer risks in Fanconi anemia: findings from the German Fanconi Anemia Registry. *Haematologica.* 2008;93(4):511-517.
25. Walther A, Tiao G. Approach to pediatric hepatocellular carcinoma. *Clin Liver Dis (Hoboken).* 2013;2(5):219-222.
26. Bruix J, Sherman M, Practice Guidelines Committee, American Association for the Study of Liver Disease. Management of hepatocellular carcinoma. *Hepatology.* 2005;42(5):1208-1236.
27. Singal AG, Yopp A, S Skinner C, Packer M, Lee WM, Tiro JA. Utilization of hepatocellular carcinoma surveillance among American patients: a systematic review. *J Gen Intern Med.* 2012;27(7):861-867.
28. Wolf E, Rich NE, Marrero JA, Parikh N, Singal AG. Utilization of hepatocellular carcinoma surveillance in patients with cirrhosis: a systematic review and meta-analysis. *Hepatology.* 2021;73(2):713-725.
29. Feldman M, Friedman LS, Brandt LJ. *Sleisenger and Fordtran's Gastrointestinal and Liver disease: Pathophysiology/Diagnosis/Management*. 10th ed. Saunders/Elsevier; 2016.
30. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. *J Hepatol.* 2018;69(1):182-236.
31. Fujiwara N, Friedman SL, Goossens N, Hoshida Y. Risk factors and prevention of hepatocellular carcinoma in the era of precision medicine. *J Hepatol.* 2018;68(3):526-549.
32. Jia L, Wang XW, Harris CC. Hepatitis B virus X protein inhibits nucleotide excision repair. *Int J Cancer.* 1999;80(6):875-879.
33. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology.* 2018;68(2):723-750.
34. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology.* 2012;142(6):1264-1273, e1261.
35. Chen JD, Yang HI, Iloeje UH, et al. Carriers of inactive hepatitis B virus are still at risk for hepatocellular carcinoma and liver-related death. *Gastroenterology.* 2010;138(5):1747-1754.
36. Yang HI, Yuen MF, Chan HL, et al. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. *Lancet Oncol.* 2011;12(6):568-574.
37. Lee HW, Ahn SH. Prediction models of hepatocellular carcinoma development in chronic hepatitis B patients. *World J Gastroenterol.* 2016;22(37):8314-8321.
38. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology.* 2004;127(5 suppl 1):S35-S50.
39. Hassan MM, Hwang LY, Hatten CJ, et al. Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. *Hepatology.* 2002;36(5):1206-1213.
40. Ghany MG, Morgan TR, AASLD-IDSA Hepatitis C Guidance Panel. Hepatitis C Guidance 2019 Update: American Association for the Study of Liver Diseases-Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. *Hepatology.* 2020;71(2):686-721.
41. Spach DH. Recommendations for Hepatitis C Screening. Accessed April 25, 2021. https://www.hepatitisc.uw.edu/go/screening-diagnosis/recommendations-screening/core-concept/all.
42. Moyer VA, US Preventive Services Task Force. Screening for hepatitis C virus infection in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2013;159(5):349-357.
43. US Preventive Services Task Force. Hepatitis C Virus Infection in Adolescents and Adults: Screening. Accessed April 25,

2021. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/hepatitis-c-screening.
44. Baumert TF, Juhling F, Ono A, Hoshida Y. Hepatitis C-related hepatocellular carcinoma in the era of new generation antivirals. *BMC Med.* 2017;15(1):52.
45. Kanwal F, Kramer J, Asch SM, Chayanupatkul M, Cao Y, El-Serag HB. Risk of hepatocellular cancer in HCV patients treated with direct-acting antiviral agents. *Gastroenterology.* 2017;153(4):996-1005, e1001.
46. El-Serag HB, Kanwal F, Richardson P, Kramer J. Risk of hepatocellular carcinoma after sustained virological response in veterans with hepatitis C virus infection. *Hepatology.* 2016;64(1):130-137.
47. Conti F, Buonfiglioli F, Scuteri A, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. *J Hepatol.* 2016;65(4):727-733.
48. Reig M, Marino Z, Perello C, et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. *J Hepatol.* 2016;65(4):719-726.
49. ANRS Collaborative Study Group on Hepatocellular Carcinoma. Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: data from three ANRS cohorts. *J Hepatol.* 2016;65(4):734-740.
50. Singal AG, Rich NE, Mehta N, et al. Direct-acting antiviral therapy not associated with recurrence of hepatocellular carcinoma in a multicenter North American cohort study. *Gastroenterology.* 2019;156(6):1683-1692, e1681.
51. Nash KL, Woodall T, Brown AS, Davies SE, Alexander GJ. Hepatocellular carcinoma in patients with chronic hepatitis C virus infection without cirrhosis. *World J Gastroenterol.* 2010;16(32):4061-4065.
52. Lok AS, Seeff LB, Morgan TR, et al. Incidence of hepatocellular carcinoma and associated risk factors in hepatitis C-related advanced liver disease. *Gastroenterology.* 2009;136(1):138-148.
53. El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology.* 2004;126(2):460-468.
54. Saunders D, Seidel D, Allison M, Lyratzopoulos G. Systematic review: the association between obesity and hepatocellular carcinoma - epidemiological evidence. *Aliment Pharmacol Ther.* 2010;31(10):1051-1063.
55. El-Serag HB, Kanwal F. Obesity and hepatocellular carcinoma: hype and reality. *Hepatology.* 2014;60(3):779-781.
56. Zhao J, Lawless MW. Stop feeding cancer: pro-inflammatory role of visceral adiposity in liver cancer. *Cytokine.* 2013;64(3):626-637.
57. Schlesinger S, Aleksandrova K, Pischon T, et al. Abdominal obesity, weight gain during adulthood and risk of liver and biliary tract cancer in a European cohort. *Int J Cancer.* 2013;132(3):645-657.
58. Dai G, Liu P, Li X, Zhou X, He S. Association between PNPLA3 rs738409 polymorphism and nonalcoholic fatty liver disease (NAFLD) susceptibility and severity: a meta-analysis. *Medicine (Baltimore).* 2019;98(7):e14324.
59. Romeo S, Kozlitina J, Xing C, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. *Nat Genet.* 2008;40(12):1461-1465.
60. Trépo E, Romeo S, Zucman-Rossi J, Nahon P. PNPLA3 gene in liver diseases. *J Hepatol.* 2016;65(2):399-412.
61. Yamamoto K, Kogiso T, Taniai M, Hashimoto E, Tokushige K. Differences in the genetic backgrounds of patients with alcoholic liver disease and non-alcoholic fatty liver disease. *JGH Open.* 2019;3(1):17-24.
62. Lee SS, Jeong SH, Byoun YS, et al. Clinical features and outcome of cryptogenic hepatocellular carcinoma compared to those of viral and alcoholic hepatocellular carcinoma. *BMC Cancer* 2013;13:335.
63. Ascha MS, Hanouneh IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. *Hepatology.* 2010;51(6):1972-1978.
64. Leung C, Yeoh SW, Patrick D, et al. Characteristics of hepatocellular carcinoma in cirrhotic and non-cirrhotic non-alcoholic fatty liver disease. *World J Gastroenterol.* 2015;21(4):1189-1196.
65. Perumpail RB, Wong RJ, Ahmed A, Harrison SA. Hepatocellular carcinoma in the setting of non-cirrhotic nonalcoholic fatty liver disease and the metabolic syndrome: US experience. *Dig Dis Sci.* 2015;60(10):3142-3148.
66. Guzman G, Brunt EM, Petrovic LM, Chejfec G, Layden TJ, Cotler SJ. Does nonalcoholic fatty liver disease predispose patients to hepatocellular carcinoma in the absence of cirrhosis? *Arch Pathol Lab Med.* 2008;132(11):1761-1766.
67. Stine JG, Wentworth BJ, Zimmet A, et al. Systematic review with meta-analysis: risk of hepatocellular carcinoma in non-alcoholic steatohepatitis without cirrhosis compared to other liver diseases. *Aliment Pharmacol Ther.* 2018;48(7):696-703.
68. Mittal S, El-Serag HB, Sada YH, et al. Hepatocellular carcinoma in the absence of cirrhosis in United States veterans is associated with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol.* 2016;14(1):124-131, e121.
69. Tobari M, Hashimoto E, Taniai M, et al. The characteristics and risk factors of hepatocellular carcinoma in nonalcoholic fatty liver disease without cirrhosis. *J Gastroenterol Hepatol.* 2020;35(5):862-869.
70. White DL, Kanwal F, El-Serag HB. Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systematic review. *Clin Gastroenterol Hepatol.* 2012;10(12):1342-1359, e1342.
71. Angulo P, Hui JM, Marchesini G, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. *Hepatology.* 2007;45(4):846-854.
72. Kishnani PS, Austin SL, Abdenur JE, et al. Diagnosis and management of glycogen storage disease type I: a practice guideline of the American College of Medical Genetics and Genomics. *Genet Med* 2014;16(11):e1.
73. Wang DQ, Fiske LM, Carreras CT, Weinstein DA. Natural history of hepatocellular adenoma formation in glycogen storage disease type I. *J Pediatr.* 2011;159(3):442-446.
74. Baheti AD, Yeh MM, O'Malley R, Lalwani N. Malignant transformation of hepatic adenoma in glycogen storage disease type-1a: report of an exceptional case diagnosed on surveillance imaging. *J Clin Imaging Sci* 2015;5:47.
75. Lee PJ. Glycogen storage disease type I: pathophysiology of liver adenomas. *Eur J Pediatr.* 2002;161(suppl 1):S46-S49.
76. Bowerman RA, Samuels BI, Silver TM. Ultrasonographic features of hepatic adenomas in type I glycogen storage disease. *J Ultrasound Med.* 1983;2(2):51-54.
77. Bali DS, Chen YT, Austin S, Goldstein JL. Glycogen storage disease type I. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews®.* University of Washington; 1993.
78. Sorensen HT, Friis S, Olsen JH, et al. Risk of liver and other types of cancer in patients with cirrhosis: a nationwide cohort study in Denmark. *Hepatology.* 1998;28(4):921-925.
79. Di Bisceglie AM, Rustgi VK, Hoofnagle JH, Dusheiko GM, Lotze MT. NIH conference. Hepatocellular carcinoma. *Ann Intern Med.* 1988;108(3):390-401.
80. Turati F, Galeone C, Rota M, et al. Alcohol and liver cancer: a systematic review and meta-analysis of prospective studies. *Ann Oncol.* 2014;25(8):1526-1535.
81. Pocha C, Xie C. Hepatocellular carcinoma in alcoholic and non-alcoholic fatty liver disease-one of a kind or two different enemies? *Transl Gastroenterol Hepatol.* 2019;4:72.

82. Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology.* 2018;67(1):358-380.
83. Xu R, Hajdu CH. Wilson disease and hepatocellular carcinoma. *Gastroenterol Hepatol (N Y).* 2008;4(6):438-439.
84. Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases. *Hepatology.* 2019;69(1):394-419.
85. Groisman IJ, Koshy R, Henkler F, Groopman JD, Alaoui-Jamali MA. Downregulation of DNA excision repair by the hepatitis B virus-x protein occurs in p53-proficient and p53-deficient cells. *Carcinogenesis.* 1999;20(3):479-483.
86. Denissenko MF, Koudriakova TB, Smith L, O'Connor TR, Riggs AD, Pfeifer GP. The p53 codon 249 mutational hotspot in hepatocellular carcinoma is not related to selective formation or persistence of aflatoxin B1 adducts. *Oncogene.* 1998;17(23):3007-3014.
87. Ozturk M. p53 mutation in hepatocellular carcinoma after aflatoxin exposure. *Lancet.* 1991;338(8779):1356-1359.
88. Ishikawa Y, Wada I, Fukumoto M. Alpha-particle carcinogenesis in Thorotrast patients: epidemiology, dosimetry, pathology, and molecular analysis. *J Environ Pathol Toxicol Oncol.* 2001;20(4):311-315.
89. Poon RT, Ng IO, Fan ST, et al. Clinicopathologic features of long-term survivors and disease-free survivors after resection of hepatocellular carcinoma: a study of a prospective cohort. *J Clin Oncol.* 2001;19(12):3037-3044.
90. Sutton FM, Russell NC, Guinee VF, Alpert E. Factors affecting the prognosis of primary liver carcinoma. *J Clin Oncol.* 1988;6(2):321-328.
91. Cazals-Hatem D, Rebouissou S, Bioulac-Sage P, et al. Clinical and molecular analysis of combined hepatocellular-cholangiocarcinomas. *J Hepatol.* 2004;41(2):292-298.
92. Stavraka C, Rush H, Ross P. Combined hepatocellular cholangiocarcinoma (cHCC-CC): an update of genetics, molecular biology, and therapeutic interventions. *J Hepatocell Carcinoma.* 2019;6:11-21.
93. Moeini A, Sia D, Zhang Z, et al. Mixed hepatocellular cholangiocarcinoma tumors: Cholangiolocellular carcinoma is a distinct molecular entity. *J Hepatol.* 2017;66(5):952-961.
94. Ross HM, Daniel HD, Vivekanandan P, et al. Fibrolamellar carcinomas are positive for CD68. *Mod Pathol.* 2011;24(3):390-395.
95. Van Eyken P, Sciot R, Brock P, Casteels-Van Daele M, Ramaekers FC, Desmet VJ. Abundant expression of cytokeratin 7 in fibrolamellar carcinoma of the liver. *Histopathology.* 1990;17(2):101-107.
96. Ward SC, Huang J, Tickoo SK, Thung SN, Ladanyi M, Klimstra DS. Fibrolamellar carcinoma of the liver exhibits immunohistochemical evidence of both hepatocyte and bile duct differentiation. *Mod Pathol.* 2010;23(9):1180-1190.
97. Hirsch TZ, Negulescu A, Gupta B, et al. BAP1 mutations define a homogeneous subgroup of hepatocellular carcinoma with fibrolamellar-like features and activated PKA. *J Hepatol.* 2020;72(5):924-936.
98. Honeyman JN, Simon EP, Robine N, et al. Detection of a recurrent DNAJB1-PRKACA chimeric transcript in fibrolamellar hepatocellular carcinoma. *Science.* 2014;343(6174):1010-1014.
99. Ros PR, Li KC. Benign liver tumors. *Curr Probl Diagn Radiol.* 1989;18(3):125-155.
100. Giannitrapani L, Soresi M, La Spada E, Cervello M, D'Alessandro N, Montalto G. Sex hormones and risk of liver tumor. *Ann N Y Acad Sci.* 2006;1089:228-236.
101. Rooks JB, Ory HW, Ishak KG, et al. Epidemiology of hepatocellular adenoma. The role of oral contraceptive use. *JAMA.* 1979;242(7):644-648.
102. Mathieu D, Kobeiter H, Maison P, et al. Oral contraceptive use and focal nodular hyperplasia of the liver. *Gastroenterology.* 2000;118(3):560-564.
103. Ramírez-Fuentes C, Martí-Bonmatí L, Torregrosa A, Del Val A, Martínez C. Variations in the size of focal nodular hyperplasia on magnetic resonance imaging. *Radiologia.* 2013;55(6):499-504.
104. Pateron D, Ganne N, Trinchet JC, et al. Prospective study of screening for hepatocellular carcinoma in Caucasian patients with cirrhosis. *J Hepatol.* 1994;20(1):65-71.
105. Rummeny E, Weissleder R, Stark DD, et al. Primary liver tumors: diagnosis by MR imaging. *AJR Am J Roentgenol.* 1989;152(1):63-72.
106. Vauthey JN, Lauwers GY, Esnaola NF, et al. Simplified staging for hepatocellular carcinoma. *J Clin Oncol.* 2002;20(6):1527-1536.
107. Chok KS, Ng KK, Poon RT, Lo CM, Fan ST. Impact of postoperative complications on long-term outcome of curative resection for hepatocellular carcinoma. *Br J Surg.* 2009;96(1):81-87.
108. Pawlik TM, Poon RT, Abdalla EK, et al. Critical appraisal of the clinical and pathologic predictors of survival after resection of large hepatocellular carcinoma. *Arch Surg.* 2005;140(5):450-457; discussion 457-458.
109. Berzigotti A, Reig M, Abraldes JG, Bosch J, Bruix J. Portal hypertension and the outcome of surgery for hepatocellular carcinoma in compensated cirrhosis: a systematic review and meta-analysis. *Hepatology.* 2015;61(2):526-536.
110. Llovet JM, Fuster J, Bruix J. The Barcelona approach: diagnosis, staging, and treatment of hepatocellular carcinoma. *Liver Transpl.* 2004;10(2 suppl 1):S115-S120.
111. Guglielmi A, Ruzzenente A, Conci S, Valdegamberi A, Iacono C. How much remnant is enough in liver resection? *Dig Surg.* 2012;29(1):6-17.
112. Abdalla EK, Hicks ME, Vauthey JN. Portal vein embolization: rationale, technique and future prospects. *Br J Surg.* 2001;88(2):165-175.
113. Ribero D, Abdalla EK, Madoff DC, Donadon M, Loyer EM, Vauthey JN. Portal vein embolization before major hepatectomy and its effects on regeneration, resectability and outcome. *Br J Surg.* 2007;94(11):1386-1394.
114. Yang JD, Larson JJ, Watt KD, et al. Hepatocellular carcinoma is the most common indication for liver transplantation and placement on the waitlist in the United States. *Clin Gastroenterol Hepatol.* 2017;15(5):767-775. e763.
115. Petrick JL, Kelly SP, Altekruse SF, McGlynn KA, Rosenberg PS. Future of hepatocellular carcinoma incidence in the United States forecast through 2030. *J Clin Oncol.* 2016;34(15):1787-1794.
116. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med.* 1996;334(11):693-699.
117. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med.* 2018;378(14):1277-1290.
118. Iwatsuki S, Starzl TE, Sheahan DG, et al. Hepatic resection versus transplantation for hepatocellular carcinoma. *Ann Surg.* 1991;214(3):221-228; discussion 228-229.
119. Duffy JP, Vardanian A, Benjamin E, et al. Liver transplantation criteria for hepatocellular carcinoma should be expanded: a 22-year experience with 467 patients at UCLA. *Ann Surg.* 2007;246(3):502-509; discussion 509-511.
120. Yao FY, Mehta N, Flemming J, et al. Downstaging of hepatocellular cancer before liver transplant: long-term outcome compared to tumors within Milan criteria. *Hepatology.* 2015;61(6):1968-1977.
121. Ma WJ, Wang HY, Teng LS. Correlation analysis of preoperative serum alpha-fetoprotein (AFP) level and prognosis of hepatocellular carcinoma (HCC) after hepatectomy. *World J Surg Oncol.* 2013;11:212.

122. Herrero JI, Sangro B, Quiroga J, et al. Influence of tumor characteristics on the outcome of liver transplantation among patients with liver cirrhosis and hepatocellular carcinoma. *Liver Transpl.* 2001;7(7):631-636.
123. Parfitt JR, Marotta P, Alghamdi M, et al. Recurrent hepatocellular carcinoma after transplantation: use of a pathological score on explanted livers to predict recurrence. *Liver Transpl.* 2007;13(4):543-551.
124. Zhao WC, Fan LF, Yang N, Zhang HB, Chen BD, Yang GS. Preoperative predictors of microvascular invasion in multinodular hepatocellular carcinoma. *Eur J Surg Oncol.* 2013;39(8):858-864.
125. Victor DW 3rd, Monsour HP Jr, Boktour M, et al. Outcomes of liver transplantation for hepatocellular carcinoma beyond the University of California San Francisco Criteria: a single-center experience. *Transplantation.* 2020;104(1):113-121.
126. Halazun KJ, Najjar M, Abdelmessih RM, et al. Recurrence after liver transplantation for hepatocellular carcinoma: a new MORAL to the story. *Ann Surg.* 2017;265(3):557-564.
127. Escartin A, Sapisochin G, Bilbao I, et al. Recurrence of hepatocellular carcinoma after liver transplantation. *Transplant Proc.* 2007;39(7):2308-2310.
128. Berenguer M, Burra P, Ghobrial M, et al. Posttransplant management of recipients undergoing liver transplantation for hepatocellular carcinoma. Working Group Report From the ILTS Transplant Oncology Consensus Conference. *Transplantation.* 2020;104(6):1143-1149.
129. Mehta N, Heimbach J, Harnois DM, et al. Validation of a Risk Estimation of Tumor Recurrence After Transplant (RETREAT) score for hepatocellular carcinoma recurrence after liver transplant. *JAMA Oncol.* 2017;3(4):493-500.
130. Guba M, von Breitenbuch P, Steinbauer M, et al. Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor. *Nat Med.* 2002;8(2):128-135.
131. Freise CE, Ferrell L, Liu T, Ascher NL, Roberts JP. Effect of systemic cyclosporine on tumor recurrence after liver transplantation in a model of hepatocellular carcinoma. *Transplantation.* 1999;67(4):510-513.
132. Vivarelli M, Cucchetti A, Piscaglia F, et al. Analysis of risk factors for tumor recurrence after liver transplantation for hepatocellular carcinoma: key role of immunosuppression. *Liver Transpl.* 2005;11(5):497-503.
133. Wang Y, Speeg KV, Washburn WK, Halff G. Sirolimus plus sorafenib in treating HCC recurrence after liver transplantation: a case report. *World J Gastroenterol.* 2010;16(43):5518-5522.
134. Zhang J, Li H, Wang GS, Jiang N, Yang Y, Chen GH. [Effects of sirolimus on the growth of transplanted hepatocellular carcinoma]. *Zhonghua Gan Zang Bing Za Zhi.* 2009;17(6):413-416.
135. Geissler EK, Schnitzbauer AA, Zülke C, et al. Sirolimus use in liver transplant recipients with hepatocellular carcinoma: a randomized, multicenter, open-label phase 3 trial. *Transplantation.* 2016;100(1):116-125.
136. Au KP, Chok KSH. Multidisciplinary approach for post-liver transplant recurrence of hepatocellular carcinoma: a proposed management algorithm. *World J Gastroenterol.* 2018;24(45):5081-5094.
137. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B. AASLD 2018 hepatitis B guidance. *Hepatology.* 2018;67(4):1560-1599.
138. Yamada R, Nakatsuka H, Nakamura K, et al. Hepatic artery embolization in 32 patients with unresectable hepatoma. *Osaka City Med J.* 1980;26(2):81-96.
139. Llovet JM, Real MI, Montaña X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet.* 2002;359(9319):1734-1739.
140. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology.* 2002;35(5):1164-1171.
141. Lewis AL, Dreher MR. Locoregional drug delivery using image-guided intra-arterial drug eluting bead therapy. *J Control Release.* 2012;161(2):338-350.
142. Lammer J, Malagari K, Vogl T, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. *Cardiovasc Intervent Radiol.* 2010;33(1):41-52.
143. Poon RT, Tso WK, Pang RW, et al. A phase I/II trial of chemoembolization for hepatocellular carcinoma using a novel intra-arterial drug-eluting bead. *Clin Gastroenterol Hepatol.* 2007;5(9):1100-1108.
144. Reyes DK, Vossen JA, Kamel IR, et al. Single-center phase II trial of transarterial chemoembolization with drug-eluting beads for patients with unresectable hepatocellular carcinoma: initial experience in the United States. *Cancer J.* 2009;15(6):526-532.
145. Brown KT, Do RK, Gonen M, et al. Randomized trial of hepatic artery embolization for hepatocellular carcinoma using doxorubicin-eluting microspheres compared with embolization with microspheres alone. *J Clin Oncol.* 2016;34(17):2046-2053.
146. Gray BN, Anderson JE, Burton MA, et al. Regression of liver metastases following treatment with yttrium-90 microspheres. *Aust N Z J Surg.* 1992;62(2):105-110.
147. Salem R, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology.* 2010;138(1):52-64.
148. Hilgard P, Hamami M, Fouly AE, et al. Radioembolization with yttrium-90 glass microspheres in hepatocellular carcinoma: European experience on safety and long-term survival. *Hepatology.* 2010;52(5):1741-1749.
149. Lewandowski RJ, Kulik LM, Riaz A, et al. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. *Am J Transplant.* 2009;9(8):1920-1928.
150. Salem R, Gordon AC, Mouli S, et al. Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology.* 2016;151(6):1155-1163. e1152.
151. Chow PKH, Gandhi M, Tan SB, et al. SIRveNIB: selective internal radiation therapy versus sorafenib in Asia-Pacific patients with hepatocellular carcinoma. *J Clin Oncol.* 2018;36(19):1913-1921.
152. Vilgrain V, Pereira H, Assenat E, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. *Lancet Oncol.* 2017;18(12):1624-1636.
153. Ricke J, Klümpen HJ, Amthauer H, et al. Impact of combined selective internal radiation therapy and sorafenib on survival in advanced hepatocellular carcinoma. *J Hepatol.* 2019;71(6):1164-1174.
154. Mohamed M, Katz AW, Tejani MA, et al. Comparison of outcomes between SBRT, yttrium-90 radioembolization, transarterial chemoembolization, and radiofrequency ablation as bridge to transplant for hepatocellular carcinoma. *Adv Radiat Oncol.* 2016;1(1):35-42.
155. Gabr A, Kulik L, Mouli S, et al. Liver transplantation following yttrium-90 radioembolization: 15-year experience in 207-patient cohort. *Hepatology.* 2021;73(3):998-1010.
156. Chen MS, Li JQ, Zheng Y, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann Surg.* 2006;243(3):321-328.

157. Lubner MG, Brace CL, Hinshaw JL, Lee FT Jr. Microwave tumor ablation: mechanism of action, clinical results, and devices. *J Vasc Interv Radiol.* 2010;21(8 suppl):S192-S203.
158. Marelli L, Stigliano R, Triantos C, et al. Treatment outcomes for hepatocellular carcinoma using chemoembolization in combination with other therapies. *Cancer Treat Rev.* 2006;32(8):594-606.
159. Veltri A, Moretto P, Doriguzzi A, Pagano E, Carrara G, Gandini G. Radiofrequency thermal ablation (RFA) after transarterial chemoembolization (TACE) as a combined therapy for unresectable non-early hepatocellular carcinoma (HCC). *Eur Radiol.* 2006;16(3):661-669.
160. Hawkins MA, Dawson LA. Radiation therapy for hepatocellular carcinoma: from palliation to cure. *Cancer.* 2006;106(8):1653-1663.
161. Krishnan S, Dawson LA, Seong J, et al. Radiotherapy for hepatocellular carcinoma: an overview. *Ann Surg Oncol.* 2008;15(4):1015-1024.
162. Ben-Josef E, Normolle D, Ensminger WD, et al. Phase II trial of high-dose conformal radiation therapy with concurrent hepatic artery floxuridine for unresectable intrahepatic malignancies. *J Clin Oncol.* 2005;23(34):8739-8747.
163. Mornex F, Girard N, Beziat C, et al. Feasibility and efficacy of high-dose three-dimensional-conformal radiotherapy in cirrhotic patients with small-size hepatocellular carcinoma non-eligible for curative therapies--mature results of the French Phase II RTF-1 trial. *Int J Radiat Oncol Biol Phys.* 2006;66(4):1152-1158.
164. Dawson LA, Eccles C, Craig T. Individualized image guided iso-NTCP based liver cancer SBRT. *Acta Oncol.* 2006;45(7):856-864.
165. Méndez Romero A, Wunderink W, Hussain SM, et al. Stereotactic body radiation therapy for primary and metastatic liver tumors: a single institution phase I-II study. *Acta Oncol.* 2006;45(7):831-837.
166. Skinner HD, Hong TS, Krishnan S. Charged-particle therapy for hepatocellular carcinoma. *Semin Radiat Oncol.* 2011;21(4):278-286.
167. Chiba T, Tokuuye K, Matsuzaki Y, et al. Proton beam therapy for hepatocellular carcinoma: a retrospective review of 162 patients. *Clin Cancer Res.* 2005;11(10):3799-3805.
168. Hong TS, Wo JY, Yeap BY, et al. Multi-institutional phase II study of high-dose hypofractionated proton beam therapy in patients with localized, unresectable hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Clin Oncol.* 2016;34(5):460-468.
169. Chadha AS, Gunther JR, Hsieh CE, et al. Proton beam therapy outcomes for localized unresectable hepatocellular carcinoma. *Radiother Oncol.* 2019;133:54-61.
170. Skinner HD, Sharp HJ, Kaseb AO, et al. Radiation treatment outcomes for unresectable hepatocellular carcinoma. *Acta Oncol.* 2011;50(8):1191-1198.
171. Seong J, Keum KC, Han KH, et al. Combined transcatheter arterial chemoembolization and local radiotherapy of unresectable hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys.* 1999;43(2):393-397.
172. Seong J, Park HC, Han KH, et al. Local radiotherapy for unresectable hepatocellular carcinoma patients who failed with transcatheter arterial chemoembolization. *Int J Radiat Oncol Biol Phys.* 2000;47(5):1331-1335.
173. Chia-Hsien Cheng J, Chuang VP, Cheng SH, et al. Unresectable hepatocellular carcinoma treated with radiotherapy and/or chemoembolization. *Int J Cancer.* 2001;96(4):243-252.
174. Guo WJ, Yu EX. Evaluation of combined therapy with chemoembolization and irradiation for large hepatocellular carcinoma. *Br J Radiol.* 2000;73(874):1091-1097.
175. Yasuda S, Ito H, Yoshikawa M, et al. Radiotherapy for large hepatocellular carcinoma combined with transcatheter arterial embolization and percutaneous ethanol injection therapy. *Int J Oncol.* 1999;15(3):467-473.
176. Hsu WC, Chan SC, Ting LL, et al. Results of three-dimensional conformal radiotherapy and thalidomide for advanced hepatocellular carcinoma. *Jpn J Clin Oncol.* 2006;36(2):93-99.
177. Ishikura S, Ogino T, Furuse J, et al. Radiotherapy after transcatheter arterial chemoembolization for patients with hepatocellular carcinoma and portal vein tumor thrombus. *Am J Clin Oncol.* 2002;25(2):189-193.
178. Kim DY, Park W, Lim DH, et al. Three-dimensional conformal radiotherapy for portal vein thrombosis of hepatocellular carcinoma. *Cancer.* 2005;103(11):2419-2426.
179. Lin CS, Jen YM, Chiu SY, et al. Treatment of portal vein tumor thrombosis of hepatoma patients with either stereotactic radiotherapy or three-dimensional conformal radiotherapy. *Jpn J Clin Oncol.* 2006;36(4):212-217.
180. Minagawa M, Makuuchi M. Treatment of hepatocellular carcinoma accompanied by portal vein tumor thrombus. *World J Gastroenterol.* 2006;12(47):7561-7567.
181. Nakagawa K, Yamashita H, Shiraishi K, et al. Radiation therapy for portal venous invasion by hepatocellular carcinoma. *World J Gastroenterol.* 2005;11(46):7237-7241.
182. Tazawa J, Maeda M, Sakai Y, et al. Radiation therapy in combination with transcatheter arterial chemoembolization for hepatocellular carcinoma with extensive portal vein involvement. *J Gastroenterol Hepatol.* 2001;16(6):660-665.
183. Yamada K, Izaki K, Sugimoto K, et al. Prospective trial of combined transcatheter arterial chemoembolization and three-dimensional conformal radiotherapy for portal vein tumor thrombus in patients with unresectable hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys.* 2003;57(1):113-119.
184. Yamada K, Soejima T, Sugimoto K, et al. Pilot study of local radiotherapy for portal vein tumor thrombus in patients with unresectable hepatocellular carcinoma. *Jpn J Clin Oncol.* 2001;31(4):147-152.
185. Zeng ZC, Fan J, Tang ZY, et al. A comparison of treatment combinations with and without radiotherapy for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombus. *Int J Radiat Oncol Biol Phys.* 2005;61(2):432-443.
186. Holliday EB, Tao R, Brownlee Z, et al. Definitive radiation therapy for hepatocellular carcinoma with portal vein tumor thrombus. *Clin Transl Radiat Oncol.* 2017;4:39-45.
187. Wei X, Jiang Y, Zhang X, et al. Neoadjuvant three-dimensional conformal radiotherapy for resectable hepatocellular carcinoma with portal vein tumor thrombus: a randomized, open-label, multicenter controlled study. *J Clin Oncol.* 2019;37(24):2141-2151.
188. Feng M, Suresh K, Schipper MJ, et al. Individualized adaptive stereotactic body radiotherapy for liver tumors in patients at high risk for liver damage: a phase 2 clinical trial. *JAMA Oncol.* 2018;4(1):40-47.
189. Giannini EG, Farinati F, Ciccarese F, et al. Prognosis of untreated hepatocellular carcinoma. *Hepatology.* 2015;61(1):184-190.
190. Lencioni R, Kudo M, Ye SL, et al. First interim analysis of the GIDEON (Global Investigation of therapeutic decisions in hepatocellular carcinoma and of its treatment with sorafeNib) non-interventional study. *Int J Clin Pract.* 2012;66(7):675-683.
191. Huang M, Liu G. The study of innate drug resistance of human hepatocellular carcinoma Bel7402 cell line. *Cancer Lett.* 1999;135(1):97-105.
192. Kaseb AO, Shindoh J, Patt YZ, et al. Modified cisplatin/interferon α-2b/doxorubicin/5-fluorouracil (PIAF) chemotherapy in patients with no hepatitis or cirrhosis is associated with improved response rate, resectability, and survival of initially unresectable hepatocellular carcinoma. *Cancer.* 2013;119(18):3334-3342.

193. Kuo MT, Zhao JY, Teeter LD, Ikeguchi M, Chisari FV. Activation of multidrug resistance (P-glycoprotein) mdr3/mdr1a gene during the development of hepatocellular carcinoma in hepatitis B virus transgenic mice. *Cell Growth Differ.* 1992;3(8):531-540.
194. Qin S, Bai Y, Lim HY, et al. Randomized, multicenter, open-label study of oxaliplatin plus fluorouracil/leucovorin versus doxorubicin as palliative chemotherapy in patients with advanced hepatocellular carcinoma from Asia. *J Clin Oncol.* 2013;31(28):3501-3508.
195. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med.* 2007;356(2):125-134.
196. Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. *J Clin Oncol.* 2009;27(20):3312-3318.
197. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med.* 2008;359(4):378-390.
198. Makker V, Rasco D, Vogelzang NJ, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: an interim analysis of a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol.* 2019;20(5):711-718.
199. Motzer RJ, Hutson TE, Glen H, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. *Lancet Oncol.* 2015;16(15):1473-1482.
200. Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med.* 2015;372(7):621-630.
201. Ikeda K, Kudo M, Kawazoe S, et al. Phase 2 study of lenvatinib in patients with advanced hepatocellular carcinoma. *J Gastroenterol.* 2017;52(4):512-519.
202. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet.* 2018;391(10126):1163-1173.
203. Balar AV, Galsky MD, Rosenberg JE, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. *Lancet.* 2017;389(10064):67-76.
204. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet.* 2016;387(10030):1837-1846.
205. Horn L, Mansfield AS, Szcz sna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med.* 2018;379(23):2220-2229.
206. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet.* 2017;389(10066):255-265.
207. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet.* 2016;387(10031):1909-1920.
208. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *N Engl J Med.* 2018;379(22):2108-2121.
209. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med.* 2018;378(24):2288-2301.
210. West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* 2019;20(7):924-937.
211. Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol.* 2012;30(17):2039-2045.
212. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol.* 2009;27(28):4733-4740.
213. Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. *J Clin Oncol.* 2014;32(13):1302-1308.
214. Tewari KS, Sill MW, Long HJ 3rd, et al. Improved survival with bevacizumab in advanced cervical cancer. *N Engl J Med.* 2014;370(8):734-743.
215. Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med.* 2003;349(5):427-434.
216. Lee M, Ryoo BY, Hsu CH, et al. LBA39 - Randomised efficacy and safety results for atezolizumab (Atezo) + bevacizumab (Bev) in patients (pts) with previously untreated, unresectable hepatocellular carcinoma (HCC). *Ann Oncol.* 2019;30:v875.
217. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med.* 2020;382(20):1894-1905.
218. Boige V, Malka D, Bourredjem A, et al. Efficacy, safety, and biomarkers of single-agent bevacizumab therapy in patients with advanced hepatocellular carcinoma. *Oncologist.* 2012;17(8):1063-1072.
219. Finn RS, Zhu AX. Targeting angiogenesis in hepatocellular carcinoma: focus on VEGF and bevacizumab. *Expert Rev Anticancer Ther.* 2009;9(4):503-509.
220. Siegel AB, Cohen EI, Ocean A, et al. Phase II trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma. *J Clin Oncol.* 2008;26(18):2992-2998.
221. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med.* 2015;372(4):311-319.
222. Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol.* 2016;17(7):883-895.
223. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med.* 2015;373(17):1627-1639.
224. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med.* 2015;373(2):123-135.
225. Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2016;375(19):1856-1867.
226. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med.* 2015;373(19):1803-1813.
227. Overman MJ, Lonardi S, Wong KYM, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. *J Clin Oncol.* 2018;36(8):773-779.
228. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol.* 2017;18(9):1182-1191.
229. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med.* 2015;372(4):320-330.

230. Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. *Lancet Oncol.* 2017;18(3):312-322.
231. Younes A, Santoro A, Shipp M, et al. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. *Lancet Oncol.* 2016;17(9):1283-1294.
232. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet.* 2017;389(10088):2492-2502.
233. Armand P, Rodig S, Melnichenko V, et al. Pembrolizumab in relapsed or refractory primary mediastinal large B-cell lymphoma. *J Clin Oncol.* 2019;37(34):3291-3299.
234. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med.* 2017;376(11):1015-1026.
235. Burtness B, Harrington KJ, Greil R, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *Lancet.* 2019;394(10212):1915-1928.
236. Chen R, Zinzani PL, Fanale MA, et al. Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. *J Clin Oncol.* 2017;35(19):2125-2132.
237. Chung HC, Piha-Paul SA, López-Martin J, et al. Pembrolizumab after two or more lines of previous therapy in patients with recurrent or metastatic SCLC: results from the KEYNOTE-028 and KEYNOTE-158 studies. *J Thorac Oncol.* 2020;15(4):618-627.
238. Chung HC, Ros W, Delord JP, et al. Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: results from the phase II KEYNOTE-158 study. *J Clin Oncol.* 2019;37(17):1470-1478.
239. Fuchs CS, Doi T, Jang RW, et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial. *JAMA Oncol.* 2018;4(5):e180013.
240. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet.* 2016;387(10027):1540-1550.
241. Khodadoust MS, Rook AH, Porcu P, et al. Pembrolizumab in relapsed and refractory mycosis fungoides and Sézary syndrome: a multicenter phase II study. *J Clin Oncol.* 2020;38(1):20-28.
242. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in tumors with mismatch-repair deficiency. *N Engl J Med.* 2015;372(26):2509-2520.
243. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. *J Clin Oncol.* 2020;38(1):1-10.
244. Mehra R, Seiwert TY, Gupta S, et al. Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma: pooled analyses after long-term follow-up in KEYNOTE-012. *Br J Cancer.* 2018;119(2):153-159.
245. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet.* 2019;393(10183):1819-1830.
246. Nghiem PT, Bhatia S, Lipson EJ, et al. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. *N Engl J Med.* 2016;374(26):2542-2552.
247. Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. *Lancet Oncol.* 2015;16(8):908-918.
248. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med.* 2019;380(12):1116-1127.
249. Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for early triple-negative breast cancer. *N Engl J Med.* 2020;382(9):810-821.
250. Shah MA, Adenis A, Enzinger PC, et al. Pembrolizumab versus chemotherapy as second-line therapy for advanced esophageal cancer: phase 3 KEYNOTE-181 study. *J Clin Oncol.* 2019;37(15 suppl):4010.
251. Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. *Lancet Oncol.* 2018;19(7):940-952.
252. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med.* 2010;363(8):711-723.
253. Tawbi HA, Forsyth PA, Algazi A, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. *N Engl J Med.* 2018;379(8):722-730.
254. Yau T, Kang Y-K, Kim T-Y, et al. Nivolumab (NIVO) + ipilimumab (IPI) combination therapy in patients (pts) with advanced hepatocellular carcinoma (aHCC): results from CheckMate 040. *J Clin Oncol.* 2019;37(15 suppl):4012.
255. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma. *N Engl J Med.* 2015;373(19):1814-1823.
256. Choueiri TK, Halabi S, Sanford BL, et al. Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: the Alliance A031203 CABOSUN trial. *J Clin Oncol.* 2017;35(6):591-597.
257. Schlumberger M, Elisei R, Müller S, et al. Overall survival analysis of EXAM, a phase III trial of cabozantinib in patients with radiographically progressive medullary thyroid carcinoma. *Ann Oncol.* 2017;28(11):2813-2819.
258. Kelley RK, Verslype C, Cohn AL, et al. Cabozantinib in hepatocellular carcinoma: results of a phase 2 placebo-controlled randomized discontinuation study. *Ann Oncol.* 2017;28(3):528-534.
259. Abou-Alfa GK, Meyer T, Cheng A-L, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *N Engl J Med.* 2018;379(1):54-63.
260. Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet.* 2013;381(9863):295-302.
261. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet.* 2013;381(9863):303-312.
262. Li J, Qin S, Xu R, et al. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2015;16(6):619-629.
263. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2017;389(10064):56-66.
264. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet.* 2014;383(9911):31-39.
265. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line

treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet.* 2014;384(9944):665-673.
266. Tabernero J, Yoshino T, Cohn AL, et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. *Lancet Oncol.* 2015;16(5):499-508.
267. Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol.* 2014;15(11):1224-1235.
268. Zhu AX, Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2019;20(2):282-296.
269. Kianmanesh R, Regimbeau JM, Belghiti J. Selective approach to major hepatic resection for hepatocellular carcinoma in chronic liver disease. *Surg Oncol Clin N Am.* 2003;12(1):51-63.
270. Lai EC, Fan ST, Lo CM, Chu KM, Liu CL, Wong J. Hepatic resection for hepatocellular carcinoma. An audit of 343 patients. *Ann Surg.* 1995;221(3):291-298.
271. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *Hepatology.* 1999;30(6):1434-1440.
272. Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. *Ann Surg.* 2002;235(3):373-382.
273. Bouattour M, Fartoux L, Rosmorduc O, et al. BIOSHARE multicenter neoadjuvant phase 2 study: Results of pre-operative sorafenib in patients with resectable hepatocellular carcinoma (HCC)—From GERCOR IRC. *J Clin Oncol.* 2016;34 (suppl 4S):abstract 252.
274. Basu A, Sadeghi S. Neoadjuvant therapies for bladder cancer in cisplatin-ineligible patients: what options do we have? *Eur Urol Focus.* 2020;6(4):623-626.
275. Liu J, Blake SJ, Yong MCR, et al. Improved efficacy of neoadjuvant compared to adjuvant immunotherapy to eradicate metastatic disease. *Cancer Discov.* 2016;6(12):1382-1399.
276. Kaseb AO, Pestana RC, Vence LM, et al. Randomized, open-label, perioperative phase II study evaluating nivolumab alone versus nivolumab plus ipilimumab in patients with resectable HCC. *J Clin Oncol.* 2019;37(4 suppl):185-185.
277. Xia Y, Qiu Y, Li J, et al. Adjuvant therapy with capecitabine postpones recurrence of hepatocellular carcinoma after curative resection: a randomized controlled trial. *Ann Surg Oncol.* 2010;17(12):3137-3144.
278. Yamamoto M, Arii S, Sugahara K, Tobe T. Adjuvant oral chemotherapy to prevent recurrence after curative resection for hepatocellular carcinoma. *Br J Surg.* 1996;83(3):336-340.
279. Lai EC, Lo CM, Fan ST, Liu CL, Wong J. Postoperative adjuvant chemotherapy after curative resection of hepatocellular carcinoma: a randomized controlled trial. *Arch Surg.* 1998;133(2):183-188.
280. Ono T, Yamanoi A, Nazmy El Assal O, Kohno H, Nagasue N. Adjuvant chemotherapy after resection of hepatocellular carcinoma causes deterioration of long-term prognosis in cirrhotic patients: metaanalysis of three randomized controlled trials. *Cancer.* 2001;91(12):2378-2385.
281. Bruix J, Takayama T, Mazzaferro V, et al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Oncol.* 2015;16(13):1344-1354.
282. Hui D, Qiang L, Jian W, Ti Z, Da-Lu K. A randomized, controlled trial of postoperative adjuvant cytokine-induced killer cells immunotherapy after radical resection of hepatocellular carcinoma. *Dig Liver Dis.* 2009;41(1):36-41.
283. Kuang M, Peng BG, Lu MD, et al. Phase II randomized trial of autologous formalin-fixed tumor vaccine for postsurgical recurrence of hepatocellular carcinoma. *Clin Cancer Res.* 2004;10(5):1574-1579.
284. Lee JH, Lee JH, Lim YS, et al. Adjuvant immunotherapy with autologous cytokine-induced killer cells for hepatocellular carcinoma. *Gastroenterology.* 2015;148(7):1383-1391.e1386.
285. Takayama T, Sekine T, Makuuchi M, et al. Adoptive immunotherapy to lower postsurgical recurrence rates of hepatocellular carcinoma: a randomised trial. *Lancet.* 2000;356(9232):802-807.
286. Akateh C, Black SM, Conteh L, et al. Neoadjuvant and adjuvant treatment strategies for hepatocellular carcinoma. *World J Gastroenterol.* 2019;25(28):3704-3721.
287. Chan AC, Lo CM, Ng IO, Fan ST. Liver transplantation for combined hepatocellular cholangiocarcinoma. *Asian journal of surgery* 2007;30(2):143-146.
288. Connell LC, Harding JJ, Shia J, Abou-Alfa GK. Combined intrahepatic cholangiocarcinoma and hepatocellular carcinoma. *Chin Clin Oncol.* 2016;5(5):66.
289. Sapisochin G, Fidelman N, Roberts JP, Yao FY. Mixed hepatocellular cholangiocarcinoma and intrahepatic cholangiocarcinoma in patients undergoing transplantation for hepatocellular carcinoma. *Liver Transpl.* 2011;17(8):934-942.
290. Rogers JE, Bolonesi RM, Rashid A, et al. Systemic therapy for unresectable, mixed hepatocellular-cholangiocarcinoma: treatment of a rare malignancy. *J Gastrointest Oncol.* 2017;8(2):347-351.
291. Kobayashi S, Terashima T, Shiba S, et al. Multicenter retrospective analysis of systemic chemotherapy for unresectable combined hepatocellular and cholangiocarcinoma. *Cancer Sci.* 2018;109(8):2549-2557.
292. Futsukaichi Y, Tajiri K, Kobayashi S, et al. Combined hepatocellular-cholangiocarcinoma successfully treated with sorafenib: case report and review of the literature. *Clin J Gastroenterol.* 2019;12(2):128-134.
293. Salimon M, Prieux-Klotz C, Tougeron D, et al. Gemcitabine plus platinum-based chemotherapy for first-line treatment of hepatocholangiocarcinoma: an AGEO French multicentre retrospective study. *Br J Cancer.* 2018;118(3):325-330.
294. Kaseb AO, Shama M, Sahin IH, et al. Prognostic indicators and treatment outcome in 94 cases of fibrolamellar hepatocellular carcinoma. *Oncology (Williston Park).* 2013;85(4):197-203.
295. Yamashita S, Vauthey JN, Kaseb AO, et al. Prognosis of fibrolamellar carcinoma compared to non-cirrhotic conventional hepatocellular carcinoma. *J Gastrointest Surg.* 2016;20(10):1725-1731.
296. Mavros MN, Mayo SC, Hyder O, Pawlik TM. A systematic review: treatment and prognosis of patients with fibrolamellar hepatocellular carcinoma. *J Am Coll Surg.* 2012;215(6):820-830.
297. Ang CS, Kelley RK, Choti MA, et al. Clinicopathologic characteristics and survival outcomes of patients with fibrolamellar carcinoma: data from the fibrolamellar carcinoma consortium. *Gastrointest Cancer Res.* 2013;6(1):3-9.
298. El-Gazzaz G, Wong W, El-Hadary MK, et al. Outcome of liver resection and transplantation for fibrolamellar hepatocellular carcinoma. *Transpl Int.* 2000;13 suppl 1:S406-S409.
299. Mayo SC, Mavros MN, Nathan H, et al. Treatment and prognosis of patients with fibrolamellar hepatocellular carcinoma: a national perspective. *J Am Coll Surg.* 2014;218(2):196-205.
300. Epstein BE, Pajak TF, Haulk TL, Herpst JM, Order SE, Abrams RA. Metastatic nonresectable fibrolamellar hepatoma: prognostic features and natural history. *Am J Clin Oncol.* 1999;22(1):22-28.

301. Peacock JG, Call JA, Olivier KR. Radiotherapy for metastatic fibrolamellar hepatocellular carcinoma. *Rare tumors* 2013;5(3):e28.
302. Mafeld S, French J, Tiniakos D, Haugk B, Manas D, Littler P. Fibrolamellar hepatocellular carcinoma: treatment with yttrium-90 and subsequent surgical resection. *Cardiovasc Intervent Radiol.* 2018;41(5):816-820.
303. Lafaro KJ, Pawlik TM. Fibrolamellar hepatocellular carcinoma: current clinical perspectives. *J Hepatocell Carcinoma* 2015;2:151-157.
304. Bower M, Newlands ES, Habib N. Fibrolamellar hepatocellular carcinoma responsive to platinum-based combination chemotherapy. *Clin Oncol (R Coll Radiol).* 1996;8(5):331-333.
305. Maniaci V, Davidson BR, Rolles K, et al. Fibrolamellar hepatocellular carcinoma: prolonged survival with multimodality therapy. *Eur J Surg Oncol.* 2009;35(6):617-621.
306. Patt YZ, Hassan MM, Lozano RD, et al. Phase II trial of systemic continuous fluorouracil and subcutaneous recombinant interferon Alfa-2b for treatment of hepatocellular carcinoma. *J Clin Oncol.* 2003;21(3):421-427.
307. Bauer U, Mogler C, Braren RF, Algül H, Schmid RM, Ehmer U. Progression after immunotherapy for fibrolamellar carcinoma. *Visc Med.* 2019;35(1):39-42.
308. De Toni EN, Roessler D. Using dual checkpoint blockade to treat fibrolamellar hepatocellular carcinoma. *Gut.* 2020;69(11):2056-2058.
309. Bazhin AV, von Ahn K, Fritz J, Werner J, Karakhanova S. Interferon-α up-regulates the expression of PD-L1 molecules on immune cells through STAT3 and p38 signaling. *Front Immunol.* 2018;9:2129.
310. Moschos SJ, Edington HD, Land SR, et al. Neoadjuvant treatment of regional stage IIIB melanoma with high-dose interferon alfa-2b induces objective tumor regression in association with modulation of tumor infiltrating host cellular immune responses. *J Clin Oncol.* 2006;24(19):3164-3171.

This page intentionally left blank

31 Small Bowel Cancer and Appendiceal Tumors

Pat Gulhati
John Paul Shen
Kanwal P. Raghav
Michael J. Overman

KEY CONCEPTS

- Small bowel neoplasms are rare with roughly 12,000 new cases per year in the United States. The two most common histologies are adenocarcinoma (30%–40%) and carcinoid tumors (40%–45%).
- Inflammatory bowel disease, Peutz-Jeghers, familial adenomatous polyposis, celiac disease, and hereditary nonpolyposis colorectal cancer and all increase the risk of developing small bowel adenocarcinomas.
- Surgery is the mainstay of curative therapy; however, patients often present with more advanced disease, especially with adenocarcinomas.
- There is no firmly established adjuvant therapy for patients with either carcinoid tumors or adenocarcinoma.
- Systemic therapy for patients with advanced disease mirrors treatment for neuroendocrine tumors for carcinoids, whereas FOLFOX (modified 5-fluorouracil and oxaliplatin), CAPOX, and regimens with irinotecan are active for patients with adenocarcinoma.
- The molecular defects in adenocarcinomas are being elucidated. To date, however, no targeted therapy has an established role in advanced disease. Mismatch repair defects (even more frequent than in colorectal cancer) are predictive of response to immune checkpoint blockade.
- Appendiceal neoplasms are very rare consist of two major types: appendiceal carcinoid tumors and appendiceal epithelial tumors, each accounting for roughly half all cases.
- No clear risk factors for appendiceal neoplasms have been identified.
- Surgery is the mainstay of curative therapy for all patients with appendiceal neoplasms. Patients with adenocarcinomas are more likely to present with advanced disease in comparison with those with carcinoid tumors.
- The histologic subtypes of epithelial appendiceal neoplasms include low- and high-grade appendiceal mucinous neoplasms and invasive adenocarcinomas that may be mucinous (low or high grade), nonmucinous, or with signet ring cell features.
- Metastatic low-grade mucinous tumors have a more indolent disease course, respond poorly to systemic therapy, and are primarily managed with surgical cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC).
- Metastatic high-grade adenocarcinomas, which include all tumors with signet ring cell features, are often treated with systemic chemotherapy. The benefit from cytoreductive surgery and HIPEC is uncertain.

SMALL BOWEL CANCER

Small bowel cancer is a rare malignancy representing approximately 3% of gastrointestinal (GI) neoplasms.[1] In 2020, it was estimated that 11,110 new cases of small bowel cancer and 1700 small bowel cancer–related deaths would occur.[1] The two most common histologies seen in cancers of the small intestine are carcinoids and adenocarcinomas.[2] Because of the nonspecific clinical presentation of small bowel adenocarcinoma (SBA) and the difficulty in imaging the small bowel, most patients with SBA present with lymph node involvement or distant metastases. Even in patients with localized disease who undergo resection with curative intent, the prognosis is poor, and no studies have yet demonstrated a clear benefit from adjuvant therapy. However, there have been some recent advances in molecular profiling as well as the use of chemotherapy, targeted therapy, and immunotherapy as palliative treatments. In this chapter, the

epidemiology, diagnosis, and treatment of small bowel cancers, in particular SBA, are reviewed.

Epidemiology

Based on an analysis of the Surveillance, Epidemiology, and End Results (SEER) database, the age-adjusted incidence rate for small bowel cancers slowly increased from 0.9 per 100,000 persons in the years 1973 to 1982 to 2.4 per 100,000 persons in the years 2013 to 2017.[3,4] The majority of this increase has been attributed to an increase in the incidence of carcinoid tumors. Carcinoids account for 39% to 45% of all cases, whereas SBA accounts for 31% to 40% of all small intestinal cancer diagnoses.[5] Most primary tumors arise in the duodenum (60%), with 25% to 29% arising in the jejunum and 10% to 13% in the ileum.[5] The incidence of histologic subtypes varies in the different sections of the small intestine, with adenocarcinomas representing 59% of duodenal cancers and carcinoids representing 57% of ileal cancers.[2,5] The median age at diagnosis is 60 years, and there is slightly increased incidence seen in men and Blacks.[5,6]

One of the more interesting aspects of SBA is its rarity in comparison with large intestine adenocarcinoma. Even though the small intestine represents approximately 70% to 80% of the length and more than 90% of the surface area of the alimentary tract, the incidence of SBA is 50- to 100-fold less than the incidence of colorectal carcinoma (CRC). Numerous theories have been proposed to explain the small intestine's relative protection from the development of malignancy. Proposed protective factors have centered on two concepts. First, the rapid turnover time of small intestinal cells results in epithelial cell shedding before the necessary acquisition of multiple genetic defects. Second, the small bowel's exposure to the carcinogenic components of our diet are limited because of rapid small bowel transit time; the lack of bacterial degradation activity that occurs in the small bowel; the relatively dilute, alkaline environment of the small bowel; and greater lymphoid infiltrate in small intestinal mucosa. In a population-based comparison of adenocarcinomas of the large (n = 261,521) and small (n = 4,18) intestine identified from the SEER registry, SBA demonstrated a distinctly worse stage-adjusted cancer-specific survival than CRC.[7]

Anatomy

The small intestine is divided into three sections. The duodenum represents the first 25 cm of the small intestine and is subdivided into four anatomic segments. The proximal portion of the first (ascending) segment of the duodenum is intraperitoneal, and then the distal portion, as well as the rest of the duodenum, becomes retroperitoneal. The second (descending) segment of the duodenum contains the ampulla of Vater, through which the pancreatic and biliary secretions exit. The third (horizontal) segment of the duodenum is the longest, and as it crosses the left border of the aorta, the fourth (ascending) segment of the duodenum begins. The duodenal–jejunal junction is characterized by the attachment of the suspensory ligament of Treitz. The next segment of the small bowel, the jejunum, is approximately 2.5 m long, and the final segment, the ileum, is approximately 3.5 m long.

Etiology

Little is known about the etiology of SBA. As seen in CRC, SBA undergoes a similar phenotypic adenoma–carcinoma transformation.[8–10] An increase in the size of small bowel adenomas and the presence of a villous histology are risk factors for the development of invasive adenocarcinoma.

Common underlying genetic or environmental factors of both large and small intestine adenocarcinomas have been suggested by studies that have demonstrated an increased risk of SBA in patients with colon adenocarcinoma and vice versa.[11] SBA has a higher likelihood of microsatellite instability (7.6%) and high tumor mutational burden (9.5%) compared with CRC (4.0% and 4.3%, respectively).[12]

The possible role of pancreaticobiliary secretions in the development of adenocarcinoma of the duodenum has been suggested by the anatomic clustering of duodenal carcinomas in the periampullary area. For example, in patients with familial adenomatous polyposis (FAP), 80% of SBAs occur in the second portion of the duodenum. One study evaluating 213 cases of duodenal carcinomas identified from the Los Angeles County tumor registry determined that 57% of the cases originated in the second part of the duodenum.[13]

Environment and Dietary Risk Factors

A number of case-control studies have analyzed associations between environmental and dietary factors and the development of SBA. Two studies have demonstrated that there is an association between the ingestion of smoked or salt-cured foods and the development of SBA.[14,15] An association between tobacco use and cancer risk has been inconsistently demonstrated. Case-control studies have demonstrated an association between an increased risk of SBA and high alcohol intake, high sugar intake, high red meat intake, low fiber intake, celiac disease, peptic ulcer disease, and prior cholecystectomy[14–18] Studies of the relationship with obesity have been conflicting, although a case-cohort study of 500,000 participants with 134 incident cases of small bowel cancer showed a statistically nonsignificant trend

toward increased risk in subjects with high body mass index (BMI) with a hazard ratio (HR) of 1.5 (95% confidence interval [CI], 0.76–2.96) for BMIs greater than 27.5 kg/m2 compared with BMIs of 22.6 to 25.0 kg/m^2.[19]

Genetic Cancer Syndromes

The genetic cancer syndromes hereditary nonpolyposis colorectal cancer (HNPCC), FAP, and Peutz-Jeghers syndrome (PJS) are all associated with SBA. The estimated lifetime risk for SBA is 1% to 4% in patients with HNPCC, 5% in those with FAP, and 13% in those with PJS[20–23] Patients with HNPCC develop SBA at a younger age, with a median age at diagnosis of 49 years. Patients with PJS, an autosomal dominant polyposis disorder characterized by multiple hamartomatous polyps throughout the intestinal tract, have a markedly increased risk for SBA, with one meta-analysis demonstrating a 520-fold increased relative risk.[24] Duodenal adenomas are seen in approximately 80% of patients with FAP, and regular endoscopic screening for the development of adenocarcinoma is required for these patients. The optimal frequency of endoscopic screening depends on a number of factors, such as the number of polyps, polyp size, polyp histology, and amount of dysplasia present.[20] With the early use of colectomy in patients with FAP, duodenal adenocarcinomas and desmoid tumors are now a more common cause of death in this population than CRC.

Inflammatory Bowel Disease and Celiac Disease

Inflammatory bowel disease (IBD), particularly Crohn disease, is associated with the development of SBA. The increase in risk varies depending on both the extent and duration of small bowel involvement. In one study, the cumulative risk of SBA in patients with Crohn disease was 0.2% at 10 years and 2.2% at 25 years.[25] Because Crohn disease frequently involves the ileum, 70% of the small bowel cancers in patients with Crohn disease occur in the ileum. Patients with Crohn disease who develop SBA appear to have a worse prognosis, with one study of 37 patients with SBA demonstrating significantly shorter overall survival (OS) in patients with Crohn disease.[26] Celiac disease is another proinflammatory condition that increases the risk of developing SBA 34-fold.[5] In general, these patients may be younger at disease onset and have better OS compared with those with SBA caused by other disorders.[5]

Molecular Profile

Accumulation of genetic defects such as loss of E-cadherin and SMAD4 and mutations in *KRAS*, *TP53*, and *SMAD4* have been implicated in the adenoma–dysplasia–carcinoma sequence of SBA.[2] In a pivotal study comparing chromosomal copy number aberrations in 85 gastric cancer, CRC, and SBAs, hierarchical clustering revealed a substantial overlap of SBA copy number profiles with matched CRCs but less overlap with profiles of gastric adenocarcinomas, indicating a genetic profile similar to CRC.[27] However, SBA is a unique molecular entity with distinct differences compared with other GI cancers, including CRC and gastric adenocarcinoma. The most commonly noted alterations were *TP53* (58.4%), *KRAS* (53.6%), *APC* (26.8%), *SMAD4* (17.4%), *PIK3CA* (16.1%), *CDKN2A* (14.5%), and *ARID1A* (12.3%).[12] The low rate of *APC* alterations in patients with SBA compared with those with CRC is a fundamental genomic difference between these malignancies. The most common potentially targetable alterations in SBA were identified in *PIK3CA* (16.1%), *ERBB2/HER2* (9.5%), *BRAF* (9.1%), *ATM* (7.6%), *FBXW7* (6.9%), *ERBB3* (6.3%), *NF1* (6.0%), *CTNNB1* (5.7%), *MDM2* (5.7%), and *PTEN* (5.7%). Although in CRC, most *BRAF* alterations are V600E, this codon is infrequently altered in patients with SBA. Similarly, despite equivalent rates of *ERBB2* alterations, only 23% alterations are amplifications in SBA, but 69% of alterations are amplifications in gastric adenocarcinoma. Interestingly, whereas tumor from patients with IBD associated SBA had higher frequencies of *CDKN2A/B*, *CASP8* and *ATRX* mutations, *APC* mutations were exclusively noted in non–IBD-associated SBA. Moreover, celiac disease–associated SBA has high rates of microsatellite instability, ranging from 50% to 73%.

Presentation and Diagnosis

Clinical Presentation

The symptoms associated with SBA are nonspecific and frequently do not occur until advanced disease is present. The most commonly reported symptoms are abdominal pain (45%–76% of patients), nausea and vomiting (31%–52%), weight loss (22%–29%), and GI bleeding (8%–34%). Delays in diagnosis are common, with one retrospective study reporting a mean delay of 7.8 months from the time of initial physician evaluation until a final diagnosis was made.[28] Unfortunately, SBA tends to be diagnosed at a later stage compared with CRC. Unlike CRC, SBA has no population-based screening given its rarity, which creates low value for screening among the general population. According to SEER–Medicare data, 33.7% of patients present with stage I/II disease compared with 52.3% of those with CRC, and 32.1% of patients with SBA are initially diagnosed with stage IV disease compared with 15.6% of those with CRC.[29]

Diagnosis

Given the nonspecific presenting symptoms, a high index of suspicion is a crucial first step in diagnosis. Because imaging of the small intestine is difficult, multiple tests may be needed. Unfortunately, there are few prospective, randomized trials comparing different visualization modalities. However, with the availability of wireless capsule endoscopy, the need for older small bowel imaging techniques has declined.

A barium small bowel follow-through study was previously the radiographic gold standard for small bowel evaluation. In patients with advanced-stage disease, this technique has a sensitivity of approximately 60% for diagnosing small bowel tumors. Enteroclysis, in which contrast material is infused directly into the small intestine through a nasogastric tube, provides a slightly higher sensitivity than small bowel follow-through. Endoscopic evaluation of the small intestine, or enteroscopy, requires expertise and is frequently unable to evaluate the entire small intestine.

The incorporation of wireless capsule endoscopy has allowed improved evaluation of the lumen of the small intestine. This technique has primarily been applied to the evaluation of obscure GI bleeding, for which it has shown superiority over other imaging and endoscopy techniques.[30] In one study evaluating capsule endoscopy in 60 patients with suspected small bowel pathology but without GI bleeding, the overall diagnostic yield of capsule endoscopy was 62%.[31] In that study, all patients had undergone upper and lower GI endoscopy, and many had undergone enteroclysis, small bowel follow-through, push enteroscopy, and abdominal computed tomography (CT). In a large, single-center, retrospective review of 562 patients who underwent capsule endoscopy, small bowel tumors were found in 8.9% of cases.[32] The major limitations of capsule endoscopy are inability to obtain biopsy and lack of therapeutic intervention capability (eg, in case of bleeding). Moreover, patients cannot have bowel obstruction, which could result in the capsule's becoming trapped in the bowel.

Three-dimensional imaging with either CT or magnetic resonance imaging is useful in identifying locoregional lymph node involvement and the presence of distant metastatic disease. For tumors of the duodenum, endoscopic ultrasonography can be useful in assessing both the tumor and nodal status. Although not directly studied for duodenal adenocarcinomas, endoscopic ultrasonography has been demonstrated to improve staging accuracy for both ampullary and pancreatic cancers.

Staging and Prognosis

The TNM (tumor, node, metastasis) staging system for SBA is shown in Table 31–1.[33] A multivariate analysis from a SEER–Medicare study identified advanced age, Black race, advanced stage, poor tumor differentiation, high comorbidity index, and distal location as poor prognostic factors. In other studies, the histopathologic factors reported to be correlated with poor survival were poorly differentiated histology, positive margins, lymphovascular invasion, lymph node involvement, and T4 tumor stage.[26,34–36]

Treatment

Surgical Management

For patients with localized disease, complete removal of the tumor with negative surgical margins and local lymph node removal are critical for a potentially curative resection. For jejunal and ileal lesions, an oncologically successful resection requires a wide local excision with lymphadenectomy. Lesions located in the duodenum generally require a pancreaticoduodenectomy; however, for small distal lesions in the third and fourth portions of the duodenum, a wide local excision may be an option. In a surgical series of 68 patients with duodenal adenocarcinoma, no differences in the 5-year OS rates, local recurrence rates, or margin-negative resection rates were seen between the 50 patients who underwent pancreatic resections and the 18 patients who underwent distal duodenal segmental resections.[37] The presence of locoregional lymph node involvement should not deter surgical intervention because well over one third of patients will survive long term.[29,38] This is in contrast to patients with lymph node–positive pancreatic cancer, of whom only 7% survive 5 years.[39] As is seen with CRC, the total lymph nodes (TLNs) assessed during surgery and the number of positive lymph nodes (PLNs) have prognostic implications in SBA. In a SEER registry retrospective review of 1991 patients, the 5-year disease specific survival rate for patients with stage II disease appeared to be associated with the TLNs assessed (44%, 69%, and 83% for 0 TLNs, 1 to 7 TLNs, and >7 TLNs, respectively).[40] Furthermore, the 5-year DSS with stage III disease was associated with the number of PLNs (58% and 37% for <3 PLNs and ≥3 PLNs, respectively).[40]

Patterns of Recurrence

Recurrence after potentially curative resection of SBA occurs most commonly at distant sites. In a series of 146 patients with SBA who underwent resection, 56 patients relapsed at a median of 25 months, with the sites of relapse reported as distant in 59%, peritoneum in 20%, abdominal wall in 7%, and local in 18%.[41] In a second study of 30 patients who underwent potentially curative resection for SBA, 21 patients experienced a relapse, with the sites of relapse being the liver

TABLE 31–1 Tumor, Node, Metastasis Staging for Adenocarcinoma of the Small Intestine

Primary Tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	High-grade dysplasia or carcinoma in situ		
T1a	Tumor invades lamina propria		
T1b	Tumor invades submucosa		
T2	Tumor invades muscularis propria		
T3	Tumor invades through the muscularis propria into the subserosa or into the nonperitonealized perimuscular tissue (mesentery or retroperitoneum) without serosal penetration		
T4	Tumor perforates the visceral peritoneum or directly invades other organs or structures (includes other loops of small intestine, mesentery of adjacent loops of bowel, and abdominal wall by way of serosa; for duodenum only, invasion of pancreas or bile duct)		
Regional Lymph Nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in one or two regional lymph nodes		
N2	Metastasis in three or more regional lymph nodes		
Distant Metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Stage Grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4	N0	M0
Stage IIIA	Any T	N1	M0
Stage IIIB	Any T	N2	M0
Stage IV	Any T	Any N	M1

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the *AJCC Cancer Staging System* (2020).

in 67% of the patients, lung in 38%, retroperitoneum in 29%, and peritoneum in 25%.[34]

Patients with duodenal adenocarcinoma have a higher rate of locoregional failure than patients with jejunal and ileal adenocarcinoma, with one study reporting a 39% rate of locoregional failure among 31 patients after curative resection of duodenal adenocarcinoma.[42] In that study, positive margin status was the strongest predictor of local recurrence, with four of the five patients who had a margin positive resection developing a local recurrence. However, distant recurrences are still predominant, with a retrospective review of recurrence patterns in 67 patients with resected duodenal adenocarcinoma revealing local recurrences in 33% of the patients and distant recurrences in 67%.[43]

Adjuvant Therapy

Currently, there is no evidence demonstrating a benefit from adjuvant therapy in patients with SBA who undergo potentially curative resection. However, owing to the rarity of SBA, only a limited number of primarily small retrospective studies have been conducted (Table 31–2). Selection bias is the major limitation of these retrospective studies because the patients selected to receive adjuvant therapy were those believed to be at highest risk for disease recurrence. One prospective phase III study conducted by the European Organization for Research and Treatment of Cancer randomized 93 eligible patients with periampullary carcinoma (defined as adenocarcinoma of the

TABLE 31–2 Reported Overall Survival of Patients Who Received Adjuvant Therapy After Resection of Small Bowel Adenocarcinoma

Reference	Time Period	Study Type	Tumor Location	Type of Adjuvant Therapy	Patients (*n*)			Median Overall Survival (Months)		
					Total	No Adjuvant Therapy	Adjuvant Therapy	No Adjuvant Therapy	Adjuvant Therapy	*P* Value
Agrawal et al[34]	1971–2005	Retrospective review	Small bowel	Not specified	30	19	11	41	56	NR
Aydin et al[114]	2003–2013	Retrospective review	Small bowel	Chemotherapy	20	10	10	64	59	0.57
Dabaja et al[41]	1978–1998	Retrospective review	Small bowel	Not specified	120	62	58	36	19	0.49
Ecker et al[115]	1998–2011	Propensity score–matched analysis	Small bowel	Chemotherapy	4746	3072	1674	44.5	63.2	<0.001
Fishman et al[54]	1986–2004	Retrospective review	Small bowel	Not specified	60	45	15	28	22	NR
Halfdanarson et al[47]	1970–2005	Retrospective review	Small bowel	Chemotherapy/radiation	58	60	45	26.5	30.2	0.36
Kelsey et al[42]	1975–2005	Retrospective review	Duodenum	5-FU/radiation	32	16	16	44%[a]	57%[a]	0.42
Klinkenbiji et al[44]	1987–1995	Randomized phase III trial	Periampullary	5-FU/radiation	93	49	44	40	40	0.74
Neoptolemos et al[45]	2000–2008	Randomized phase III trial	Periampullary	Chemotherapy	428	144	284	35.2	43.1	0.25
Overman et al[46]	1990–2008	Retrospective review	Small bowel	Chemotherapy/radiation	54	24	30	NR	NR	0.84
Sohn et al[38]	1984–1996	Retrospective review	Duodenum	5-FU/radiation	48	37	11	35	27	0.73
Solaini et al[116]	2000–2013	Retrospective review	Duodenum	Not specified	150	NR	NR	52	84	0.83
Swartz et al[117]	1994–2003	Retrospective review	Periampullary	Not specified	25	11	14	21	41	NR

[a]Five-year overall survival rate.
5-FU, 5-fluorouracil; NR, not reported.

distal common bile duct, ampulla of Vater, or duodenum) to receive either no adjuvant therapy or concurrent 5-fluorouracil (5-FU) and radiation therapy.[44] The 5-year OS rates were similar in the two groups, but 30% of the patients assigned to receive adjuvant therapy did not actually receive it, and no description of the results in the duodenal adenocarcinoma subgroup were reported. Another randomized phase III trial, European Study Group for Pancreatic Cancer (ESPAC-3), randomized 428 patients with periampullay carcinoma after resection to receive no adjuvant therapy or 5-FU or gemcitabine.[45] Although primary analysis did not identify significant survival benefit with either adjuvant chemotherapy compared with observation, multivariate analysis after adjusting for prognostic variables, including age, bile duct cancer, poor tumor differentiation, and PLNs, demonstrated a statistically significant survival benefit associated with adjuvant chemotherapy.

In a series by Kelsey et al,[42] no differences in the 5-year OS rates were seen between the patients who did or did not receive adjuvant therapy after resection of duodenal adenocarcinoma. However, in the subgroup of patients who had undergone a margin-negative resection, the 5-year OS rates were 53% in the patients who underwent resection only and 83% in the patients who had resection and adjuvant chemoradiation therapy (P =.07). A trend toward improvement of disease-free survival (DFS) and OS was seen in patients receiving adjuvant therapy in a retrospective series at MD Anderson Cancer Center (MDACC) (n = 54).[46] However, in the subgroup analyses in patients with high-risk disease, defined by a lymph node ratio of 10% or greater, adjuvant therapy was associated with significant improvement in OS.[46] In contrast, in a single-institution retrospective review at Mayo Clinic, no benefit of adjuvant chemotherapy or chemoradiotherapy was seen in patients with resected SBA.[47]

Limited data are available regarding a neoadjuvant (preoperative) treatment approach for patients with duodenal adenocarcinoma. In one report in which 11 patients underwent neoadjuvant chemoradiation therapy followed by resection for duodenal adenocarcinoma, a complete pathologic response was seen in two patients, and none of the 11 patients had histopathologic nodal involvement at the time of surgery.[42]

The MD Anderson Approach to Nonmetastatic Disease

At MDACC, patients with high-risk, resected SBA are typically offered postoperative adjuvant chemotherapy. In general, patients who are considered to be at high risk are those with lymph node involvement and positive resection margins. The lack of proven benefit from adjuvant chemotherapy for this tumor type must be discussed with the patient. However, the rationale for considering adjuvant chemotherapy is based on

1. The known poor prognosis of patients with high-risk disease
2. The predominantly systemic relapse pattern for small intestinal adenocarcinoma
3. The proven activity of chemotherapy in the treatment of metastatic small intestinal adenocarcinoma
4. The known benefit of adjuvant chemotherapy in large intestinal adenocarcinoma, which appears to have a number of similarities to small intestinal adenocarcinoma
5. The extremely limited amount of high-quality data to support or refute the role of adjuvant therapy for SBA

Based on the substantial activity of a 5-FU and platinum combination in the metastatic disease setting, we generally use the combination of capecitabine and oxaliplatin (CAPOX) as adjuvant therapy for nonmetastatic SBA. In addition to systemic chemotherapy, radiation therapy is considered for patients with duodenal adenocarcinoma who are at high risk for a local recurrence based on the presence of positive margins or T4 disease.

Metastatic Disease

In general, chemotherapy for metastatic SBA has been based on the principles used for treating patients with colon cancer. Several single-institution retrospective series have demonstrated a survival benefit in patients with metastatic or unresectable SBA who received chemotherapy compared with patients who did not receive chemotherapy.[41,48]

Most of the studies evaluating chemotherapy for SBA have been retrospective, with only seven prospective phase II studies reported (Table 31–3). One multicenter study conducted by the Eastern Cooperative Oncology Group reported on the combination of 5-FU, doxorubicin, and mitomycin C (FAM) in 39 patients with adenocarcinomas of the duodenum, jejunum, ileum, or ampulla of Vater. The overall response rate (ORR) was 18%, with a median OS of 8 months.[49] A single-institution study conducted at MDACC evaluated CAPOX in 30 patients with metastatic or locally advanced small bowel or ampullary adenocarcinomas. The ORR was 50%, with a median time to progression (TTP) of 9.8 months and OS of 20.3 months.[50] An example of a response to CAPOX chemotherapy in a patient treated in that study is shown in Figure 31–1. In 33 patients treated with continuous infusional 5-FU and leucovorin in combination with oxaliplatin (modified 5-FU and oxaliplatin [FOLFOX] regimen), the ORR was 48.5%, and the median OS was 15.2 months.[51] Another prospective, multicenter, first-line study (n = 23) using CAPOXIRI (capecitabine, oxaliplatin, and irinotecan) showed an ORR of 39% and a median OS of 12.7 months.[52]

TABLE 31–3 Reported Response and Overall Survival for Patients Treated with Systemic Chemotherapy, Targeted Therapy, or Immunotherapy for Metastatic Small Bowel Adenocarcinoma

Reference	Year	Study Type	Disease Status	Patients (*n*)	Type of Systemic Therapy	Overall Response Rate (%)	Median Overall Survival (Months)
Aldrich et al[57]	2019	Retrospective review	Metastatic	20	Taxane-based therapy	30	10.7
Pedersen et al[5]	2019	Prospective phase II trial	Metastatic	30	Pembrolizumab	8	6.9
Gulhati et al[59]	2018	Prospective phase II trial	Metastatic	8	Panitumumab	0	5.7
Gulhati et al[58]	2017	Prospective phase II trial	Metastatic	23	CAPOX + bevacizumab	48	12.9
McWilliams et al[52]	2012	Prospective phase II trial	Metastatic	23	CAPOXIRI	39	12.7
Xiang et al[51]	2012	Prospective phase II trial	Metastatic	33	FOLFOX	49	15.2
Zaanan et al[48]	2010	Retrospective review	Metastatic	93	5-FU–based therapy	26	17.8
Overman et al[50]	2009	Prospective phase II trial	Metastatic, LAD	30	CAPOX	50	20.3
Overman et al[56]	2008	Retrospective review	Metastatic	29	5-FU + platinum	41	14.8
Fishman et al[56]	2006	Retrospective review	Metastatic, LAD	44	Various agents	29	18.6
Locher et al[55]	2005	Retrospective review	Metastatic, LAD	20	5-FU + platinum	21	14.0
Gibson et al[49]	2005	Prospective phase II trial	Metastatic	38	FAM	18	8
Enzinger et al[118]	2005	Prospective phase I trial	Metastatic	4	5-FU + cisplatin + irinotecan	50	NS
Czaykowski et al[119]	2007	Retrospective review	Metastatic, LAD	16	5-FU–based therapy	6	15.6
Goetz et al[120]	2003	Prospective phase I trial	Metastatic, LAD	5	5-FU + oxaliplatin + irinotecan	40	NS
Polyzos et al[121]	2003	Case series	Metastatic	3	Irinotecan	0	NS
Crawley et al[53]	1998	Retrospective review	Metastatic, LAD	8	ECF +5-FU–based therapy	37	13
Jigyasu et al[122]	1984	Retrospective review	Metastatic	14	5-FU–based therapy	7	9
Ouriel et al[123]	1984	Retrospective review	Metastatic	14	5-FU–based therapy	NS	10.7
Morgan et al[124]	1977	Retrospective review	Metastatic	7	5-FU–based therapy	0	NS
Rochlin et al[125]	1965	Retrospective review	NS	11	5-FU	36	NS

CAPOX, capecitabine and oxaliplatin; CAPOXIRI, capecitabine, oxaliplatin, and irinotecan; ECF, 5-FU, epirubicin, and cisplatin; FAM, 5-FU, doxorubicin, and mitomycin C; FOLFOX, 5-fluorouracil and oxaliplatin; 5-FU, 5-fluorouracil; LAD, locally advanced, unresectable disease; NS, not significant.

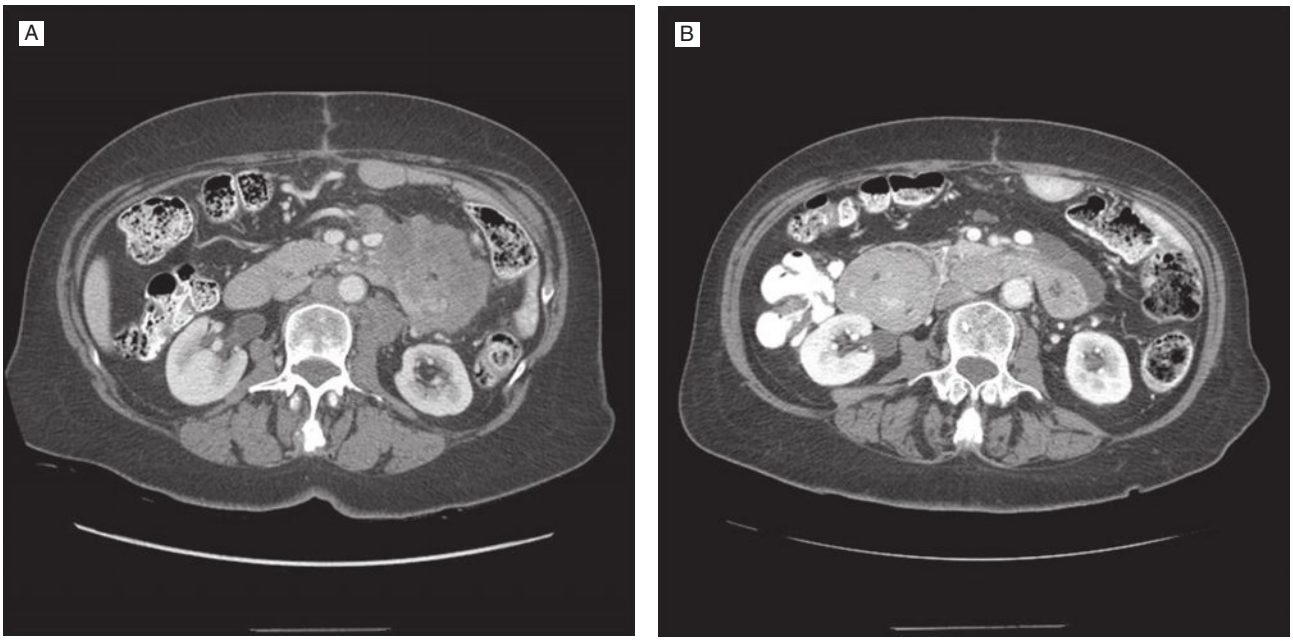


FIGURE 31–1 **Radiographic response to capecitabine and oxaliplatin (CAPOX) chemotherapy in a patient with locally advanced small bowel adenocarcinoma. Pretreatment (A) and posttreatment (B) computed tomography scans.**

Several retrospective studies have confirmed the substantial activity of 5-FU combined with a platinum agent for metastatic SBA, with response rates of 18% to 46%.[53–56] In one of the largest retrospective studies to date, a total of 80 patients with metastatic SBA were treated with various regimens: 29 received 5-FU with a platinum (19 received cisplatin, four received carboplatin, and six received oxaliplatin), 41 received 5-FU–based therapy without a platinum (32 received 5-FU alone, three received FAM, three received 5-FU and mitomycin, and three received other 5-FU combinations), and 10 received non–platinum-based and non–5-FU–based therapy.[56] Patients who received 5-FU combined with a platinum agent had a higher ORR (46% vs 16%; P <.01) and longer median progression-free survival (PFS) (8.7 vs 3.9 months; P <.01) than patients who received other chemotherapy regimens. Although not statistically significant, there was also a trend toward improved median OS times in patients who received 5-FU plus a platinum agent (14.8 vs 12.0 months; P =.1). A French multicenter study in SBA receiving frontline chemotherapy with 5-FU (n = 10), FOLFOX (n = 48), (5FU + irinotecan) (n = 19), and 5-FU-cisplatin (n = 16) demonstrated median PFSs of 7.7, 6.9, 6.0, and 4.8 months, respectively.[48] The corresponding median OSs were 13.5, 17.8, 10.6, and 9.3 months, respectively.[48] In the subgroup analysis, patients treated with 5-FU–cisplatin had decreased PFS (P <.01) and OS (P =.02) compared with those treated with oxaliplatin-based chemotherapy.[48]

Irinotecan-based chemotherapy is also active against metastatic SBA. One retrospective study reported that five of 12 patients responded to irinotecan-based therapy (three patients responded to 5-FU plus irinotecan, one responded to capecitabine plus irinotecan, and one responded to single-agent irinotecan).[54] A second study of salvage therapy with irinotecan in the second-line setting noted stable disease (SD) in four of eight treated patients.[55] Among the 19 patients in the Association des Gastro-Entérologues Oncologues (AGEO) study treated with 5-FU plus irinotecan, one had a partial response (PR), and SD was seen in seven patients.[48] Responses to gemcitabine-based therapy have also been noted, although the number of patients treated has been small. Although taxanes have not been classically used for treatment of patients with SBA, a recent single-center retrospective study evaluating the activity of taxanes in SBA demonstrated clinical activity with responses noted in 30% patients, SD in 35%, and PD in 35% patients.[57] Median TTP and OS were 3.8 and 10.7 months, respectively.

The remaining prospective phase II studies evaluated the role of targeted therapy and immunotherapy in patients with metastatic SBA. A single-institution study conducted at MDACC evaluated CAPOX with bevacizumab (anti–vascular endothelial growth factor [VEGF] antibody) in 30 patients with advanced small bowel or ampullary adenocarcinomas. The ORR was 48.3%, with a median PFS of 8.7 months and median OS of 12.9 months.[58] An exploratory analysis comparing this regimen to a prior phase II clinical trial of CAPOX alone

from the same institution did not demonstrate significant difference in ORR or PFS. Another phase II study conducted at MDACC evaluated the efficacy of panitumumab (anti–epidermal growth factor receptor [EGFR] antibody) in metastatic *RAS* wild-type SBA or ampullary adenocarcinoma given the known benefits of EGFR antibodies in metastatic CRC.[59] The study was stopped early because of futility with no responses in nine patients, SD in two patients, and PD in seven patients. Median PFS and OS were 2.4 and 5.7 months, respectively. No patients had extended RAS mutations (exons 2/3/4), but two patients had BRAF G469A, and one patient had PIK3CA H1074R mutations. The authors proposed that these findings may relate to the primarily midgut and foregut derivation of the small bowel and ampulla. Finally, the ZEBRA trial was a prospective, multicenter phase II study evaluating pembrolizumab (anti–programmed cell death protein 1 [PD-1] antibody) in SBA patients given the more frequent microsatellite instability, greater programmed cell death ligand 1 expression compared to CRC.[60] Median PFS and OS were 2.8 and 6.9 months, respectively. Both microsatellite instability–high (MSI-H) patients achieved PR and remained alive without progression. Of patients with microsatellite SD, disease control rate was 50% with a PR noted. The findings from these studies taken together with the differences in mutational profiles between SBA and CRC described previously suggest that approaches to SBA should not be extrapolated from CRC but should be based on data derived from SBA.

The MD Anderson Approach to Metastatic Disease

The substantial response rates and prolonged OS reported with modern-day chemotherapy combinations in SBA strongly argue for an aggressive approach in treating patients with metastatic SBA. Given the encouraging results with CAPOX and FOLFOX for metastatic SBA, we generally recommend these regimens at MDACC. After frontline CAPOX or FOLFOX chemotherapy, patients are then treated with an irinotecan-based regimen. In addition, patients with limited metastatic disease who respond to initial chemotherapy are considered for surgical resection if all disease sites can be successfully excised. Data for use of anti-VEGF and anti-EGFR targeted antibodies in SBA are limited, and further investigation into their clinical benefit is indicated. Although anti–PD-1 immunotherapy is approved for use in MSI-H SBA, further studies are needed to comprehensively evaluate the benefit from these agents in microsatellite-stable SBA. More effective treatments for patients with SBA remain needed, and participation in clinical trials for this rare tumor type is strongly encouraged. A proposed treatment algorithm for SBA is presented in Figure 31–2.

APPENDICEAL TUMORS

Appendiceal tumors encompass a rare and diverse group of neoplasms. Epidemiologic studies based on the SEER database have shown a steady increase in incidence from approximately 0.2 cases per 100,000 in the 1970s, to approximately 0.6 per 100,000 in 2000, to current estimates of between 1 and 4 per 100,000.[61–63] There are no definitive risk factors for developing appendiceal cancer.[64] In comparison, this is 10- to 40-fold less common than colon cancer, which in the United States has an incidence of approximately 40 per 100,000. Historically, appendiceal tumors have been grouped together with CRCs, and as of 2020, the National Comprehensive Cancer Network guidelines still suggest that patients with appendiceal tumors should be treated similar to those with colon tumors. However, there is a growing body of evidence that appendiceal tumors, in which outcomes are strongly determined by histologic subtype, are quite distinct from CRC at the molecular level.[65,66] Recognizing the clear differences in biology, natural history, and response to therapy between CRC and appendix cancer, there is now an effort underway to develop national guidelines specifically for appendiceal tumors. Appendiceal tumors comprise two major types: appendiceal carcinoid tumors and appendiceal epithelial tumors, each accounting for roughly half of all appendiceal neoplasms.[67] This section on appendiceal tumors discusses the management of these two tumor types (carcinoid and epithelial) as well as the unusual clinical syndrome of pseudomyxoma peritonei (PMP).

Incidence

Data derived from the SEER database of the National Cancer Institute between 1973 and 1998 revealed that the most common histologic subtypes of malignant tumors of the appendix were adenocarcinomas (67%) and carcinoids (33%).[68] However, this SEER analysis captured neither adenomatous tumors nor benign carcinoids. The SEER subtypes of adenocarcinoma were mucinous type (56%), nonmucinous intestinal type (38%), and signet ring cell type (6%). A more recent SEER-based analysis of 7170 tumors again found mucinous adenocarcinoma most common (39%) followed by nonmucinous adenocarcinoma (also called colonic type) (33%), goblet cell carcinoid (13%), malignant carcinoid (9%), and signet ring cell carcinoma (6.5%).[62] Alternatively, in a separate study of 7970 appendectomy specimens, tumors were identified in 1% of specimens, with carcinoids representing 57% of all tumors identified.[67] Adenomas and adenocarcinomas represented 18% and 11% of the identified tumors, respectively.

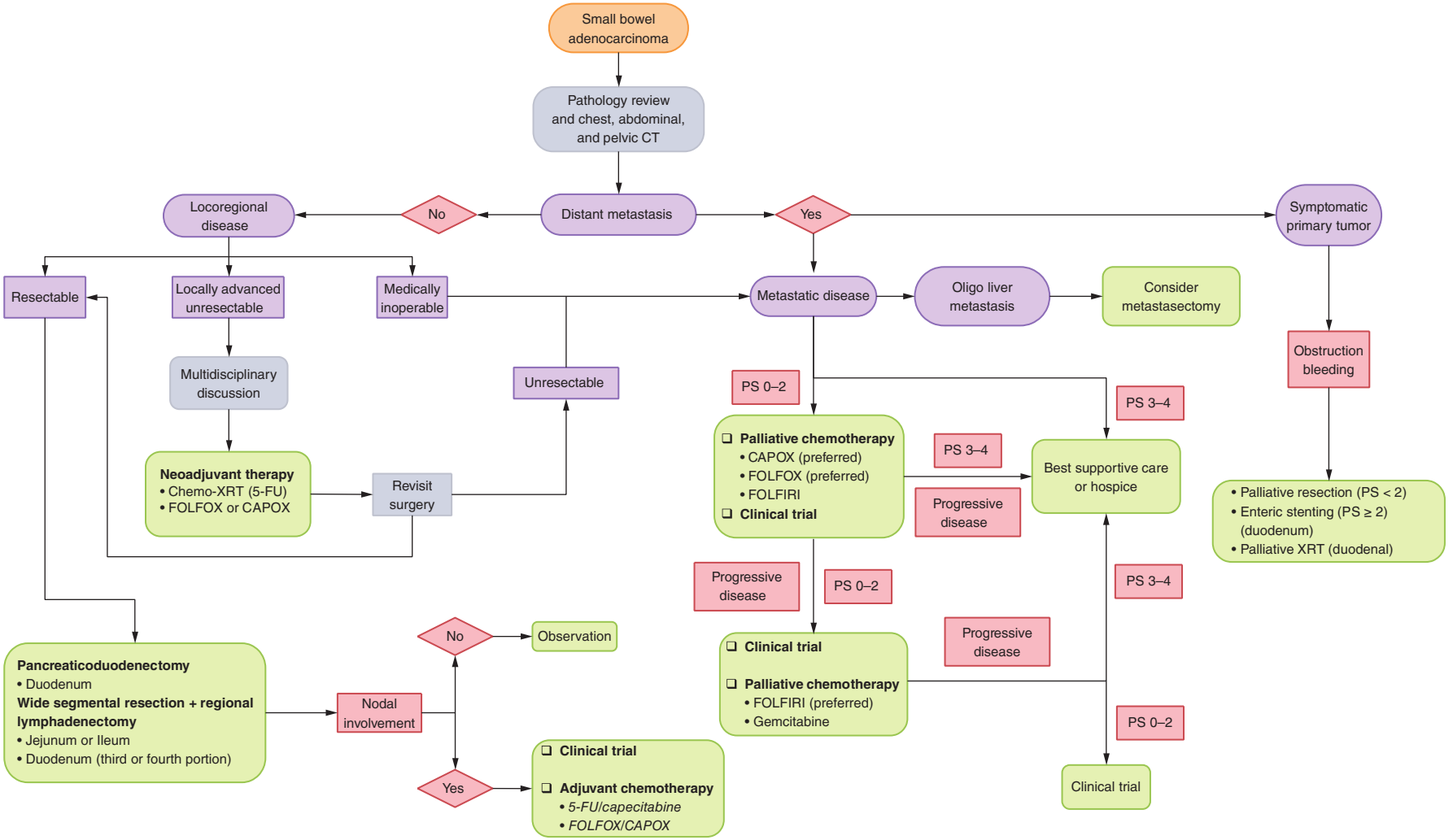


FIGURE 31–2 Treatment algorithm for small bowel adenocarcinoma. (Reproduced with permission from Raghav K. and Overman M. J. Small bowel adenocarcinomas—existing evidence and evolving paradigms. *Nat Rev Clin Oncol*. 2013 Sep;10(9):534-544.)

CHAPTER 31

Presentation and Prognosis

Appendiceal tumor presentation is bimodal; tumors are generally either identified incidentally at the time of pathological review of appendectomy specimens or only after the tumor has spread to the peritoneal space. Symptoms of appendicitis are most often the presenting symptom for early-stage tumors, especially with tumors located at the base of the appendix where obstruction is more likely to occur. Presenting symptoms of advanced appendiceal disease reflect the nonspecific abdominal symptoms associated with peritoneal involvement: abdominal pain and distention, altered bowel motility, and early satiety. Metastatic carcinoid tumors may also present with symptoms related to the carcinoid syndrome such as episodic flushing, wheezing, and diarrhea. Patient age at presentation differs depending on histologic subtype of the tumor, with carcinoid tumors occurring in younger patients (goblet cell carcinoid, 54 years; malignant carcinoid, 43 years) relative to adenocarcinomas (mucinous, 59 years; nonmucinous, 64 years; signet ring, 58 years).[62]

The prognosis for patients with appendiceal cancer is strongly dependent on the histopathologic subtype of the tumor, with patients who have carcinoids having a significantly better survival than do patients with adenocarcinomas (Fig. 31–3).[68] However, longitudinal data in appendiceal cancer can be difficult to interpret because of inconsistent terminology in describing the multiple subtypes of appendiceal tumors.[69] In 2016, a consensus classification and reporting system was adopted that has greatly helped to standardize the histopathologic categorization of appendix cancer.[70] Importantly, these guidelines distinguished mucinous neoplasms without infiltrative invasion as a separate entity from adenocarcinoma, which by definition had presence of infiltrative invasion. Mucinous neoplasms without infiltrative invasion were further subdivided into low grade (low-grade appendiceal mucinous neoplasm [LAMN]) and high grade (HAMN). Uniform criteria for PMP, a unique clinical syndrome with spread of tumor and ascites within the peritoneal cavity but not to distant organs, were also developed differentiating PMP from acellular mucin.[69]

As would be expected, patients with early-stage tumors identified incidentally at the time of appendectomy have a better prognosis than patients who are diagnosed after symptoms develop. For these early-stage patients, the distinction between LAMN and adenocarcinoma has important prognostic implications. In a study of 107 patients with localized LAMN of adenocarcinoma, no LAMNs confined to the appendix experienced recurrence at a median follow-up period of 6 years.[71] LAMNs that had extra-appendiceal spread did recur and had OS rates of 100%, 86%, and 45%, at 3, 5, and 10 years, respectively. In contrast, mucinous adenocarcinomas were more likely to have extra-appendiceal spread and had worse OS, of 90% and 44% at 3 and 5 years, respectively.

The importance of grade is captured in the eighth edition of the American Joint Committee on Cancer

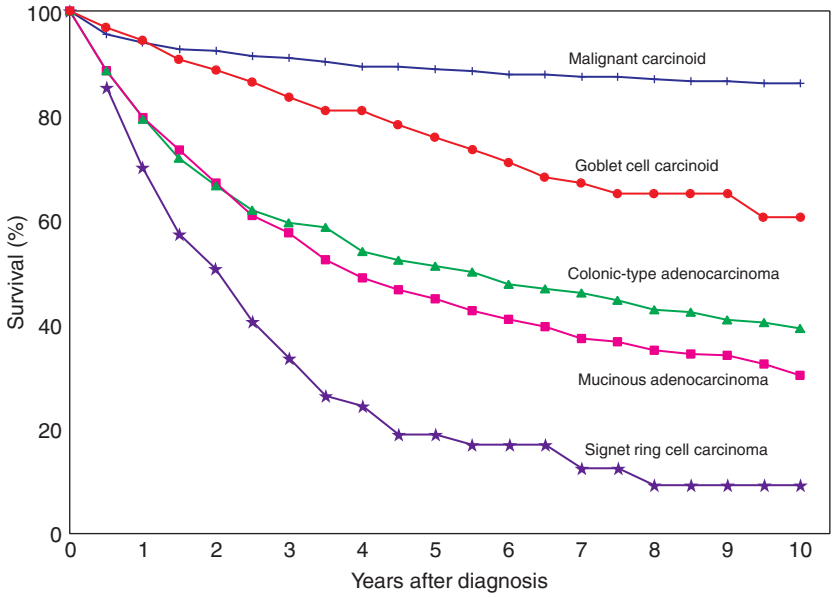


FIGURE 31–3 **Overall survival of malignant appendiceal cancers according to the Surveillance, Epidemiology and End Results registry (SEER), stratified by histological subtype. (Reproduced with permission from McCusker ME, Coté TR, Clegg LX, et al. Primary malignant neoplasms of the appendix, *Cancer* 2002 Jun 15;94(12):3307-3312.)**

(AJCC) staging for appendix cancer, which differentiates between stages IVA and IVB (Table 31–4).[33,66] There have been conflicting reports regarding the prognosis of patients with mucinous adenocarcinoma relative to those with nonmucinous or colonic-type adenocarcinoma,[72] with recent report that mucinous moderately differentiated adenocarcinomas appear to have a prognosis more akin to mucinous well-differentiated carcinomas as opposed to mucinous poorly differentiated carcinomas.[73] Despite these nuances, grade trumps all clinico-molecular parameters with regards to the prognostic impact in appendiceal adenocarcinomas.[66] Among carcinoid tumors, pure malignant carcinoids have the best OS (median, 396 months) followed by goblet cell carcinoids (median, 162 months). Goblet cell carcinoids, also called goblet cell tumor (GCT), adenocarcinoma ex goblet cell carcinoid, or mixed adenoneuroendocrine carcinoma, have a mixed histologic appearance that includes neuroendocrine cells and goblet cells, as well as features of adenocarcinoma, increasing percentage of the adenocarcinoma proportion associated with worse outcomes.[74]

TABLE 31–4 Tumor, Node, Metastasis Staging for Appendiceal Carcinomas

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (intramucosal carcinoma; invasion of the lamina propria or extension into but not through the muscularis mucosae)
Tis(LAMN)	LAMN confined by the muscularis propria; acellular mucin or mucinous epithelium may invade into the muscularis propria T1 and T2 are not applicable to LAMN; acellular mucin or mucinous epithelium that extends into the subserosa or serosa should be classified as T3 or T4a, respectively
T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into the subserosa or the mesoappendix
T4	Tumor invades the visceral peritoneum, including the acellular mucin or mucinous epithelium involving the serosa of the appendix or mesoappendix, and/or directly invades adjacent organs or structures
T4a	Tumor invades through the visceral peritoneum, including the acellular mucin or mucinous epithelium involving the serosa of the appendix or serosa of the mesoappendix
T4b	Tumor directly invades or adheres to adjacent organs or structures
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three regional lymph nodes are positive (tumor in lymph node measuring ≥0.2 mm) or any number of tumor deposits is present, and all identifiable lymph nodes are negative
N1a	One regional lymph node is positive
N1b	Two or three regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumor deposits in the subserosa or mesentery
N2	Four or more regional lymph nodes are positive
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a[a]	Intraperitoneal acellular mucin, without identifiable tumor cells in the disseminated peritoneal mucinous deposits
M1b	Intraperitoneal metastasis only, including peritoneal mucinous deposits containing tumor cells
M1c	Metastasis to sites other than peritoneum

[a]For specimens containing acellular mucin without identifiable tumor cells, efforts should be made to obtain additional tissue for thorough histologic examination to evaluate for cellularity.

(*Continued*)

TABLE 31–4 Tumor, Node, Metastasis Staging for Appendiceal Carcinomas *(Cont.)*

Histologic Grade (G)				
GX	Grade cannot be assessed			
G1	Well differentiated			
G2	Moderately differentiated			
G3	Poorly differentiated			
Stage Grouping				
Stage 0	Tis or Tis(LAMN)	N0	M0	
Stage I	T1	N0	M0	
	T2	N0	M0	
Stage IIA	T3	N0	M0	
Stage IIB	T4a	N0	M0	
Stage IIC	T4b	N0	M0	
Stage IIIA	T1	N1	M0	
	T2	N1	M0	
Stage IIIB	T3	N1	M0	
	T4	N1	M0	
Stage IIIC	Any T	N2	M0	
Stage IVA	Any T	Any N	M1a	
	Any T	Any N	M1b	G1
Stage IVB	Any T	Any N	M1b	G2, G3, Gx
Stage IVC	Any T	Any N	M1c	Any G

LAMN, low-grade appendiceal mucinous neoplasm.
Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging System (2020).

Appendiceal Carcinoid Tumors

Similar to other intestinal carcinoid tumors, appendiceal carcinoid tumors arise from neuroendocrine cells within the lamina propria and submucosa. Appendiceal carcinoid tumors can secrete serotonin and vasoactive substances responsible for the carcinoid syndrome, although this is rarely seen in patients in the absence of extensive liver metastases. Appendiceal carcinoid tumors are usually seen in young patients and are seen slightly more often in women.[75,76] Goblet cell carcinoids or GCT, overall a rare histologic variant of carcinoid tumors, are actually more common in the appendix than pure carcinoid tumors. Characterized by malignant cells that demonstrate both exocrine and neuroendocrine characteristics, GCTs have outcomes in between that of a carcinoid and that of an adenocarcinoma (see Fig. 31–3).

Management of Appendiceal Carcinoids

Because most appendiceal carcinoid tumors are discovered incidentally from an appendectomy specimen, a critical and somewhat controversial oncologic question relates to the need for performing a more complete surgical staging procedure. For appendiceal cancers, a complete surgical staging procedure would entail a right hemicolectomy with complete removal of the base of the appendix, mesoappendix, and draining lymph nodes.

The most useful criteria for determining the need for a complete right hemicolectomy are tumor size (≥2 cm in diameter) and mesoappendix involvement.[77] In a retrospective study of appendiceal carcinoids, Moertel et al[78] reported no metastases in 127 patients with tumors smaller than 2 cm, whereas metastatic disease was seen in three of the 14 patients with tumors 2 to 3 cm in size and four of the nine patients with tumors 3 cm or larger. Patients with GCT are generally treated as having an appendiceal adenocarcinoma. Of note, a small study found no benefit in using 68Ga-DOTATATE positron emission tomography–computed tomography (PET-CT) for follow-up in these patients.[79]

For patients with metastatic malignant carcinoid tumors, the use of somatostatin analogues can alleviate the symptoms of the carcinoid syndrome but rarely causes objective tumor regression. Given the slow-growing nature of appendiceal carcinoid tumors, local modality therapies such as hepatic embolization or surgical resection may also be beneficial in selected patients with metastatic disease. For additional information on management of this type of tumor, please refer to Chapter 34 on neuroendocrine cancers.

Appendiceal Epithelial Tumors

Little is known about the risk factors or cause of epithelial tumors of the appendix. Historically viewed as a subset of CRC, epithelial tumors of the appendix have a markedly different biology and natural history relative to that of adenocarcinomas of the colorectum and do not align with any of the consensus molecular subtype (CMS) of CRC.[80] In particular, a subset of appendiceal epithelial tumors that have disseminated peritoneal mucinous deposits derived from a ruptured appendiceal mucinous adenoma can demonstrate excellent long-term survival with aggressive cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC).[81,82] This contrasts the result of the recent PRODIGE (Partenariat de Recherche en Oncologie Digestive) 7 trial in patients with CRC that showed no additional benefit to HIPEC in addition to CRS.[83] It is thought that most appendiceal epithelial tumors begin as a mucinous adenoma with appendiceal distention caused by excessive mucin production. On gross inspection or radiographic evaluation, this dilated mucin-filled appendix is frequently referred to as a mucocele. With progressive growth, the appendiceal lumen can become obstructed and result in increased intraluminal pressure within the appendix, which can cause the appendix to rupture. Appendiceal rupture represents the critical step in the dissemination of the mucinous appendiceal tumor to the peritoneal cavity. For this reason, it is critical that care is taken when surgically removing an appendiceal mucocele to prevent rupture and peritoneal seeding during a routine appendectomy.[71] When resecting an appendiceal mucocele, the peritoneum should be inspected closely to evaluate any evidence of dissemination to the peritoneal cavity. During pathological examination of the appendix, any fluid or mucus in the peritoneal spaces surrounding the appendix should undergo cytologic examination.[77] In patients with localized disease, the presence of carcinoma (as opposed to LAMN, which does not have invasive features) requires a completion right hemicolectomy for oncologic staging.

Histopathologic Subtypes of Epithelial Appendiceal Tumors

As noted previously, the often inconsistent and ambiguous terminology of appendiceal tumors was updated with consensus guidelines in 2016.[70] Here we will use the new consensus terminology but also list historical terminology for reference.

Pseudomyxoma Peritonei

PMP, literally translated from Latin as "false mucinous tumor of the peritoneum," is a term originally used by Werth in 1884 to describe the pathological findings in a patient with a ruptured ovarian cystadenoma who had copious gelatinous intraperitoneal ascites (Fig. 31–4).[84] This term has been applied broadly to include any mucinous tumor type involving the peritoneal cavity with any histologic grade of differentiation. PMP is a clinical syndrome of malignant mucinous peritoneal dissemination and can sometimes arise from tumors other than the appendix (colon, ovary, urachus, pancreas); notably, it does not reference the histopathologic characteristics of the tumor of origin.[69] To reduce confusion and better segregate patients by clinical outcome, PMP is now subdivided into three groups: low-grade mucinous PMP, high-grade mucinous PMP, and high-grade mucinous PMP with signet ring cells.

Low-Grade Mucinous Pseudomyxoma Peritonei

Low-grade mucinous PMP, previously referred to as disseminated peritoneal adenomucinosis (DPAM),[85] is characterized by peritoneal lesions composed of abundant extracellular, mucin-containing, scant, and simple to focally proliferative mucinous epithelium with little cytologic atypia or mitotic activity, with or without an associated appendiceal mucinous adenoma.[85] In essence, the underlying epithelium in low-grade mucinous PMP may have low-grade adenomatous changes but may not have any evidence of infiltrative invasion or carcinoma. However, there must be observed neoplastic cells; mucin without neoplastic cells is termed *acellular mucin*. Notably, in the setting of an appendiceal primary tumor, acellular mucin within the abdominal cavity is classified pM1a by the *AJCC Cancer Staging Manual*, eighth edition, whereas deposits with tumor cells are classified M1b.[33] Low-grade mucinous PMP

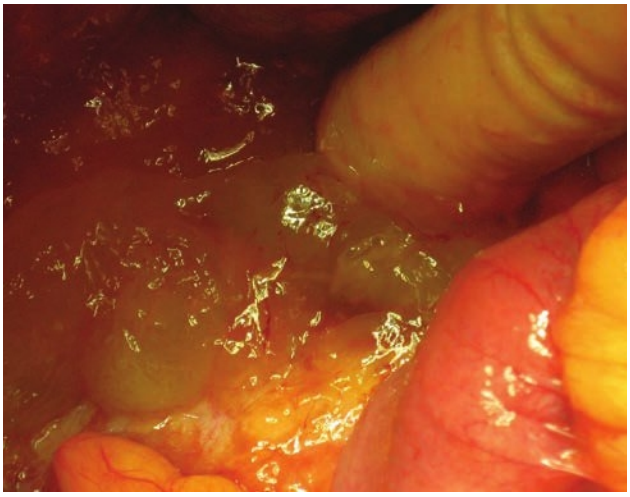


FIGURE 31–4 Peritoneal mucin in a patient undergoing surgical cytoreduction.

subgroup of tumors demonstrates the classic PMP clinical syndrome of massive amounts of benign-appearing mucinous ascites that over time slowly fill the entire peritoneal cavity (Fig. 31–5). Although spread to the peritoneal cavity is present, these tumors do not metastasize to regional lymph nodes or via hematogenous spread to the liver or other distant sites.

Patients with low-grade mucinous PMP typically present with gradually increasing abdominal girth. For women, DPAM may present as a new ovarian mass, and for men, it may present as a new-onset hernia. In women, secondary involvement of the ovaries is common, and because the histopathologic features of low-grade mucinous PMP from a primary ovarian tumor can be quite similar to those of appendiceal origin, a thorough pathological examination of the appendix should be conducted.[86] When molecular and immunohistochemical evaluations have been performed on patients with both appendix and ovarian involvement, these evaluations have generally demonstrated the primary site of disease as the appendix[87–89]

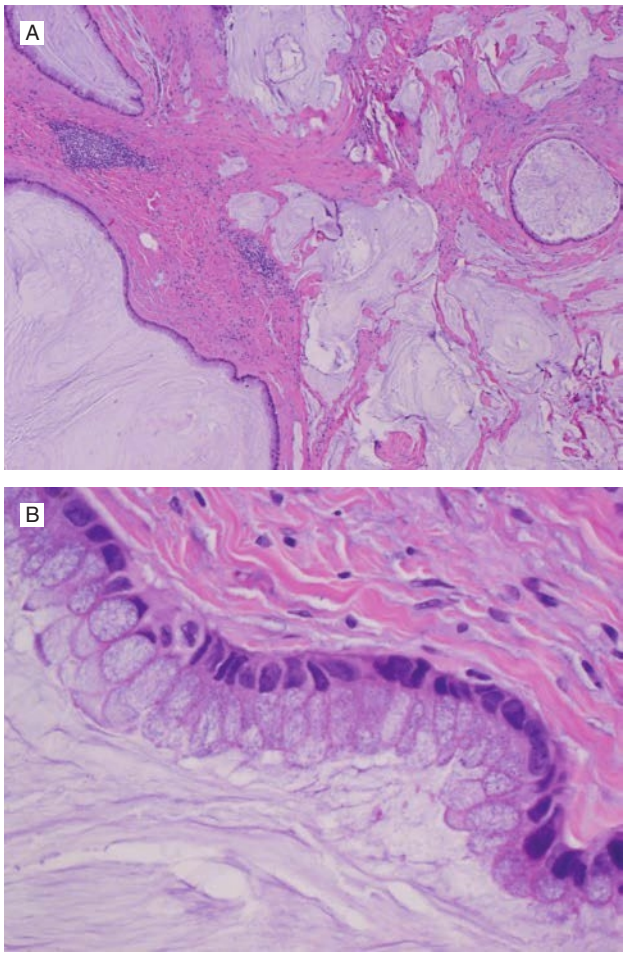


FIGURE 31–5 Histology from a patient with well differentiated mucinous appendiceal adenocarcinoma with the clinical syndrome of pseudomyxoma peritonei (PMP). A. Adenoma-like epithelium with acellular mucin pools dissecting through the fibrous stroma with chronic inflammation (×40). B. Adenoma-like epithelium with abundant acellular mucin (×400).

High-Grade Mucinous Pseudomyxoma Peritonei and Pseudomyxoma Peritonei-Grade Mucinous Pseudomyxoma Peritonei with Signet Ring Cells

If evidence of destructive, infiltrative invasion or high-grade cytologic atypia is present, then the pathological diagnosis of high-grade mucinous PMP should be used[69] Previously referred to as peritoneal mucinous carcinomatosis (PMCA),[85] these tumors are characterized by peritoneal lesions composed of more cellular mucinous epithelium with the architectural and cytologic features of carcinoma, with or without an associated primary mucinous adenocarcinoma. If high-grade features are found, even focally, the lesion should be classified as high grade, which makes adequate sampling and review of the complete resected specimen critical. High-grade mucinous PMP with signet ring cells, previously called peritoneal mucinous carcinomatosis with signet ring cells (PMCA-S), is included as a separate category given the worse prognosis associated with signet ring cells. In an analysis of 109 patients with clinical features of PMP, the 5- and 10-year survival rates for patients with low-grade disease were 75% and 68%, respectively. This was in stark contrast to those with high-grade disease, who had 5- and 10-year survival rates of 14% and 3%[90] (Fig. 31–6).

Mucinous Appendiceal Adenocarcinoma

The most common type of epithelial appendiceal tumor, like PMP, mucinous appendiceal adenocarcinoma really behaves like two distinct disease entities with low-grade tumors having a much more indolent clinical course relative to high-grade tumors. These tumors are differentiated from LAMN and HAMN by the presence of infiltrative invasion and by definition more than 50% of the cross-sectional area histologically comprises extracellular mucin.[69] The consensus guidelines recognize a trinary well-, moderately, or poorly differentiated grading scheme with poorly differentiated carcinomas showing little or no gland formation. A study of 201 mucinous appendiceal carcinomas has shown the trinary grading systems is strongly predictive of survival with 94%, 71%, of 30% of patients alive at 5 years for well-, moderately, and poorly differentiated tumors, respectively.[91] Although mucinous appendiceal adenocarcinoma are invasive tumors with distant metastatic potential, the majority of these tumors remain localized to the peritoneal cavity. Even in the subset of patients with aggressive-appearing

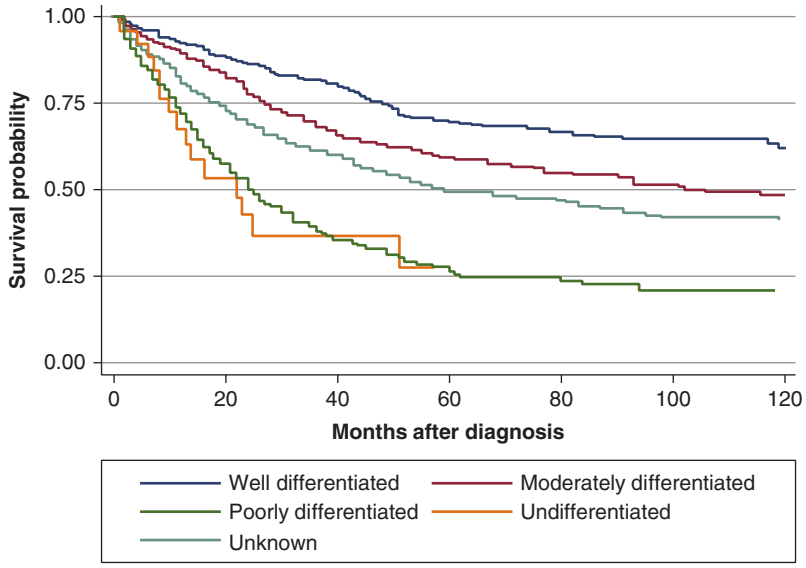


FIGURE 31–6 **Overall survival of appendiceal adenocarcinoma stratified by histological grade. (Reproduced with permission from Overman MJ, Fournier K, Hu CY, et al: Improving the AJCC/TNM staging for adenocarcinomas of the appendix: the prognostic impact of histological grade, *Ann Surg* 2013 Jun;257(6):1072-1078.)**

histologies, the rate of distant hematogenous metastases remains low. In one retrospective study of 90 appendiceal adenocarcinomas with either poor differentiation or signet ring cell morphology, the rate of extraperitoneal metastases was only 17%.[92]

Nonmucinous or Colonic-Type Adenocarcinoma

Occurring somewhat less frequently than mucinous tumors, nonmucinous or colonic-type adenocarcinomas of the appendix demonstrate a different tumor biology than mucinous appendiceal tumors. These cancers are generally more aggressive and less likely be well differentiated and appear to behave more like colonic adenocarcinomas. In a study by Kabbani et al,[93] 43% of patients with nonmucinous appendiceal adenocarcinoma had evidence of extraperitoneal metastases. The patients with nonmucinous carcinomas in this study had a significantly worse OS and DFS than those with mucinous carcinomas, although given the critical importance of grade in determining survival in mucinous tumors, it is difficult to make this direct comparison.

Molecular Profiles

Recent large sequencing studies, including independent cohorts of 703 and 266 appendiceal tumors have revealed several key molecular differences between appendiceal tumors and CRC and between different subtypes of appendiceal tumors.[65] Most notably, *APC* mutation, which is a hallmark feature of CRC, is uncommon in all subtypes of appendix cancer. Similarly, appendix tumors have less frequent *TP53* mutation (Fig. 31–7).[66] The frequency of *GNAS* mutation is much higher in appendix cancer, with a particularly strong enrichment in low-grade tumors. Nearly all *GNAS* mutations occur in codon R201, with R201H and R201C being the most common substitutions. Of note, Although *GNAS*-specific chemical inhibitors do not yet exist, the cystine in the R201C mutation could be targeted similar to that in *KRAS* G12C. The frequency of *KRAS* mutation is similar in appendix cancer and CRC. Unfortunately, the incidence of currently "actionable" mutations in genes such as *HER2* and *EGFR* is quite rare in appendiceal tumors, as is microsatellite instability. Importantly, low-grade appendiceal adenocarcinomas have distinct molecular profile from high-grade tumors characterized by frequent mutation in *GNAS* and *KRAS* and absence of *TP53* mutation (Fig. 31–8).[65,66] These molecular differences and the distinct indolent disease course of low-grade tumors suggests strongly that low-grade appendix adenocarcinoma is a distinct disease entity from high-grade appendix adenocarcinoma.

There are limited transcriptomic data on appendiceal cancer, although a pilot study of microarray gene expression profiling of 26 appendiceal adenocarcinomas showed clear differences between appendiceal adenocarcinoma and CRC.[94] A second study of 24 additional tumors identified a 139 gene signature associated with poor prognosis specifically in low-grade tumors.[95] Unsupervised clustering of appendiceal tumors with all of the TCGA tumors and cancer cell lines from the Cancer Cell Line Encyclopedia[96] using the Celligner method[97] has shown that appendiceal tumors cluster

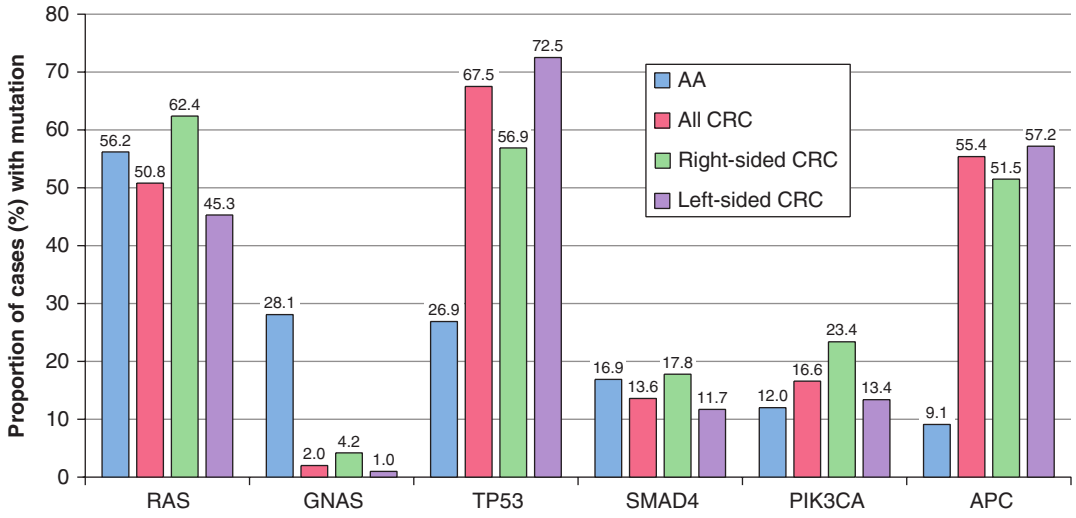


FIGURE 31–7 **Frequency (percentage) of mutations (>3% incidence) in tumor tissue from patients with appendix cancer (a) and distribution of mutation (top six most frequently mutated genes) by grade or differentiation as compared to colorectal cancer (CRC). (Reproduced with permission from Raghav K, Shen JP, Jácome AA, et al: Integrated clinico-molecular profiling of appendiceal adenocarcinoma reveals a unique grade-driven entity distinct from colorectal cancer, *Br J Cancer* 2020 Oct;123(8):1262-1270.)**

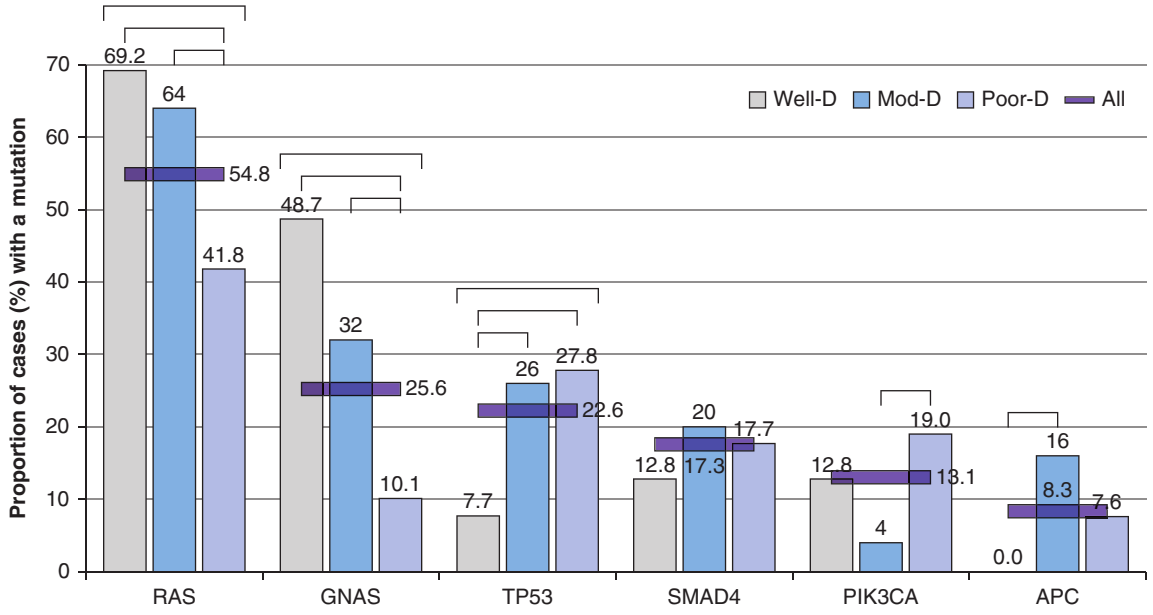


FIGURE 31–8 **Frequency of the top six cancer mutations in appendiceal adenocarcinomas stratified by grade. Comparisons are shown for only significant differences (P <.05). D, differentiated; Mod, moderately; Poor, poorly. (Reproduced with permission from Raghav K, Shen JP, Jácome AA, et al: Integrated clinico-molecular profiling of appendiceal adenocarcinoma reveals a unique grade-driven entity distinct from colorectal cancer, *Br J Cancer* 2020 Oct;123(8):1262-1270.)**

closely together, away from any other tumor type and also away from any cell line model. This indicates that appendiceal cancer is a distinct entity from CRC and that currently, there are no representative cell line models of appendix cancer. Gene Set Enrichment Analysis of appendix cancer transcriptomes has shown upregulation of the eukaryotic translation initiation factor 4E (eIF4E) as well as RAF and EGFR in the RAS-MAPK (mitogen-activated protein kinase) pathway.

The ability to measure circulating tumor DNA (ctDNA) in the blood has proven valuable in many GI malignancies; however, the sensitivity of these "liquid biopsies," particularly in low-grade appendiceal tumors, seems to be low. The ultimate answer to this

question will require a cohort of patients with paired blood and tissue sequencing; however, a 73-gene panel identified a mutation in blood in only 61% of patients versus an expected 94% based on tissue sequencing.[65,98] Interestingly, the disparity was much greater for mutations in gene characteristic of low-grade tumors, such as *GNAS* (34% vs 2.6%, 13-fold), relative to mutations characteristic of high-grade tumors, such as *TP53* (35% vs 23%, 1.5-fold), suggesting that low-grade tumors are less likely to shed DNA into the blood. The prognostic implications of having detectable ctDNA in the blood remain unknown, but this could potentially have value as a biomarker of high-risk disease.

Treatment

Cytoreductive Surgery

Because of the relative rarity of this disease, prospective randomized clinical trials studying the treatment of appendiceal epithelial tumors are lacking. The majority of data evaluating the various treatment modalities in this disease have been derived from retrospective, single-institution studies. Surgical cytoreduction has been the primary mode of therapy for these tumors based on the following factors:

1. Lack of extraperitoneal disease spread
2. Primarily mucinous nature of peritoneal deposits
3. Indolent growth rate (for low-grade tumors)
4. Limited activity of systemic chemotherapy
5. Lack of an effective systemic mucolytic agent

The goal of surgical cytoreduction is complete tumor removal from the peritoneal cavity. Because of the large surface area of the peritoneum, surgical cytoreduction to remove all visible sites of disease can be challenging. Optimal CRS may involve removal of the appendix, right colon, intraperitoneal tumor debulking, resection of multiple abdominal and pelvic organs with peritoneal tumor studding, and stripping of all involved parietal peritoneum.[99] After successful surgical cytoreduction, patients can experience reaccumulation of mucinous peritoneal implants, which may be complicated by fibrosis from prior surgery, requiring repeated surgical cytoreductive procedures.

In a 97-patient series from Memorial Sloan Kettering Cancer Center, in which surgical resection alone represented the primary treatment modality in more than two thirds of the patients, the 5-year OS rates were 90% for patients with low-grade and 50% for patients with high-grade tumors.[81] In the 55% of patients who underwent a complete cytoreduction of all visible tumors, 91% had recurrent disease. The average number of surgical cytoreductions that patients underwent in this study was 2.2, with a range of 1 to 6.[81] These findings are contrasted by a retrospective analysis of 512 peritoneal metastatic appendiceal tumors in which only 26% developed recurrence.[100] The median time to recurrence was 26 months. Repeat CRS was attempted in 26% of these patients and was associated with better survival than for recurrent patients who did not undergo a second CRS. These data suggest that in patients who develop recurrence after an extended disease-free interval, repeat CRS can be attempted with favorable results for at least some patients.

Hyperthermic Intraperitoneal Chemotherapy

In an attempt to diminish the rate of disease recurrence after CRS, the administration of intraperitoneal chemotherapy after a surgical cytoreduction has been used to try to treat any residual microscopic disease in the peritoneal cavity. Historically, a number of methods of delivering intraperitoneal chemotherapy have been used, although the most commonly used method is HIPEC administered at the time of cytoreduction. At MDACC, after complete CRS, the standard procedure is to administer heated mitomycin C at a dose of 25 mg/m^2 for patients who are chemotherapy naïve or 20 mg/m^2 for patients who have received previous chemotherapy in a volume of 5 to 6.5 L of electrolyte solution at a flow rate of 3 to 3.5 L/min. Intraoperative hemodynamic monitoring and thermal monitoring are essential for optimal outcomes in these patients. The HIPEC is continued for 90 minutes with vigorous shaking of the closed abdomen. On completion of HIPEC, necessary bowel anastomoses are performed, and gastrostomy and jejunostomy tubes are placed for postoperative management of nutritional deficiencies and prolonged gastric ileus.

Intraperitoneal administration of chemotherapy offers an advantage of providing high local concentrations of drug directly to the targeted peritoneal surfaces, and hyperthermia provides a synergistic antitumor effect when combined with chemotherapy.[101] However, as a locally applied modality, the maximum penetration into tumor tissue is usually limited to 2 to 5 mm from the surface.[102] At present, no randomized study has compared the benefit of adding HIPEC to surgical cytoreduction, although single-institution series have indirectly suggested a benefit when DFS rates of patients treated with surgical cytoreduction and HIPEC (37%–57%)[87,103] are compared with the historical rates of surgical cytoreduction alone (9%–12%).[81,88]

CRS with HIPEC represents an aggressive treatment requiring significant surgical expertise and should only be conducted at centers experienced in performing peritoneal cytoreduction. Operation time is approximately 8 to 12 hours, with an average hospital stay of 20 to 25 days. The 30-day postoperative mortality and morbidity rates range from 0% to 12% and 12% to 56%, respectively.[87,89] In one of the largest retrospective multi-institutional registry-based

study of 2298 patients with PMP originating from an appendiceal mucinous neoplasm undergoing CRS, the reported median OS was 16.3 years, with a 10-year survival rate of 63%.[104] The treatment-related mortality was 2%, and major operative complications occurred in 24% of cases.[104] A high peritoneal carcinomatosis index (PCI), lack of complete cytoreduction, and lack of HIPEC were associated with poorer PFS and OS.[104]

The prognosis for patients undergoing CRS with HIPEC is primarily dependent on two critical factors: histologic classification and completeness of surgical resection. A quantitative score, the completeness of cytoreduction (CC) score proposed by Sugarbaker and colleagues,[82] categorizes the CC based on the size of nodules remaining at the end of surgery: CC-0 (no visible disease), CC-1 (nodules <0.25 cm), CC-2 (nodules 0.25 to <2.5 cm), and CC-3 (nodules ≥2.5 cm). In an analysis of 224 patients with low-grade histology, Sugarbaker et al[82] found that whereas patients with complete cytoreduction (CC-0 or CC-1) had a 5-year OS rate of 86%, patients with incomplete cytoreduction (CC-2 or CC-3) had a 5-year OS rate of 20% (P <.0001) (Fig. 31–9). The importance of CC has been confirmed by other authors, although various methods of categorizing CC have been used.[87,103]

Additional prognostic measures include the PCI, a quantitative measure of the size and distribution of nodules on the peritoneal surface; the previous surgical score, a measure of the extent of prior cytoreduction; and the extent of disease on the small bowel and small bowel mesentery.[81,82,105,106] The prognostic value of these different factors relates primarily to their ability to predict the likelihood of obtaining a complete cytoreduction. For patients who cannot undergo complete CRS, the benefit obtained from an incomplete cytoreduction remains uncertain. If complete CRS cannot be performed, a surgical cytoreduction is generally considered only if there are particular symptoms that can be palliated by tumor debulking. Given that HIPEC has limited tumor penetration, use of HIPEC should be limited to patients with a complete or near-complete CRS.

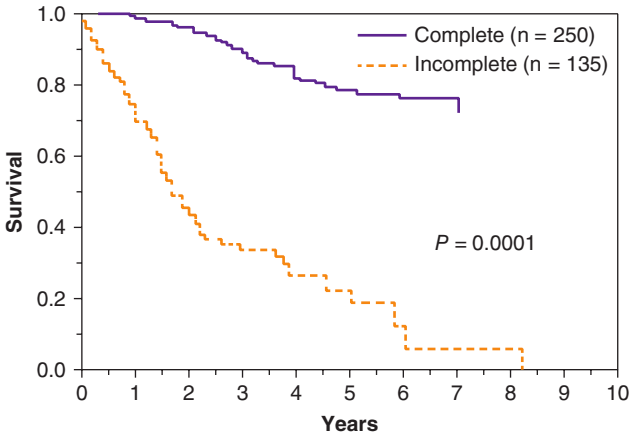


FIGURE 31–9 Overall survival for 385 cases with the mucinous epithelial tumors of the appendix according to completeness of surgical cytoreduction (CC). Complete cytoreduction defined as a CC score of CC-0 or CC-1, and an incomplete cytoreduction is defined as a score of CC-2 or CC-3. (Reproduced with permission from Sugarbaker PH. Results of treatment of 385 patients with peritoneal surface spread of appendiceal malignancy. *Ann Surg Oncol***. 1999;6(8):727-731.)**

Systemic Chemotherapy

The role of systemic chemotherapy has not been well delineated in appendiceal epithelial tumors and has generally been used in patients who are not candidates for surgical cytoreduction.[99] The challenges of using systemic chemotherapy to treat appendiceal tumors are numerous. Because it is a rare disease, it has been difficult to conduct clinical trials specifically for appendiceal tumors. Factors further complicating the development of effective chemotherapy include the marked heterogeneity between low- and high-grade tumors, the relatively slow-growing nature of the disease, the primarily mucinous component of the tumors, and challenges in radiographically measuring disease response. In the absence of data specific to appendiceal adenocarcinoma, chemotherapy developed for CRC has traditionally be used for these tumors. Traditionally, PMP has been considered resistant to systemic chemotherapy, although a phase II study evaluating the use of concurrent mitomycin C and capecitabine in patients with advanced, unresectable high- or low-grade mucinous PMP has suggested a role for systemic chemotherapy.[107] In this study of 39 patients, a clinical benefit rate of 38% was determined based on the definition of either semiquantitative reductions in mucinous deposition or stabilization of previously progressive disease, with a 2-year cancer-related mortality rate of 39%.[107]

There is now growing recognition that given differences in natural history, somatic mutation profiles and gene expression high- and low-grade appendiceal tumors need to be treated as separate entities with respect to chemotherapy. A 2016 review of 25,992 tumors from the SEER database found stage IV well-differentiated mucinous appendiceal adenocarcinomas demonstrated no benefit from systemic chemotherapy.[108] This finding was confirmed by a similar study of 639 metastatic well-differentiated

mucinous appendiceal adenocarcinoma patients showing 5 year survival benefit from surgical resection (HR, 0.4) but not chemotherapy (HR, 1.1).[109] Currently, a randomized trial for well-differentiated appendiceal tumors is underway at MDACC to confirm these findings prospectively; reporting is expected in 2021.

Although colon cancer chemotherapy—namely, fluoropyridines (5-FU, capecitabine) oxaliplatin, and/or irinotecan—is commonly used for patients with high-grade appendiceal cancer, there are few published data to support this practice. Shapiro et al[99] retrospectively reviewed data collected from 54 patients (26 moderate or poorly differentiated) who were suboptimal surgical cytoreductive candidates, showing radiographic stabilization or response to therapy in 55% of patients with median PFS of 7.6 months and median OS of 56 months. The largest study specifically of high-grade appendiceal adenocarcinoma is a retrospective review of 142 patients by Lieu et al.[92] This showed a response rate of 44%, median PFS of 6.9 months, and median OS of 1.7 years. Patients with response to chemotherapy and complete CRS were associated with improved PFS and OS. A small Japanese case series showed disease control in 6 of 8 patients with FOLFOX.[110] Regarding the combination of systemic treatment with surgery, in a study of 109 high-grade tumors, adjuvant chemotherapy after CRS plus HIPEC was associated with improved PFS (12.6 months vs 6.8 months; P <.01), but interestingly, no benefit was seen from neoadjuvant treatment.[111] There are also retrospective reports suggesting that combining bevacizumab with chemotherapy may improve survival outcomes in surgically unresectable appendiceal epithelial neoplasms.[112,113]

The MD Anderson Approach to Epithelial Appendiceal Tumors

Unlike CRC, appendiceal epithelial malignancies have a more indolent natural history that is determined primarily by their underlying histopathology. At MDACC, patients with LAMN and well- to moderately differentiated mucinous adenocarcinoma are evaluated initially for CRS. Patients with a complete cytoreduction (CC-0 or CC-1) are treated with HIPEC using intraperitoneal mitomycin at 42°C. If a complete CRS is not obtained, if radiographic imaging indicates that obtaining a complete cytoreduction is highly unlikely, or if medical comorbidities preclude a surgical procedure, then patients are considered for systemic chemotherapy. Also, HIPEC is used at MDACC for the control of refractory ascites in select patients with low-grade tumors. We have found that the use of HIPEC in patients who have undergone an incomplete CRS can provide long-term control of ascites and should be considered in patients with refractory ascites.

Given the indolent nature of well- to moderately differentiated mucinous adenocarcinoma, systemic chemotherapy is generally reserved for patients who either have clear evidence of disease progression on radiographic imaging or have significant tumor-related symptoms. Frontline chemotherapy is fluoropyrimidine based, and additional agents may be added based on the perceived tolerance of more aggressive combinations. Given the generally good prognosis of these patients and limited data supporting the efficacy of CRC-like chemotherapy in these tumors, it is critical that treatment is closely aligned with quality of life and that cumulative toxicities are kept to a minimum.

The use of multiagent systemic chemotherapy, as administered in patients with CRC, is the treatment of choice for patients who have signet ring cells, poorly differentiated tumors, or nonmucinous tumors. Because patients with poorly differentiated or signet ring cell appendiceal adenocarcinomas have consistently shown worse outcomes after aggressive CRS, our approach has been only to consider surgical cytoreduction in these patients after initial treatment with systemic chemotherapy. In a retrospective study from MDACC, Lieu et al showed that patients with stage IV poorly differentiated or signet ring cell morphology appendiceal adenocarcinomas had a median OS of 24 months, similar to the known OS for patients with metastatic CRC.[92] With regard to targeted agents, it is not standard practice at MDACC to use either VEGF inhibitors or EGFR inhibitors in appendiceal epithelial tumors. MSI-H is rare in appendiceal cancer, but these patients are treated with immunotherapy similar to those with MSI-H colon cancer. Given the lack of data supporting systemic chemotherapy and lack of a true standard-of-care regimen, patients should be enrolled on clinical trials whenever possible. To help facilitate trial enrollment, all metastatic appendiceal tumors are routinely molecularly profiled for somatic mutation in common cancer genes, microsatellite instability, and HER2 overexpression. Now that it is possible to obtain these data in a Clinical Laboratory Improvement Amendments (CLIA) fashion, moving forward this molecular profiling will include RNA_Seq.

Because of the rarity of appendiceal tumors, our understanding of these tumors is limited, and further research into the molecular characteristics of these tumors is needed. The role of CRS is well established for appendiceal epithelial tumors. The use of systemic chemotherapy in patients with appendiceal epithelial tumors needs further study, in particular for low-grade tumors in which CRC-like chemotherapy seems to provide no benefit.

MD ANDERSON PRACTICE TIPS: SMALL BOWEL CANCER

- Predisposing conditions for SBA should be considered; specifically, testing for both mismatch repair and celiac disease should be done.
- Approach adjuvant therapy for SBA similar to the general principles from colon adenocarcinoma, but stage for stage, outcomes for SBA tend to be worse.
- All patients with metastatic disease should be profiled as a number of targetable alterations can be identified such as HER2 alterations and mismatch repair deficiency.
- For metastatic SBA, start with 5-FU–based chemotherapy (FOLFOX, FOLFIRI, or FOLFOXIRI). Use of concomitant bevacizumab can be considered, but use of anti-EGFR drugs (cetuximab and panitumumab) appears to have limited activity.
- Taxane-based therapy has demonstrated activity and can be considered in later lines of therapy in the absence of clinical trials, but referral to clinical trials is always preferred.

MD ANDERSON PRACTICE TIPS: APPENDICEAL TUMORS

- Grade is critical in all mucinous appendiceal neoplasms for both prognosis and management. Ensure adequate sampling has occurred, and if uncertainty exists, consider discussion with pathology.
- Given the mucinous nature of these cancers in most cases (especially low-grade tumors) and the desire for peritoneal cavity evaluation, PET scans should not be used in routine care.
- For low-grade (well-differentiated) mucinous adenocarcinomas, ensure multidisciplinary discussions and early surgery referral because they represent a favorable prognostic entity that is best managed with surgery.
- Avoid use of chemotherapy in patients with low-grade (well-differentiated) mucinous adenocarcinomas because these tumors tend to be nonresponsive to chemotherapy.
- In nonmucinous and high-grade mucinous appendiceal adenocarcinomas, systemic 5-FU–based chemotherapy should be used because these histologic types are chemoresponsive, and the benefit from upfront CRS is uncertain.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(1):7-30.
2. Raghav K, Overman MJ. Small bowel adenocarcinomas—existing evidence and evolving paradigms. *Nat Rev Clin Oncol*. 2013;10(9):534-544.
3. Howlader N, Noone AM, Krapcho M, et al, eds. SEER cancer statistics review, 1975-2017, National Cancer Institute. https://seer.cancer.gov/csr/1975_2017
4. Weiss NS, Yang CP. Incidence of histologic types of cancer of the small intestine. *J Natl Cancer Inst*. 1987;78(4):653-656.
5. Pedersen KS, Raghav K, Overman MJ. Small bowel adenocarcinoma: etiology, presentation, and molecular alterations. *J Natl Compr Canc Netw*. 2019;17(9):1135-1141.
6. Scélo G, Boffetta P, Hemminki K, et al. Associations between small intestine cancer and other primary cancers: an international population-based study. *Int J Cancer*. 2006;118(1):189-196.
7. Overman MJ, Hu CY, Kopetz S, et al. A population-based comparison of adenocarcinoma of the large and small intestine: insights into a rare disease. *Ann Surg Oncol*. 2012;19(5):1439-1445.
8. Sellner F. Investigations on the significance of the adenoma-carcinoma sequence in the small bowel. *Cancer*. 1990;66(4):702-715.
9. Ryan DP, Schapiro RH, Warshaw AL. Villous tumors of the duodenum. *Ann Surg*. 1986;203(3):301-306.
10. Joesting DR, Beart RW Jr, van Heerden JA, Weiland LH. Improving survival in adenocarcinoma of the duodenum. *Am J Surg*. 1981;141(2):228-231.
11. Neugut AI, Santos J. The association between cancers of the small and large bowel. *Cancer Epidemiol Biomarkers Prev*. 1993;2(6):551-553.
12. Schrock AB, Devoe CE, McWilliams R, et al. Genomic profiling of small-bowel adenocarcinoma. *JAMA Oncol*. 2017;3(11):1546-1553.
13. Ross RK, Hartnett NM, Bernstein L, Henderson BE. Epidemiology of adenocarcinomas of the small intestine: is bile a small bowel carcinogen? *Br J Cancer*. 1991;63(1):143-145.
14. Wu AH, Yu MC, Mack TM. Smoking, alcohol use, dietary factors and risk of small intestinal adenocarcinoma. *Int J Cancer*. 1997;70(5):512-517.
15. Chow WH, Linet MS, McLaughlin JK, et al. Risk factors for small intestine cancer. *Cancer Causes Control*. 1993;4(2):163-169.
16. Neugut AI, Jacobson JS, Suh S, et al. The epidemiology of cancer of the small bowel. *Cancer Epidemiol Biomarkers Prev*. 1998;7(3):243-251.
17. Schatzkin A, Park Y, Leitzmann MF, et al. Prospective study of dietary fiber, whole grain foods, and small intestinal cancer. *Gastroenterology*. 2008;135(4):1163-1167.
18. Delaunoit T, Neczyporenko F, Limburg PJ, et al. Pathogenesis and risk factors of small bowel adenocarcinoma: a colorectal cancer sibling? *Am J Gastroenterol*. 2005;100(3):703-710.
19. Boffetta P, Hazelton WD, Chen Y, et al. Body mass, tobacco smoking, alcohol drinking and risk of cancer of the small intestine—a pooled analysis of over 500,000 subjects in the Asia Cohort Consortium. *Ann Oncol*. 2012;23(7):1894-1898.
20. Groves CJ, Saunders BP, Spigelman AD, Phillips RK. Duodenal cancer in patients with familial adenomatous polyposis (FAP): results of a 10 year prospective study. *Gut*. 2002;50(5):636-641.
21. Giardiello FM, Brensinger JD, Tersmette AC, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. *Gastroenterology*. 2000;119(6):1447-1453.
22. Aarnio M, Mecklin JP, Aaltonen LA, et al. Life-time risk of different cancers in hereditary non-polyposis colorectal cancer (HNPCC) syndrome. *Int J Cancer*. 1995;64(6):430-433.
23. Vasen HF, Wijnen JT, Menko FH, et al. Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. *Gastroenterology*. 1996;110(4):1020-1027.
24. Laforest A, Aparicio T, Zaanan A, et al. ERBB2 gene as a potential therapeutic target in small bowel adenocarcinoma. *Eur J Cancer*. 2014;50(10):1740-1746.
25. Palascak-Juif V, Bouvier AM, Cosnes J, et al. Small bowel adenocarcinoma in patients with Crohn's disease compared with small bowel adenocarcinoma de novo. *Inflamm Bowel Dis*. 2005;11(9):828-832.
26. Abrahams NA, Halverson A, Fazio VW, et al. Adenocarcinoma of the small bowel: a study of 37 cases with emphasis on histologic prognostic factors. *Dis Colon Rectum*. 2002;45(11):1496-1502.
27. Haan JC, Buffart TE, Eijk PP, et al. Small bowel adenocarcinoma copy number profiles are more closely related to colorectal than to gastric cancers. *Ann Oncol*. 2012;23(2):367-374.
28. Maglinte DD, O'Connor K, Bessette J, et al. The role of the physician in the late diagnosis of primary malignant tumors of the small intestine. *Am J Gastroenterol*. 1991;86(3):304-308.
29. Young JI, Mongoue-Tchokote S, Wieghard N, et al. Treatment and survival of small-bowel adenocarcinoma in the united states: a comparison with colon cancer. *Dis Colon Rectum*. 2016;59(4):306-315.
30. Lewis BS, Eisen GM, Friedman S. A pooled analysis to evaluate results of capsule endoscopy trials. *Endoscopy*. 2005;37(10):960-965.
31. Sturniolo GC, Di Leo V, Vettorato MG, et al. Clinical relevance of small-bowel findings detected by wireless capsule endoscopy. *Scand J Gastroenterol*. 2005;40(6):725-733.
32. Cobrin GM, Pittman RH, Lewis BS. Increased diagnostic yield of small bowel tumors with capsule endoscopy. *Cancer*. 2006;107(1):22-27.
33. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin*. 2017;67(2):93-99.
34. Agrawal S, McCarron EC, Gibbs JF, et al. Surgical management and outcome in primary adenocarcinoma of the small bowel. *Ann Surg Oncol*. 2007;14(8):2263-2269.
35. Talamonti MS, Goetz LH, Rao S, et al. Primary cancers of the small bowel: analysis of prognostic factors and results of surgical management. *Arch Surg*. 2002;137(5):564-570; discussion 570-571.
36. Wu TJ, Yeh CN, Chao TC, et al. Prognostic factors of primary small bowel adenocarcinoma: univariate and multivariate analysis. *World J Surg* 2006;30(3):391-398; discussion 399.
37. Bakaeen FG, Murr MM, Sarr MG, et al. What prognostic factors are important in duodenal adenocarcinoma? *Arch Surg*. 2000;135(6):635-641; discussion 641-642.
38. Sohn TA, Lillemoe KD, Cameron JL, et al. Adenocarcinoma of the duodenum: factors influencing long-term survival. *J Gastrointest Surg*. 1998;2(1):79-87.
39. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin*. 2008;58(2):71-96.
40. Overman MJ, Hu CY, Wolff RA, Chang GJ. Prognostic value of lymph node evaluation in small bowel adenocarcinoma: analysis of the Surveillance, Epidemiology, and End Results database. *Cancer*. 2010;116(23):5374-5382.
41. Dabaja BS, Suki D, Pro B, et al. Adenocarcinoma of the small bowel: presentation, prognostic factors, and outcome of 217 patients. *Cancer*. 2004;101(3):518-526.
42. Kelsey CR, Nelson JW, Willett CG, et al. Duodenal adenocarcinoma: patterns of failure after resection and the role of chemoradiotherapy. *Int J Radiat Oncol Biol Phys*. 2007;69(5):1436-1441.
43. Barnes G Jr, Romero L, Hess KR, Curley SA. Primary adenocarcinoma of the duodenum: management and survival in 67 patients. *Ann Surg Oncol*. 1994;1(1):73-78.

44. Klinkenbijl JH, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. *Ann Surg*. 1999;230(6):776-782; discussion 782-784.
45. Neoptolemos JP, Moore MJ, Cox TF, et al. Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs observation on survival in patients with resected periampullary adenocarcinoma: the ESPAC-3 periampullary cancer randomized trial. *JAMA*. 2012;308(2):147-156.
46. Overman MJ, Kopetz S, Lin E, et al. Is there a role for adjuvant therapy in resected adenocarcinoma of the small intestine. *Acta Oncol*. 2010;49(4):474-479.
47. Halfdanarson TR, McWilliams RR, Donohue JH, Quevedo JF. A single-institution experience with 491 cases of small bowel adenocarcinoma. *Am J Surg*. 2010;199(6):797-803.
48. Zaanan A, Costes L, Gauthier M, et al. Chemotherapy of advanced small-bowel adenocarcinoma: a multicenter AGEO study. *Ann Oncol*. 2010;21(9):1786-1793.
49. Gibson MK, Holcroft CA, Kvols LK, et al. Phase II study of 5-fluorouracil, doxorubicin, and mitomycin C for metastatic small bowel adenocarcinoma. *Oncologist*. 2005;10(2):132-137.
50. Overman MJ, Varadhachary GR, Kopetz S, et al. Phase II study of capecitabine and oxaliplatin for advanced adenocarcinoma of the small bowel and ampulla of Vater. *J Clin Oncol*. 2009;27(16):2598-2603.
51. Xiang XJ, Liu YW, Zhang L, et al. A phase II study of modified FOLFOX as first-line chemotherapy in advanced small bowel adenocarcinoma. *Anticancer Drugs*. 2012;23(5):561-566.
52. McWilliams RR, Foster NR, Mahoney MR, et al. Pharmacogenetic dosing by UGT1A1 genotype as first-line therapy for advanced small-bowel adenocarcinoma: a North Central Cancer Treatment Group (NCCTG) trial. *J Clin Oncol*. 2012;30(4 suppl):314.
53. Crawley C, Ross P, Norman A, et al. The Royal Marsden experience of a small bowel adenocarcinoma treated with protracted venous infusion 5-fluorouracil. *Br J Cancer*. 1998;78(4):508-510.
54. Fishman PN, Pond GR, Moore MJ, et al. Natural history and chemotherapy effectiveness for advanced adenocarcinoma of the small bowel: a retrospective review of 113 cases. *Am J Clin Oncol*. 2006;29(3):225-231.
55. Locher C, Malka D, Boige V, et al. Combination chemotherapy in advanced small bowel adenocarcinoma. *Oncology*. 2005;69(4):290-294.
56. Overman MJ, Kopetz S, Wen S, et al. Chemotherapy with 5-fluorouracil and a platinum compound improves outcomes in metastatic small bowel adenocarcinoma. *Cancer*. 2008;113(8):2038-2045.
57. Aldrich JD, Raghav KPS, Varadhachary GR, et al. Retrospective analysis of taxane-based therapy in small bowel adenocarcinoma. *Oncologist*. 2019;24(6):e384-e386.
58. Gulhati P, Raghav K, Shroff RT, et al. Bevacizumab combined with capecitabine and oxaliplatin in patients with advanced adenocarcinoma of the small bowel or ampulla of Vater: a single-center, open-label, phase 2 study. *Cancer*. 2017;123(6):1011-1017.
59. Gulhati P, Raghav K, Shroff R, et al. Phase II study of panitumumab in RAS wild-type metastatic adenocarcinoma of small bowel or ampulla of Vater. *Oncologist*. 2018;23(3):277-e226.
60. Pedersen K, Overman MJ, Foster NR, et al. Trial in progress: a multicenter phase II study of pembrolizumab in patients with advanced small bowel adenocarcinomas. *J Clin Oncol*. 2018;36(4 suppl):TPS535.
61. Marmor S, Portschy PR, Tuttle TM, Virnig BA. The rise in appendiceal cancer incidence: 2000-2009. *J Gastrointest Surg*. 2015;19(4):743-750.
62. Mo S, Zhou Z, Ying Z, et al. Epidemiology of and prognostic factors for appendiceal carcinomas: a retrospective, population-based study. *Int J Colorectal Dis*. 2019;34(11):1915-1924.
63. Yan Q, Zheng W, Luo H, et al. Incidence and survival trends for appendiceal mucinous adenocarcinoma: an analysis of 3237 patients in the Surveillance, Epidemiology, and End Results database. Future *Oncol*. 2019;15(34):3945-3961.
64. Kelly KJ. Management of appendix cancer. *Clin Colon Rectal Surg*. 2015;28(4):247-255.
65. Ang CS, Shen JP, Hardy-Abeloos CJ, et al. Genomic landscape of appendiceal neoplasms. *JCO Precis Oncol*. 2018;(2):1-18.
66. Raghav K, Shen JP, Jácome AA, et al. Integrated clinico-molecular profiling of appendiceal adenocarcinoma reveals a unique grade-driven entity distinct from colorectal cancer. *Br J Cancer*. 2020;123(8):1262-1270.
67. Connor SJ, Hanna GB, Frizelle FA. Appendiceal tumors: retrospective clinicopathologic analysis of appendiceal tumors from 7,970 appendectomies. *Dis Colon Rectum*. 1998;41(1):75-80.
68. McCusker ME, Coté TR, Clegg LX, Sobin LH. Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program, 1973-1998. *Cancer*. 2002;94(12):3307-3312.
69. Carr NJ, Bibeau F, Bradley RF, et al. The histopathological classification, diagnosis and differential diagnosis of mucinous appendiceal neoplasms, appendiceal adenocarcinomas and pseudomyxoma peritonei. *Histopathology*. 2017;71(6):847-858.
70. Carr NJ, Cecil TD, Mohamed F, et al. A consensus for classification and pathologic reporting of pseudomyxoma peritonei and associated appendiceal neoplasia: the results of the Peritoneal Surface Oncology Group International (PSOGI) modified Delphi process. *Am J Surg Pathol*. 2016;40(1):14-26.
71. Misdraji J, Yantiss RK, Graeme-Cook FM, et al. Appendiceal mucinous neoplasms: a clinicopathologic analysis of 107 cases. *Am J Surg Pathol*. 2003;27(8):1089-1103.
72. Xie X, Zhou Z, Song Y, et al. The management and prognostic prediction of adenocarcinoma of appendix. *Sci Rep*. 2016;6:39027.
73. Overman MJ, Fournier K, Hu CY, et al. Improving the AJCC/TNM staging for adenocarcinomas of the appendix: the prognostic impact of histological grade. *Ann Surg*. 2013;257(6):1072-1078.
74. Taggart MW, Abraham SC, Overman MJ, et al. Goblet cell carcinoid tumor, mixed goblet cell carcinoid-adenocarcinoma, and adenocarcinoma of the appendix: comparison of clinicopathologic features and prognosis. *Arch Pathol Lab Med*. 2015;139(6):782-790.
75. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer*. 2003;97(4):934-959.
76. Sandor A, Modlin IM. A retrospective analysis of 1570 appendiceal carcinoids. *Am J Gastroenterol*. 1998;93(3):422-428.
77. Sugarbaker PH. Epithelial appendiceal neoplasms. *Cancer J*. 2009;15(3):225-235.
78. Moertel CG, Weiland LH, Nagorney DM, Dockerty MB. Carcinoid tumor of the appendix: treatment and prognosis. *N Engl J Med*. 1987;317(27):1699-1701.
79. Clift AK, Kornasiewicz O, Drymousis P, et al. Goblet cell carcinomas of the appendix: rare but aggressive neoplasms with challenging management. *Endocr Connect*. 2018;7(2):268-277.
80. Guinney J, Dienstmann R, Wang X, et al. The consensus molecular subtypes of colorectal cancer. *Nat Med*. 2015;21(11):1350-1356.
81. Miner TJ, Shia J, Jaques DP, et al. Long-term survival following treatment of pseudomyxoma peritonei: an analysis of surgical therapy. *Ann Surg*. 2005;241(2):300-308.
82. Sugarbaker PH, Chang D. Results of treatment of 385 patients with peritoneal surface spread of appendiceal malignancy. *Ann Surg Oncol*. 1999;6(8):727-731.

83. Quenet F, Elias D, Roca L, et al. A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis. PRODIGE 7. *Eur J Surg*. 2019;45(2):e17.
84. Shepherd FA, Pereira JR, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med*. 2005;353(2):123-132.
85. Ronnett BM, Zahn CM, Kurman RJ, et al. Disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis. A clinicopathologic analysis of 109 cases with emphasis on distinguishing pathologic features, site of origin, prognosis, and relationship to "pseudomyxoma peritonei." *Am J Surg Pathol*. 1995;19(12):1390-1408.
86. Ronnett BM, Kurman RJ, Zahn CM, et al. Pseudomyxoma peritonei in women: a clinicopathologic analysis of 30 cases with emphasis on site of origin, prognosis, and relationship to ovarian mucinous tumors of low malignant potential. *Hum Pathol*. 1995;26(5):509-524.
87. Stewart JH 4th, Shen P, Russell GB, et al. Appendiceal neoplasms with peritoneal dissemination: outcomes after cytoreductive surgery and intraperitoneal hyperthermic chemotherapy. *Ann Surg Oncol*. 2006;13(5):624-634.
88. Gough DB, Donohue JH, Schutt AJ, et al. Pseudomyxoma peritonei. Long-term patient survival with an aggressive regional approach. *Ann Surg*. 1994;219(2):112-119.
89. Sugarbaker PH, Alderman R, Edwards G, et al. Prospective morbidity and mortality assessment of cytoreductive surgery plus perioperative intraperitoneal chemotherapy to treat peritoneal dissemination of appendiceal mucinous malignancy. *Ann Surg Oncol*. 2006;13(5):635-644.
90. Ronnett BM, Yan H, Kurman RJ, et al. Patients with pseudomyxoma peritonei associated with disseminated peritoneal adenomucinosis have a significantly more favorable prognosis than patients with peritoneal mucinous carcinomatosis. *Cancer*. 2001;92(1):85-91.
91. Grotz TE, Royal RE, Mansfield PF, et al. Stratification of outcomes for mucinous appendiceal adenocarcinoma with peritoneal metastasis by histological grade. *World J Gastrointest Oncol*. 2017;9(9):354-362.
92. Lieu CH, Lambert LA, Wolff RA, et al. Systemic chemotherapy and surgical cytoreduction for poorly differentiated and signet ring cell adenocarcinomas of the appendix. *Ann Oncol*. 2012;23(3):652-658.
93. Kabbani W, Houlihan PS, Luthra R, et al. Mucinous and nonmucinous appendiceal adenocarcinomas: different clinicopathological features but similar genetic alterations. *Mod Pathol*. 2002;15(6):599-605.
94. Levine EA, Blazer DG 3rd, Kim MK, et al. Gene expression profiling of peritoneal metastases from appendiceal and colon cancer demonstrates unique biologic signatures and predicts patient outcomes. *J Am Coll Surg*. 2012;214(4):599-606; discussion 606-607.
95. Levine EA, Votanopoulos KI, Qasem SA, et al. Prognostic molecular subtypes of low-grade cancer of the appendix. *J Am Coll Surg*. 2016;222(4):493-503.
96. Barretina J, Caponigro G, Stransky N, et al. The Cancer Cell Line Encyclopedia enables predictive modelling of anticancer drug sensitivity. *Nature*. 2012;483(7391):603-607.
97. Warren A, Chen Y, Jones A, et al. Global computational alignment of tumor and cell line transcriptional profiles. *Nat Commun*. 2021;12(1):22.
98. Shaib WL, Zakka K, Staley C 3rd, et al. Blood-based next-generation sequencing analysis of appendiceal cancers. *Oncologist*. 2020;25(5):414-421.
99. Shapiro JF, Chase JL, Wolff RA, et al. Modern systemic chemotherapy in surgically unresectable neoplasms of appendiceal origin: a single-institution experience. *Cancer*. 2010;116(2):316-322.
100. Lord AC, Shihab O, Chandrakumaran K, et al. Recurrence and outcome after complete tumour removal and hyperthermic intraperitoneal chemotherapy in 512 patients with pseudomyxoma peritonei from perforated appendiceal mucinous tumours. *Eur J Surg Oncol*. 2015;41(3):396-399.
101. Witkamp AJ, de Bree E, Van Goethem R, Zoetmulder FA. Rationale and techniques of intra-operative hyperthermic intraperitoneal chemotherapy. *Cancer Treat Rev*. 2001;27(6):365-374.
102. Los G, Verdegaal EM, Mutsaers PH, McVie JG. Penetration of carboplatin and cisplatin into rat peritoneal tumor nodules after intraperitoneal chemotherapy. *Cancer Chemother Pharmacol*. 1991;28(3):159-165.
103. Smeenk RM, Verwaal VJ, Antonini N, Zoetmulder FA. Survival analysis of pseudomyxoma peritonei patients treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Surg*. 2007;245(1):104-109.
104. Chua TC, Moran BJ, Sugarbaker PH, et al. Early- and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *J Clin Oncol*. 2012;30(20):2449-2456.
105. Glehen O, Mohamed F, Sugarbaker PH. Incomplete cytoreduction in 174 patients with peritoneal carcinomatosis from appendiceal malignancy. *Ann Surg*. 2004;240(2):278-285.
106. Yan TD, Bijelic L, Sugarbaker PH. Critical analysis of treatment failure after complete cytoreductive surgery and perioperative intraperitoneal chemotherapy for peritoneal dissemination from appendiceal mucinous neoplasms. *Ann Surg Oncol*. 2007;14(8):2289-2299.
107. Farquharson AL, Pranesh N, Witham G, et al. A phase II study evaluating the use of concurrent mitomycin C and capecitabine in patients with advanced unresectable pseudomyxoma peritonei. *Br J Cancer*. 2008;99(4):591-596.
108. Asare EA, Compton CC, Hanna NN, et al. The impact of stage, grade, and mucinous histology on the efficacy of systemic chemotherapy in adenocarcinomas of the appendix: analysis of the National Cancer Data Base. *Cancer*. 2016;122(2):213-221.
109. Lu P, Fields AC, Meyerhardt JA, et al. Systemic chemotherapy and survival in patients with metastatic low-grade appendiceal mucinous adenocarcinoma. *J Surg Oncol*. 2019;120(3):446-451.
110. Hiraide S, Komine K, Sato Y, et al. Efficacy of modified FOLFOX6 chemotherapy for patients with unresectable pseudomyxoma peritonei. *Int J Clin Oncol*. 2020;25(4):774-781.
111. Blackham AU, Swett K, Eng C, et al. Perioperative systemic chemotherapy for appendiceal mucinous carcinoma peritonei treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *J Surg Oncol*. 2014;109(7):740-745.
112. Raghav KP, Shetty AV, Kazmi SM, et al. Impact of molecular alterations and targeted therapy in appendiceal adenocarcinomas. *Oncologist*. 2013;18(12):1270-1277.
113. Choe JH, Overman MJ, Fournier KF, et al. Improved survival with anti-VEGF therapy in the treatment of unresectable appendiceal epithelial neoplasms. *Ann Surg Oncol*. 2015;22(8):2578-2584.
114. Aydin D, Sendur MA, Kefeli U, et al. Evaluation of bevacizumab in advanced small bowel adenocarcinoma. *Clin Colorectal Cancer* 2017;16:78-83.
115. Ecker BL, McMillan MT, Datta J, et al. Efficacy of adjuvant chemotherapy for small bowel adenocarcinoma: A propensity score-matched analysis. *Cancer* 2016;122:693-701.
116. Solaini L, Jamieson NB, Metcalfe M, et al. Outcome after surgical resection for duodenal adenocarcinoma in the UK. *Br J SurgHYPERLINK "https://pubmed.ncbi.nlm.nih.gov/?term=%22Br+J+Surg%22%5Bjour%5D" HYPERLINK "https://www.ncbi.nlm.nih.gov/nlmcatalog?term=%22Br+J+Surg%22%5BTitle+*

Abbreviation%5D" HYPERLINK "https://pubmed.ncbi.nlm.nih.gov/25776995/". 2015;102(6):676-81.
117. Swartz MJ, Hughes MA, Frassica DA, et al, Adjuvant concurrent chemoradiation for node-positive adenocarcinoma of the duodenum. *Arch Surg*. 2007;142(3):285-288.
118. Enzinger PC, Zhu A., Blaszkowsky L., et. al. Phase I Dose-finding and Pharmacologic Study of Cisplatin, Irinotecan, and either capecitabine or infusional 5-FU in Patients with Advanced Gastrointestinal Malignancies [abstract 28]. American Society of Clinical Oncology Gastrointestinal Cancers Symposium. 2005.
119. Czaykowski P and Hui D. Chemotherapy in small bowel adenocarcinoma: 10-year experience of the British Columbia Cancer Agency. *Clin Oncol (R Coll Radiol)*. 2007;19(2):143-149.
120. Goetz MP, Elrichman C, Windebank AJ, et al. Phase I and pharmacokinetic study of two different schedules of oxaliplatin, irinotecan, Fluorouracil, and leucovorin in patients with solid tumors. *J Clin Oncol.* 2003;21(20):3761-3769.
121. Polyzos A, Kouraklis G, Giannopoulos A, et al. Irinotecan as salvage chemotherapy for advanced small bowel adenocarcinoma: a series of three patients. *J Chemother*. 2003;15(5):503-506.
122. Jigyasu D, Bedikian AY, Stroehlein JR. Chemotherapy for primary adenocarcinoma of the small bowel. *Cancer* 1984; 53(1): 23–5.
123. Ouriel K, Adams JT. Adenocarcinoma of the small intestine. *Am J Surg*. 1984;147(1):66–71.
124. Morgan DF and Busuttil RW. Primary adenocarcinoma of the small intestine. *Am J Surg*. 1977;134(3):331-333.
125. Rochlin DB, Smart CR, Silva A. Chemotherapy of malignancies of the gastrointestinal tract. *Am J Surg*. 1965;109:43-46.

32 Colorectal Cancer

Arvind Dasari
Benny Johnson
Christine Parseghian
Kanwal P. Raghav
Scott Kopetz

KEY CONCEPTS

- Although the overall incidence of incidence of colorectal cancer (CRC) has decreased, its incidence in those younger than 50 years of age (ie, early-onset CRC) has significantly increased over the past 2 to 3 decades, accounting for an estimated one of every 10 cases currently being diagnosed in the United States.
- Surgery is the cornerstone of curative therapy in locoregional CRC. Adjuvant chemotherapy with a fluoropyrimidine typically in combination with oxaliplatin is standard-of-care adjuvant therapy for patients with stage III and IV and high-risk stage II colon cancer. Recent data support tailoring duration of therapy (3 months vs 6 months) based on pathologic stage for stage III colon cancer.
- In patients with locally advanced rectal adenocarcinoma, the paradigm has shifted to a total neoadjuvant therapy approach in which systemic chemotherapy in addition to neoadjuvant radiation is administered before surgery. Ongoing studies are evaluating deintensifying such trimodality therapy by omitting surgery or radiation in select patients.
- Biomarker testing that includes mismatch repair deficiency should be performed in all patients with CRC; expanded *RAS* (*KRAS* and *NRAS* exons 2,3, 4), $BRAF^{V600E}$ mutation, and *HER2neu* amplification should be performed in all patients with metastatic CRC. *NTRK* fusion and *POLE* mutations are rare but targetable aberrations in metastatic CRC (mCRC). All patients with mCRC should be evaluated for resectable disease at diagnosis and at each restaging.
- Most patients with mCRC are treated with fluoropyrimidine-based combination chemotherapy with oxaliplatin, irinotecan, or both in the first- and second-line settings. Monoclonal antibodies (mAbs) against the vascular endothelial growth factor axis or epidermal growth factor receptor (EGFR) may be used in combination with such chemotherapy. The use of anti-EGFR antibodies should be limited to *RAS* wild-type patients and to those with tumors arising in the left colon at least in the first-line setting. Patients with incurable metastatic disease should be considered for periods of less intensive therapy during their treatment course as the clinical situation warrants. Patients with mismatch repair–deficient mCRC are responsive to immunotherapy and should be treated with such agents, including in the first-line setting.
- A biologic doublet therapy of encorafenib (BRAF inhibitor) in combination with cetuximab (EGFR mAb) is now standard of care for patients with previously treated $BRAF^{V600E}$ mutant mCRC. Regorafenib and TAS-102 are oral agents for patients with refractory disease in later lines of therapy. Ongoing trials are evaluating role of anti-Her2neu therapy in patients with *Her-2neu* amplification and rechallenge with anti-EGFR antibodies in patients with prior clinical benefit and subsequent progression.

Colorectal cancer (CRC) is currently the third most common cancer in incidence in the United States and accounts for about 8.5% of all cancer-related deaths (nearly 148,000 new cases and 53,000 deaths each year).[1] This chapter reviews our current understanding of CRC; describes the known genetic mutations and risk factors; and outlines emerging screening, prevention, and therapeutic strategies, with particular emphasis on the approach taken at MD Anderson Cancer Center (MDACC).

EPIDEMIOLOGY AND ETIOLOGY OF COLORECTAL NEOPLASIA

Carcinogenesis: The Adenoma–Adenocarcinoma Sequence

Colorectal neoplasia results from three different pathways driving carcinogenesis, including chromosomal instability, microsatellite instability (MSI),

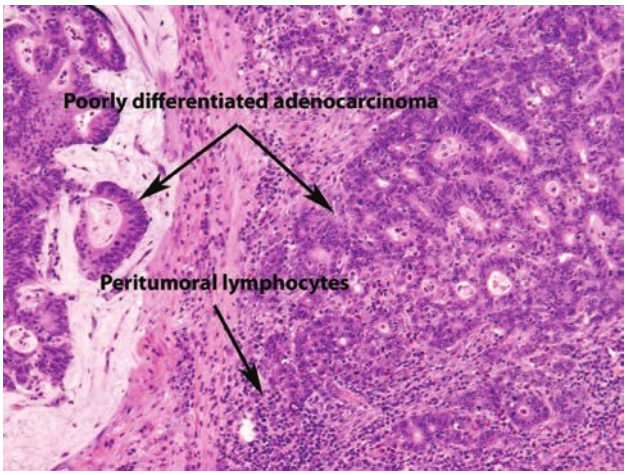


FIGURE 32–1 **Photomicrograph of a tumor with microsatellite instability. *Upper arrows* point to poorly differentiated malignant cells with some glandular differentiation and mucin. *Lower arrow* shows peritumoral lymphocytes clustering near areas of malignant cells and permeating the local stroma. CAPOX, capecitabine and oxaliplatin; dMMR, deficient mismatch repair; 5-FU, 5-fluorouracil; FOLFOX, 5-fluorouracil, leucovorin calcium, and oxaliplatin; LV, leucovorin.**

and CpG island methylation. The chromosomal instability pathway identifies early mutations in genes such as the tumor suppressor *APC* and the K-*ras* oncogene and later genetic events, including *PIK3CA* oncogene and the tumor suppressor gene *p53*. Histology that suggests an MSI tumor may include mucinous features, poor differentiation, or the presence of tumor-infiltrating lymphocytes (Fig. 32–1).

Consensus Molecular Subtype Classification

Patterns in RNA expression have been shown to define four molecular subtypes of CRC, with important prognostic differences.[2] The first consensus molecular subtype (CMS), CMS1, defines a subgroup with immune activation, and encompasses the majority of MSI and *BRAF*-mutated tumors. CMS2, or the canonical subgroup, is the most common and includes features of MYC activation and *TP53* mutations. CMS3 is a less common subtype with metabolic dysregulation and high rates of *KRAS* mutation. CMS4 is an immune-excluded subtype with active stromal features, including transforming growth factor β signaling. The ability of these subgroups to define treatment response has been proposed but is not yet integrated into treatment guidelines.[3]

TABLE 32–1 Lifetime Risks of Colorectal Cancer

Characteristic	Incidence (%)
General population	5
Personal history of colorectal cancer	15–20
Inflammatory bowel disease	15–40
Adenomatous polyps: personal	Variable
Hereditary nonpolyposis colorectal cancer mutation	70–80
Familial adenomatous polyposis	>95

Risk Factors

Genetic predisposition, acquired (somatic) or inherited genetic (germline) mutations, interplay with further environmental, dietary, or other less-well-understood factors in CRC carcinogenesis. Personal or family histories of CRC or polyps, older age, and inflammatory bowel disease (IBD) have all been associated with an increased risk of CRC (Table 32–1).

Modifiable Risk Factors

A diet rich in saturated fat, tobacco use, and excess alcohol use have been associated with an increased risk of colon cancer. Fiber has previously been associated with lower CRC risk; however, after correction for other dietary factors, it is no longer considered protective.[4]

Obesity and Insulin Resistance

Increased body mass index (BMI) and central obesity are risk factors for CRC. The Framingham Study found that a BMI above 30 increases the risk of colon cancer by 50% among middle-aged (30–54 years) individuals and by 2.4-fold for those aged 55 to 79 years, and waist circumference was a stronger predictor than BMI.[5] Independent of body mass index, insulin resistance and diabetes mellitus have also been associated with CRC.[6]

Adenomatous Polyps

Carcinoma is present in 5% of adenomas, in which the potential for malignant transformation is 8 to 10 times higher for villous and tubulovillous adenomas than tubular adenomas. Just over 1% of adenomatous polyps smaller than 1 cm in size are malignant, whereas up to 40% of adenomas larger than 2 cm are malignant.

Inflammatory Bowel Disease

Patients with IBD (ulcerative colitis or Crohn disease) are at increased risk of developing CRC based on the duration and extent of active disease, colitis,

and mucosal dysplasia. Recognizing the increased risk of CRC for patients with IBD, appropriate screening should be instituted.

Familial Syndromes

About 20% of all CRC cases are attributed to inherited autosomal dominant syndromes, including familial adenomatous polyposis (FAP), Gardner syndrome, and hereditary nonpolyposis colorectal cancer (HNPCC) (see Table 32–1).

Familial Adenomatous Polyposis

FAP is caused by a mutation of *APC* leading to the functional loss of both *APC* alleles, one inherited as a germline mutation and the other mutated in early childhood. FAP has high penetrance, manifesting as thousands of adenomatous polyps; some invariably progress to cancer, thereby warranting a prophylactic colorectal resection. The onset of malignancy in untreated patients occurs at about 42 years, with invasive cancer developing 20 to 30 years later.

Hereditary Nonpolyposis Colorectal Cancer

HNPCC (also known as Lynch syndrome) is caused by germline mutations in the DNA mismatch repair genes. Additional mutations involving tumor suppressor genes and oncogenes rapidly accumulate within these DNA repair–deficient cells, leading to malignant transformation in only 3 to 5 years.

MUTYH-Associated Polyposis

MutY homolog–associated polyposis is caused by biallelic mutations in the base excision repair gene *MUTYH*. Patients with the syndrome are characterized by oligopolyposis, usually more than 15 but fewer than 100 polyps. The onset of adenomas is older than in those with classic FAP but similar to attenuated adenomatous polyposis (45–55 years of age).

Early-Onset Colorectal Cancer

In contrast to the declining incidence of CRC in screening-eligible patient (age older than 45–50 years), the incidence of CRC in younger adults has substantially increased over the past 2 to 3 decades. It is now estimated that 1 in 10 diagnoses in the United States are in younger patients, with the number of young patients with rectal cancer representing as much as 1 in 5 diagnoses.[7] The cause of this increase in not clear because hereditary syndromes do not appears commonly in these patients. Efforts to understand the environmental exposures, comorbidities, and lifestyle factors are ongoing.

SCREENING FOR COLORECTAL NEOPLASIA

The current recommendation of the US Preventative Services Task Force is to use any accessible screening method, recognizing the major hurdles to improving outcomes are caused by poor screening compliance and less about specific testing characteristics.[8] At MDACC, we recommend colonoscopy screening starting at the age of 45 to 50 years as a preferred modality.

Detection Methods

Stool-Based Testing

Meta-analysis of four randomized trials investigating the role of fetal occult blood testing (FOBT) demonstrated an increased detection of early-stage CRCs and a reduction in CRC mortality.[9] Fecal immunohistochemistry tests (FITs) use antibodies for hemoglobin and appear more sensitive than FOBT; however, studies demonstrating mortality reduction have not been completed. DNA testing of stool uses detection of mutation and methylation markers from shed epithelial cells from adenomas or adenocarcinomas. Although sensitivity appears higher than FIT, mortality reduction has not been directly confirmed with this screening approach.

Blood-Based Testing

Carcinoembryonic antigen (CEA) is not recommended as a screening test because of poor sensitivity and specificity. Septin 9 DNA testing in blood is approved by the Food and Drug Administration (FDA) for patients refusing a colonoscopy but not recommended as a screening method because of low sensitivity.

Sigmoidoscopy

Flexible sigmoidoscopy is relatively safe and inexpensive suitable for screening large populations at low risk in combination with FOBT. However, adenomas in the distal colon are not indicative of proximal lesions, and sigmoidoscopy may miss nearly 50% of all colonic lesions.[10] Patients with adenomas detected by flexible sigmoidoscopy should have a full colonoscopy.

Computed Tomography Colonography (Virtual Colonoscopy)

Virtual colonoscopy (VC) involves reconstruction of three-dimensional images of the colon from the two-dimensional data obtained by a spiral computed tomography (CT) scanner. Bowel preparation is required, but the technique is less invasive and does not require sedation. However, VC lacks the advantage of a colonoscopy for direct access to colonic tissue for biopsies.

Colonoscopy

Colonoscopy not only enables full visualization of the entire colon but also allows for biopsy or removal of any suspicious lesions.

Despite widespread use, the colonoscopy for the purposes of cancer screening has not been studied in a randomized prospective trial until the Nordic-European Initiative on CRC (Nordic) study (NCT00883792). This multinational trial randomized patients aged 55 to 64 years to either once-only screening colonoscopy with removal of all lesions or no screening, which is the standard of care in these trial countries.[11] After a 15-year follow-up period, the primary endpoints of cumulative CRC–specific death and incidence will be evaluated. Preliminary results showed that 0.5 of the participants were diagnosed with CRC, and 30.7% had adenomas, of which 10.4% were high-risk adenomas. Detection rates were similar in the proximal and distal colon.[12]

Genetic Testing and Counseling

Genetic testing for *APC* mutations, *MUTYH* mutations, and DNA mismatch repair gene mutations are now available to identify carriers. A patient with classic FAP or with oligopolyposis but negative *APC* mutation testing should undergo *MUTYH* mutation testing given the incidence (7%–29%) of biallelic *MUTYH* in patients with polyposis with negative *APC* testing results.[13]

All patients with CRC at MDACC are screened for MSI. MSI, which is a hallmark of HNPCC, also occurs in about 15% of spontaneous colon cancers.

Immunohistochemical (IHC) stains done on sections from the diagnostic biopsy assess tumors for loss of heterozygosity in hMSH2, hMSH6, or hMLH1 gene loci. Further testing for germline mutations may follow an uninformative IHC stain. In particular, the absence of the MLH1 protein on IHC staining calls for the testing of the *BRAF* gene, in which a *BRAF* mutation signifies the downregulation of *MLH1* gene expression not through a germline mutation but rather somatic promoter hypermethylation. Furthermore, up to 10% of all MSIs may be missed through conventional IHC methods, highlighting MSI testing by polymerase chain reaction (PCR) if suspicion is high.[14] At MDACC, all young patients with CRC are offered the opportunity to meet with a genetic counselor to discuss the option and implications of genetic testing.

PREVENTION STRATEGIES

Primary Prevention

In primary prevention, broad-based interventions may decrease the risk of CRC for those at average risk. Americans currently have a 1 in 20 lifetime risk of developing CRC. Consequently, primary preventive strategies may have a significant impact on the overall incidence of CRC.

Nonsteroidal Antiinflammatory Drugs

For more than 20 years, data suggested that nonsteroidal antiinflammatory agents such as sulindac slow or prevent the formation of adenomatous polyps, particularly in patients with FAP.[15] Prostaglandin E_2, an important modulator of cell proliferation and malignant transformation, is formed by the catalytic activity of two predominant isoforms of cyclooxygenase. Cyclooxygenase 1 (COX-1) is constitutively active and widely expressed; it appears to regulate tissue repair and homeostasis. COX-2 is an inducible enzyme that appears to play a role in inflammation and tumor promotion. In a study of patients with FAP, the selective COX-2 inhibitor celecoxib at a higher dose significantly reduced the number of adenomas compared with placebo or a lower dose of celecoxib.[16] A prospective, placebo-controlled study of 600 mg aspirin per day in patients with HNPCC, a secondary per protocol analysis suggested that it may reduce cancer incidence, although further validation is required.[17]

However, the increased incidence of stroke and myocardial infarctions make the use of COX-2 inhibitors as primary chemoprevention unclear.[16] Aspirin has primary chemopreventive properties, with the risk of CRC substantially reduced among women who were regular users of aspirin for at least 20 years.[18] An additional prospective cohort study of male physicians followed over 4 years showed that regular users of aspirin (≥2 times per week) had a lower risk of developing CRC during the study period (relative risk [RR], 0.68; 95% confidence interval [CI], 0.52–0.92).[19]

Secondary Prevention

Aspirin also has secondary chemopreventive benefits. In a large randomized, placebo-controlled trial, aspirin demonstrated a benefit for patients with a prior history of CRC, showing a significantly reduced risk of developing adenomatous polyps compared with the placebo group (RR, 0.65; 95% CI, 0.46–0.91), a finding that was confirmed in other studies.[20,21] In contrast, the Cancer and Leukemia Group B (CALGB)/SWOG 80702 study evaluating the role of celecoxib for prevention of recurrence did not show any improvement in progression-free survival (PFS) or overall survival (OS) in the adjuvant setting in patients with stage III colon cancer.[22]

DIAGNOSTIC EVALUATION AND STAGING

Clinical Presentation

Colonic lesions in any location can cause change in bowel habits and bleeding, which may manifest as

melena, hematochezia, a positive hemoccult test result, or iron deficiency anemia in addition to weight loss, anorexia, and other constitutional symptoms. Unexplained iron deficiency anemia warrants an evaluation of the gastrointestinal (GI) tract.

Preoperative Staging for Colonic Neoplasms

In patients found to have a colonic neoplasm not requiring urgent surgery, a complete history, physical examination, and full colonoscopy with biopsies should be performed. Laboratory evaluation should include a complete blood cell count with differential, electrolytes, liver function studies, CEA level, serum urea nitrogen (BUN), and creatinine. Imaging studies should include CT of the chest and CT scan or magnetic resonance imaging (MRI) of the abdomen and pelvis.

Rectal Cancer Staging

Patients with newly diagnosed rectal cancer at MDACC are staged with endorectal ultrasonography (EUS) or pelvic MRI. The EUS is more accurate than CT for assessing the depth of tumor invasion into the bowel wall and perirectal lymph node involvement. A pelvic MRI to evaluate the mesorectal planes and perirectal lymph nodes allows improved accuracy of preoperative staging. At MDACC, patients also receive a CT scan of the chest and abdomen, with a dedicated MRI of the pelvis with rectal protocol in the preoperative setting.

TABLE 32–2 Tumor (T), Node (N), Metastasis (M) Staging of Colorectal Cancer

T	N	M	Stage
Tis	N0	M0	0
T1, T2	N0	M0	I
T3	N0	M0	IIA
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T1–T2	N1/N1c	M0	IIIA
T1	N2a	M0	IIIA
T3–T4a	N1/N1c	M0	IIIB
T2–T3	N2a	M0	IIIB
T1–T2	N2b	M0	IIIB
T4a	N2a	M0	IIIC
T3–T4a	N2b	M0	IIIC
T4b	N1-N2	M0	IIIC
Any T	Any N	M1a	IVA
Any T	Any N	M1b	IVB
Any T	Any N	M1c	IVC

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging System (2020).

Pathology

More than 95% of all colorectal malignancies are adenocarcinomas that are well differentiated, moderately differentiated, poorly differentiated, and undifferentiated. Other subtypes include mucinous and signet ring cell, which confer a poorer prognosis. These tumors are more likely to be present in younger patients and more commonly spread to the peritoneum. Treatment, however, does not differ from the more typical adenocarcinoma subtypes.

Pathologic Staging

Currently, the widely accepted system is the American Joint Committee on Cancer tumor, node, metastasis classification system (Table 32–2) to guide treatment.

MANAGEMENT OF NONMETASTATIC COLON CANCER

Although surgery is the cornerstone of curative intent therapy for patients with CRC, almost half of such patients undergoing curative resection will ultimately die of subsequent development of metastatic disease. Further systemic therapy is administered in these patients to improve survival by eliminating residual microscopic disease not evident at the time of surgery.

Surgical Management of Colon Cancer

Resection for localized colon cancer involves en bloc removal of the affected segment of bowel along with the adjacent mesentery to the origin of the primary feeding vessel inclusive of the draining lymph nodes. Care should be taken to have proximal and distal margins of at least 5 to 7 cm and at least 12 lymph nodes in the resected specimen. In patients with locally advanced T4 tumors involving adjacent organs, en bloc, multivisceral resection without disturbing the plane of adherence is vital and is associated with improved local and distant relapse rates.[23–27] Colectomy may done via open or laparoscopic approaches; multiple, randomized trials and meta-analyses suggesting comparable outcomes with the two approaches but with faster recovery with the latter. In the Clinical Outcomes of Surgical Therapy (COST) trial, 872 patients with colon adenocarcinoma were randomly assigned to open versus laparoscopic colectomy. In the laparoscopic group, although the operative time was longer, duration of

hospital stay and parenteral analgesia were slightly shorter.[28,29] Of note, 21% of the laparoscopic cases had to be converted to an open procedure however.[28,29] Other studies have also shown improved quality of life and higher likelihood of initiating adjuvant chemotherapy with laparoscopic over open colectomy.[30] The COST trial and several other randomized studies have also shown no difference in long-term outcomes including local recurrence, disease-free survival and OS rates between the two approaches.[28,29,31–34] Data also suggest that outcomes are significantly better in hospitals with higher annual case volumes.[29] Such data highlight the importance of adequate experience with this technique for optimizing outcomes. More recently, robotic approaches have been evaluated against laparoscopic approaches in observational studies. These studies suggest that robotic approaches are more expensive and are associated with longer operating time but possibly with better short-term outcomes such as blood loss, hospital stay, and return of postoperative bowel function.[35–38] Our recommendation is that minimally invasive surgeries only be performed in centers with high volumes and by experienced surgeons. These approaches should be avoided in complex situations involving extensive adhesions, obstruction, perforation, or involvement of adjacent organs.

Evidence Regarding Adjuvant Therapy for Colon Cancer

Although there are no randomized data defining the optimal time interval to starting adjuvant therapy after surgery, it is usually started after complete recovery from surgery, typically 4 to 8 weeks after surgery and as mandated by most completed adjuvant trials.[39–44]

Patients with stage III colon cancer typically receive 3 to 6 months of adjuvant chemotherapy with a fluoropyrimidine in combination with oxaliplatin. Improvement in DFS with addition of oxaliplatin to fluoropyrimidine was demonstrated by two large phase III trials. The European MOSAIC (Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer) trial randomized 2246 (60% with stage III) patients to FOLFOX (infusional 5-fluorouracil [5-FU], leucovorin calcium, and oxaliplatin) versus 5-FU and leucovorin. This trial demonstrated an improvement in the primary endpoint of 5-year DFS from 67% to 73% for patients with the addition of oxaliplatin to 5-FU.[43] An OS benefit was noted in the stage III subgroup (10-year, OS 67% vs 59%; hazard ratio [HR], 0.80; $P = .016$).[43] The North American NSABP C-07 trial that randomized 2407 patients (70% with stage III) to bolus weekly 5-FU/LV bolus 5FU, leucovorin (bFU/LV) with (FLOX) or without oxaliplatin also showed an improvement in the primary endpoint of 5-year DFS with the addition of oxaliplatin (69% vs 64%; HR, 0.82; 95% CI, 0.69–0.93).[40] However, this was at a cost of increased GI toxicities related to bFU/LV (≥grade 3 diarrhea, 32% vs 38%; vomiting, 8% vs 13%; and dehydration 12% vs 17% with bFU/LV vs FLOX) and thus the preferred method of administration of 5-FU is ambulatory infusional therapy.[40] Both the MOSAIC and National Surgical Adjuvant Breast and Bowel Project (NSABP) CO-7 trials mandated a total duration of adjuvant therapy for 6 months that is associated with significant toxicities, especially oxaliplatin-related neuropathy. More than 90% of patients in the MOSAIC trial developed neuropathy during chemotherapy, including 13% with grade 3 or greater symptoms. After a follow-up period of 48 months, grade 1, 2, or 3 neuropathy was persistent in 12%, 3%, and 0.7% of patients, respectively. Although all these trials used 5-FU, other randomized trials and pooled analyses convincingly support the substitution of 5-FU with capecitabine in the adjuvant setting.[45–47]

The IDEA (International Duration Evaluation of Adjuvant Chemotherapy) Collaboration was a prospective combined analysis of six international phase III trials investigating noninferiority of 3 versus 6 months of adjuvant chemotherapy (either FOLFOX or CAPOX [capecitabine and oxaliplatin] per physicians' choice) for stage III colon cancer with the primary endpoint of 3-year DFS.[48] The study narrowly failed to show noninferiority of 3 months of adjuvant therapy compared with 6 months (3-year DFS, 74.6% vs 75.5%; HR, 1.07; 95% CI, 1.00–1.15; noninferiority HR boundary, 1.12). However, prespecified subgroup analyses based on type of regimen suggested that noninferiority for 3 months was noted with CAPOX (0.95; 95% CI, 0.85–1.06) but not with FOLFOX (HR, 1.16; 95% CI, 1.06–1.26). Furthermore, an exploratory analysis in low-risk (T1–T3 and N1) patients demonstrated noninferiority of 3 versus 6 months (3-year DFS, 83.1% and 83.3%, respectively; HR, 1.01; 95% CI, 0.90–1.12) and superiority of 6 months over 3 months in those with high-risk (T4 or N2) disease (3-year DFS, 64.4% vs 62.7%; HR, 1.12; 95% CI, 1.03–1.23).[48] After a longer follow-up period, updated results showed that the 5-year DFS was 69.1% versus 70.8% (HR, 1.08; 95% CI, 1.01–1.15; false discovery rate adjusted $P = .22$); 5-year OS rate was 82.4% versus 82.8% (HR, 1.02; 95% CI, 0.95–1.11), and absolute 5-year OS rate difference was -0.4% (95% CI, -2.1% to 1.3%).[49] Together, these data suggest highlight the implications of risk stratification based on the pathologic and the potential for shortening duration of therapy with CAPOX, especially in low-risk patients.

The evidence for adjuvant therapy for patients with stage II disease is less robust (Fig. 32–2). To date, the largest randomized study of patients with stage II disease, QUASAR (Quick and Simple and Reliable),

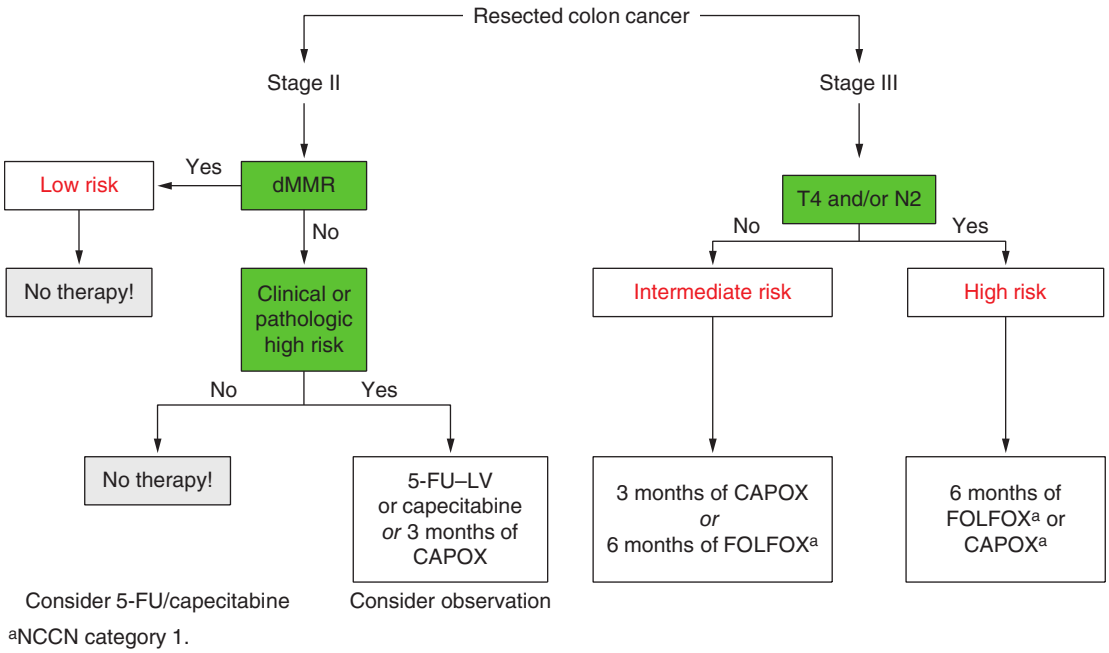


FIGURE 32–2 **Decision algorithm for adjuvant therapy in colon cancer.**

showed a modest survival benefit of 3.6% in patients receiving adjuvant 5-FU versus observation after surgical resection.[50] However, this study had several critical limitations, including enrollment of patients with rectal cancer (29%), limited number of lymph nodes evaluated (median, 6) and use of radiation in some patients (14%).[50] Other pooled analyses have shown small improvements in DFS (5%–10%) but without improvement in OS for adjuvant 5-FU over observation in stage II colon cancer.[51–54] Subgroup analyses of stage II patients from the MOSAIC and NSABP C-07 trials showed no statistically significant benefit in either OS or DFS with the addition of oxaliplatin to 5-FU.[43] These findings were also supported by a pooled analysis of the Adjuvant Colon Cancer End Points (ACCENT) database.[55–57] However, a subset of stage II patients at a higher risk of recurrence may be identified based on histopathological features. These features are defined by the National Comprehensive Cancer Network (NCCN) as T4 tumors (stage IIB/IIC); poorly differentiated histology (excluding microsatellite instability–high [MSI-H] cancers); lymphovascular invasion; perineural invasion; bowel obstruction; localized perforation; margins that are close, indeterminate, or positive; and inadequate sampling of lymph nodes (<12 nodes examined).[58] Data from randomized trials suggest that such patients with high-risk stage II colon cancer may derive modest benefit from the additional of oxaliplatin to a fluoropyrimidine. In exploratory analyses of the MOSIAC trial, there was a trend toward improvement in DFS (82% vs 77%) and OS (85% vs 83.3%) without reaching statistical significance in this subset.[43] A preplanned pooled analyses of 3273 patients with high-risk stage II colon cancer from four trials within the IDEA collaboration failed to show noninferiority of 3 versus 6 months of adjuvant therapy (80.7% vs 84%; DFS HR, 1.18; 80% CI, 1.05–1.31; $P = .404$; noninferiority boundary, 1.2). As with the stage III patients, toxicities were significantly lower in the 3-month group, and there appeared to be a trend toward difference in DFS based on type of regimen (CAPOX: HR, 1.02; 80% CI, 0.88–1.17; $P = .087$ and FOLFOX: HR, 1.42; 80% CI, 1.19–1.70; $P = .894$).[59]

Approximately 20% to 25% of stage II and 10% to 15% of stage III patients are MSI-H deficient mismatch repair (dMMR) that has prognostic and perhaps predictive implications for adjuvant therapy.[60–62] Substantial data suggest that patients with dMMR have a decreased likelihood to develop recurrent disease with some studies suggesting that the recurrence rate may be as low as half that of proficient mismatch repair (pMMR) tumors.[63] This positive prognostic effect of dMMR also appears to be more pronounced in stage II rather than in stage III colon cancer.[60–62] Some of these studies have also suggested that dMMR may also be a negative predictive marker for benefit from single-agent fluoropyrimidine, although some other studies have suggested otherwise.[60,64–66]

Irinotecan has no established role in the adjuvant setting. Three randomized phase III trials failed to show an improvement in DFS or OS in the adjuvant setting. Furthermore, data have not supported the addition of bevacizumab, cetuximab, or panitumumab in the adjuvant setting.[41,44,67–72]

Emerging Directions

Role of Immunotherapy in Adjuvant Therapy

Although immunotherapy is rapidly emerging as the cornerstone for management of patients with metastatic dMMR CRC, whether it has benefit in the adjuvant setting is being explored in an ongoing trial (Alliance A021502; NCT02912559).

Role of Neoadjuvant Therapy

The role of neoadjuvant chemotherapy in colon cancer is unclear but may be considered in patients with locally advanced tumors in whom margins may be compromised or in whom surgery may need to be delayed because of comorbidities or other causes. The FOxTROT trial randomized 1052 patients with T3–T4 N0-2 colon cancer to surgery upfront followed by 6 months of adjuvant oxaliplatin-based chemotherapy or to 6 weeks of preoperative oxaliplatin-based chemotherapy followed by surgery and then 18 additional weeks of chemotherapy. There was only a trend toward improvement in the primary endpoint of 2-year DFS (13.6% vs 17.2%; HR, 0.75; 95% CI, 0.55–1.04). However, the preoperative chemotherapy group had lower rates of incomplete resection (5% vs 10%; $P = .001$) and improved histologic downstaging of both pathologic tumor and nodal stage (including a 4% pathological complete response rate [pCR]) without increased perioperative complications.[73]

Role of Circulating Tumor DNA

Circulating tumor DNA (ctDNA) are short fragments of DNA (130–150 base pairs) released by cancer cells through apoptosis, necrosis, or secretion into the circulation.[74] Given the short half-life between 16 minutes to 2.5 hours, ctDNA is a sensitive real-time marker of tumor burden.[74] The presence of ctDNA after curative intent therapy, minimal residual disease (MRD) likely represents existence of radiographically undetectable micrometastases.[75–79] Rapidly accumulating data suggest very high specificity and positive predictive value (90%–100% for both) for clinical recurrence in patients with ctDNA-defined MRD.[75–80] The sensitivity of ctDNA for detection of MRD is also improving with newer methods and assays providing increasing lead time between detection of ctDNA and clinical recurrence approaching 8 to 9 months currently.[75,76,81] Given the high specificity and positive predictive value coupled with the lead time allowing for intervention, ongoing trials are evaluating escalation of therapy in patients with stage II MRD-positive colon cancer and similar efforts are being planned in stage III colon as well.[80,81] As sensitivity of MRD assays further improves, it is likely that they may be used for de-escalation of adjuvant therapy in stage III patients. Together, we anticipate that these data will likely establish ctDNA as an integral biomarker in the adjuvant setting.[80,81]

The MDACC Approach to Nonmetastatic Colon Cancer

When patients present to MDACC with a diagnosis of colon cancer, a detailed history, including family history; routine laboratory tests, including CEA level; and imaging (CT of the chest; CT or MRI of the abdomen and pelvis) are obtained. Previous endoscopic findings and pathology are reviewed and are tested for MSI. Patients without metastatic disease or contraindications to surgery should undergo primary resection with curative intent (Fig. 32–3). Surgery may consist of segmental resection or subtotal colectomy, depending on the underlying colonic pathology (multifocal cancer, FAP, HNPCC, and so on); pathologic staging is then determined from the surgical specimens. Patients with stage 0 or I tumors are placed on surveillance only. Patients with stage II colon cancer have a 75% to 80% chance of long-term DFS with surgical resection alone. For stage II patients, a thorough discussion regarding the evidence and morbidity associated with treatment while taking into consideration high-risk features, mismatch repair (MMR) testing results, and patient preferences. In patients with dMMR stage II colon cancer and without high-risk features, observation is recommended. Few data are available for the benefit of adjuvant therapy in dMMR stage II patients with high-risk features, and a thorough discussion is required, especially in those with T4b tumors. All patients with dMMR undergoing adjuvant therapy should receive a fluoropyrimidine in combination with oxaliplatin. In patients with standard-risk pMMR stage II colon cancer, a thorough discussion is recommended, and patients are advised that any 5-year survival benefit is likely to be less than 5%. After such a discussion, if wishing to proceed with adjuvant therapy, they are offered single-agent fluoropyrimidine for 3 to 6 months. Patients with pMMR and high-risk stage II colon cancer may be offered adjuvant chemotherapy for 3 to 6 months, and the inclusion of oxaliplatin needs to be individualized based on the observed risk factors, patient preferences, and comorbidities. Stage III patients are offered combination chemotherapy with fluoropyrimidine and oxaliplatin irrespective of MMR status. Patients with low-risk disease (T1–T3 and N1) are offered 3 months of CAPOX or 3 to 6 months of FOLFOX. Patient with high-risk disease are offered 3 to 6 months of CAPOX or 6 months of FOLFOX. Adjuvant therapy should begin within 4 to 8 weeks after surgery unless postoperative complications warrant a delay.

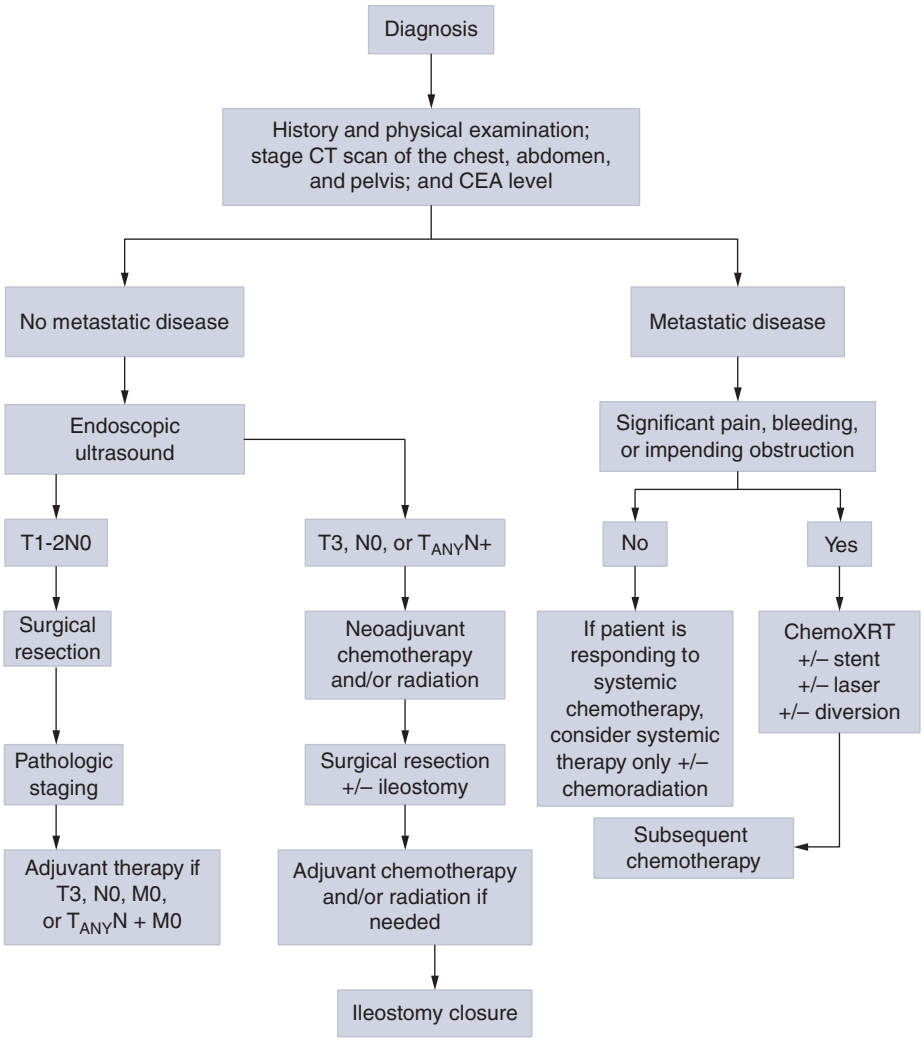


FIGURE 32–3 **Diagnostic and therapeutic algorithm for rectal cancer. CEA, carcinoembryonic antigen; Chemo-XRT, chemotherapy and radiation; CT, computed tomography.**

Surveillance for Patients with Resected Colon Cancer

After active therapy is completed, patients undergo clinical evaluations every 3 to 6 months for the first 3 years during the period of highest risk of recurrence, then every 6 and 12 months for the following 2 years, and annually thereafter. Of all recurrences, 80% occur within the first 3 years after surgical resection.[56] Colonoscopy is recommended 1 year after surgery and every 3 years thereafter at a minimum. Laboratory studies, including CEA level, are checked every 3 to 6 months; abdominopelvic CT or MRI and chest radiography or CT of the chest are obtained every 6 to 12 months. At 5 years, patients are followed with surveillance colonoscopy (every 3 years), annual physical examination, and CEA level.

MANAGEMENT OF NONMETASTATIC RECTAL CANCER

Given the higher risk of locoregional recurrence with rectal cancer compared with colon cancers, most patients with stages II and III rectal cancer undergo neoadjuvant therapy followed by surgery with total mesorectal excision (see Fig. 32–3). A total mesorectal excision (TME) involves an en bloc removal of the mesorectum through sharp dissection, including associated vascular and lymphatic structures, fatty tissue, and mesorectal fascia, while sparing the autonomic nerves. In general, more than two thirds of the patients with rectal cancer will be able to have a sphincter-saving procedure, whether it is a low anterior resection

or a proctectomy with a coloanal anastomosis. An abdominoperineal resection (APR), which includes removal of the rectum, anus, sphincter muscles, and a permanent colostomy, is reserved for patients with tumor involvement of sphincter muscles or with poor preoperative sphincter function.

Perioperative Therapy for Rectal Cancer

Two European studies have supported the use of preoperative therapy for resectable rectal cancer. The German Arbeitsgemeinschaft Internistische Onkologie (AIO) trial comparing preoperative and postoperative chemoradiation in T3 or T4 tumors showed a lower pelvic recurrence rate in the preoperative chemoradiation arm (6% vs 13% postoperatively, respectively; $P = .0006$).[82] In patients who were believed to require APR, chemoradiation also led to increased sphincter preservation rates (39% vs 19%; $P = .004$). Only 54% of patients in the postoperative arm received the full radiation dose, and 50% received full-dose chemotherapy compared with 92% and 89%, respectively, in the preoperative arm ($P < .001$).[82]

Standard radiotherapy doses are 45 Gy in 25 fractions followed by a 5.4-Gy boost. Concurrent chemotherapy with a fluoropyrimidine, typically capecitabine (over infusional 5-FU) is recommended as a radiosensitizer. Addition of agents other than a fluoropyrimidine to chemoradiation must be within the context of clinical trials. Results of multiple, large, randomized trials that evaluated addition of oxaliplatin and irinotecan to a fluoropyrimidine during chemoradiation have all shown increased toxicities without a convincing improvement in pCR, DFS, or OS.[83–96] Data from small, nonrandomized trials suggest that addition of anti–vascular endothelial growth factor (VEGF) agents may increase pCR rates but at the cost of postoperative complications. However, studies with anti-EGFR antibodies are mixed, perhaps related to lack of appropriate biomarker-based patient selection.[97–101]

Preoperative short-course radiotherapy (ie, 25 Gy administered over five fractions) has consistently shown to improve local control over surgery alone.[102–105] However, the initial studies that evaluated this approach suggested high rates of long-term toxicities, including fecal incontinence, bowel obstruction, and sexual dysfunction.[106–109] ore recent trials have allayed these concerns and have also provided additional data suggesting that this approach is comparable to conventional long-course chemoradiation for rates of local, distant recurrences, DFS, OS, and toxicities.[110,111]

An alternative approach to preoperative therapy, especially in patients with high-risk tumors such as those at risk for margin-positive resection, advanced disease (T4, node positive) or with low-lying tumors may be considered for total neoadjuvant therapy (TNT) in which systemic chemotherapy is administered before surgery in addition to neoadjuvant radiation. The rationales for this approach are to improve downstaging of tumors in the short term and to improve DFS and OS by better treatment of systemic disease through increased compliance to chemotherapy that is also administered earlier in the treatment course. The phase III PRODIGE (Partenariat de Recherche en Oncologie Digestive) 23 trial randomized 461 patients with locally advanced rectal cancer to neoadjuvant long-course chemoradiation versus induction FOLFIRINOX for six cycles followed by long-course chemoradiation before surgery.[112] Patients were allowed to receive additional adjuvant chemotherapy (capecitabine or FOLFOX) for a total of 6 months of perioperative chemotherapy. This trial showed an improvement in the primary endpoint of 3-year DFS with the TNT approach (75.7% vs 68.5%; HR, 0.69; 95% CI, 0.49–0.97). There was also an improvement in the pCR rate (27.5% vs 11.7%; $P < .001$) with the TNT approach.[112] The phase III RAPIDO (Rectal Cancer And Pre-operative Induction Therapy Followed by Dedicated Operation) trial randomized 920 patients with locally advanced rectal cancer to long-course chemoradiation versus short-course radiation followed by consolidation FOLFOX or CAPOX followed by surgery and subsequent adjuvant chemotherapy (for a total of 6 months of perioperative chemotherapy).[113] Similar to the PRODIGE 23 trial, the TNT arm in the RAPIDO trial also showed a statistically significant improvement in the primary endpoint of 3-year disease-related treatment failure (19.8% vs 26.6%; HR, 0.69; 95% CI, 0.53–0.89) and in the pCR rate (27.7% vs 13.8%; $P < .001$).[113] Both trials showed that the TNT approach did not affect compliance to chemoradiation, adjuvant therapy, or risk of surgical complications. Together, these data show the safety and benefit of the TNT approach. However, the optimal sequencing of radiation and chemotherapy ("induction" vs "consolidation" chemotherapy), modality of radiotherapy (short course vs long course), and chemotherapy regimen (fluoropyrimidine with oxaliplatin with or without irinotecan) remain to be defined.

Alternative approaches aiming to eliminate a component of the trimodality approach, either radiation or surgery, are also under investigation. Data from multiple nonrandomized studies suggest that patients with a complete clinical response (cCR) at the completion of neoadjuvant therapy may undergo careful observation (ie, "watch and wait") in lieu of radical surgery.[114–120] The largest of these studies was a registry that included 880 patients with cCR who underwent watch and wait. After a median follow-up period of 3.3 years, 88% of all local regrowth was diagnosed within 2 years with the 2-year cumulative incidence of local regrowth being 25.2% (97% within the bowel

wall).[121] Of the 213 patients with local recurrence, details regarding salvage surgery was available in 148 with 78% of these patients requiring a TME and the rest having local excision. Five-year disease-specific survival for the entire group was 94%, and 5-year OS was 85%.[121] Some studies have raised concern about increased risk of distant recurrence with the wait-and-watch approach compared with those noted to have pCR with surgery; whether these distant recurrences may have be prevented with surgery is uncertain. Several randomized trials are current underway evaluating this approach in patients with cCR.

Given the concern for radiation related side effects in both the short and long terms, upfront chemotherapy to enable selective use of radiation in those with inadequate response is also being evaluated. This approach is being tested in the ongoing phase II/III Alliance (N0148) trial that is evaluating chemoradiation therapy versus induction FOLFOX in patients with mid–high-lying rectal cancers (NCT01515787).

Adjuvant Therapy for Rectal Cancer

In patients receiving neoadjuvant short-course radiation or chemoradiation without further neoadjuvant systemic chemotherapy, most expert groups and consensus guidelines recommend adjuvant chemotherapy for up to 4 months. Although data from randomized trials comparing adjuvant therapy with observation do not convincingly show a survival benefit, these trials have several limitations. First, a significant proportion of patients (25%–50%) never start adjuvant therapy because of postoperative complications, slow recovery, patient preference, or other factors.[85,86,122] Second, even in those starting adjuvant therapies, there may be a significant delay in initiating therapy. There is also significant debate whether adjuvant chemotherapy may be tailored based on the degree of pathological response. Robust nonrandomized data convincingly show that patients with pCR have a very low risk of recurrence and adjuvant therapy maybe deintensified in these patients to fluoropyrimidine alone. Whether adjuvant therapy may be omitted completely with pCR is uncertain. In patients with poor pathologic response, data show benefit with addition of oxaliplatin. The ADORE (Adjuvant Oxaliplatin in Rectal cancer) trial randomized 321 patients with pathologic stage stage II or III tumors postoperatively (and hence avoiding dropout before initiation of adjuvant therapy) to 5-FU or FOLFOX and showed an improvement in the primary endpoint of 3-year DFS (71.6% vs 62.9% 0.657; 95% CI, 0.434–0.994; $P = .047$).[123] These findings were also supported by a meta-analysis of three randomized trials comparing adjuvant 5-FU with or without oxaliplatin after neoadjuvant chemoradiation with improvement in DFS (HR, 0.85; 95% CI, 0.73–0.99).[124]

In patients treated with TNT and receiving neoadjuvant chemotherapy for at least 4 months, no further adjuvant chemotherapy is recommended.

The MDACC Approach to Nonmetastatic Rectal Cancer

Patients are evaluated with history, including family cancer history, physical examination with a digital rectal examination, inguinal lymph node exam, proctoscopy, and cross0sectional imaging studies of the chest, abdomen (typically CT with contrast) and pelvis. MRI of the pelvis (and EUS as needed) are obtained in all patients as pretreatment staging. The patency of the colonic lumen is evaluated by proctoscopy, flexible sigmoidoscopy, or colonoscopy before starting therapy. Given the limitations with delivery of adjuvant therapy as discussed and robust prospective data showing improvement in both sphincter preservation and DFS with neoadjuvant chemotherapy, our practice patterns have increasingly shifted toward the TNT approach. Treatment decisions are based on risk stratification and made in a multidisciplinary fashion involving radiation, medical, and surgical oncologists; pathologists; radiologists; and gastroenterologists. In patients with rectal cancer deemed low risk (T3N0, mid–high rectum, without EMVI or threatened CRM) neoadjuvant chemotherapy with FOLFOX or CAPOX is offered for 3 months followed by surgery. For patients with low-risk but low-lying tumors wanting sphincter preservation and for those with high-risk features, the TNT approach with chemotherapy for 4 months in addition to radiotherapy is recommended. In these patients, the choices of chemotherapy (FOLFOX, CAPOX, FOLFIRINOX), radiotherapy regimens (long-course chemoradiation vs short-course radiation) and sequencing modalities are made based on the clinical situation and patient preferences while awaiting further data.

In patients receiving neoadjuvant chemoradiation, capecitabine is given as the radiation sensitizer (825 mg/m^2 twice daily, Monday–Friday, on days of radiation therapy only). Bowel exclusion techniques during simulation minimize the small bowel in the field. We conduct a toxicity evaluation every 1 to 2 weeks during radiation to ensure symptom control. Electrolytes, renal function, and hematologic parameters are checked weekly. Topical barrier creams are prescribed for grades 1 to 3 perineal radiation dermatitis. If grade 2 or higher nonhematologic toxicity develops (excluding radiation dermatitis), concurrent chemotherapy is held until resolution, but radiation is continued. After chemoradiation, perianal pain and ulceration, anorexia, and diarrhea typically subside within 2 to 3 weeks.

Approximately 8 to 10 weeks after completion of neoadjuvant therapy, patients undergo repeat evaluation

with physical examination, proctoscopy, MRI of the pelvis, and then surgical resection.

In the adjuvant setting, chemotherapy is offered to those who received radiotherapy alone as neoadjuvant therapy. Patients with stage III rectal cancer and no contraindication to oxaliplatin are advised to receive it as a component of FOLFOX or CAPOX. Patients with a pCR after preoperative 5-FU–based chemoradiation may receive single-agent 5-FU–based adjuvant therapy rather than FOLFOX. The choice of adjuvant therapy may vary based on degree of response to single-agent fluoropyrimidine-based therapy and the patient's underlying comorbidities.

Postoperative Chemoradiation

Patients who have undergone surgery as their initial intervention may require postoperative chemoradiation and systemic therapy when they present to MDACC after surgery. For patients with T3N0M0 or T2N1 disease, radiotherapy is often omitted if the tumor was located in the high pelvis (>10 cm from the anal verge), there is good nodal sampling (>12 lymph nodes), and the radial margin is negative (>2 mm) because pelvic tumor control is excellent without the use of chemoradiation.[125,126] In all other stage II and III rectal cancer cases, local failure is high enough to warrant the use of chemoradiation. In addition, 4 months of systemic therapy with either capecitabine or 5-FU–leucovorin is typically integrated with chemoradiation. Patients at higher risk of distant metastasis often receive chemotherapy first with FOLFOX.

Surveillance for Patients with Rectal Cancer

Follow-up for patients with resected rectal cancer is very similar to that for colon cancer. Patients with a sphincter-preserving procedure also require periodic proctoscopies for local relapses and anastomotic strictures. A rising CEA without other clinical or CT evidence of relapse prompts a pelvic MRI or positron emission tomography (PET)–CT, particularly for local recurrence.

In patients with cCR defined as no apparent residual tumor on endoscopy, MRI and CT after completion of neoadjuvant therapy wishing for a watch-and-wait approach, a thorough discussion of the pros and cons, including the current evidence, is done. Patients are additionally monitored with a proctoscopy every 3 to 4 months for the first 2 years and every 6 months for the next 3 years.

Management of Locally Recurrent Disease

Locally recurrent rectal cancer presents a therapeutic challenge for which salvage surgery may not be feasible. The collective experience at MDACC suggests that systemic therapy has limited activity against locally recurrent disease with few durable responses. Palliative radiation is delivered as external-beam radiotherapy or brachytherapy catheters. Aggressive use of narcotics and intrathecal analgesics or neurolytic blocks is used for pain control concurrently with aggressive bowel management.

For the subset of patients who may be surgical candidates, treatment planning is vetted in our multidisciplinary conference. In our experience, pelvic MRI is superior to CT for distinguishing posttreatment changes from viable tumor while identify resectable disease. Biopsy confirmation of recurrence is always recommended; EUS has not been particularly useful with locally recurrent rectal tumors.

Before salvage surgery, additional chemoradiation may be considered using a hypofractionated schedule to a total dose of 39 Gy (if at least 1 year has elapsed since prior pelvic radiation). Radiosensitization with 5-FU or capecitabine is also considered. Approximately 6 to 8 weeks after completion of chemoradiation, a final decision about surgery is made. In most cases, the operative strategy may also include intraoperative radiotherapy or insertion of brachytherapy catheters for high-dose afterloading. Postoperative chemotherapy after aggressive preoperative chemoradiation is at the discretion of the treating physician. However, there is broad agreement that surgery for locally recurrent disease is not indicated in patients with unresectable metastatic disease, given the overall poor prognosis, significant morbidity, and prolonged recovery associated with this complex pelvic surgery.

SYSTEMIC THERAPY FOR METASTATIC DISEASE

Since the late 1950s, systemic chemotherapy with 5-FU has been the mainstay of palliative treatment for patients with metastatic disease. During the ensuing decades, a variety of 5-FU schedules have been used, including bolus injections administered either weekly (Roswell Park regimen) or daily for 5 days (Mayo regimen) and continuous infusion given via central catheter and portable pump. When 5-FU is administered as a bolus injection, leucovorin is often added to enhance binding of 5-FU to its target, thymidylate synthase. After a long period of uncertainty regarding the optimal dose and schedule of 5-FU with leucovorin, infusional 5-FU regimens have been recognized as superior to bolus regimens.

Oncologists now have access to several drugs with activity in the first-, second-, and third-line settings. It is important for oncologists to have a general understanding of these drugs and their roles in the treatment of metastatic disease.

Capecitabine: An Orally Bioavailable Fluoropyrimidine

Capecitabine is an oral fluoropyrimidine that is converted to 5-FU primarily in tumor tissues by the enzyme, thymidine phosphorylase (TP). Concentrations of TP are relatively higher in tumor tissue than normal tissue, which accounts for the preferential intratumoral release of 5-FU. Two large phase III trials compared capecitabine with a bolus regimen of 5-FU, and the results were subsequently pooled.[127,128] The response rates were superior with capecitabine, and the median survival was equivalent, with less neutropenia and mucositis among patients receiving capecitabine.

In patients with contraindications to combination chemotherapy, capecitabine monotherapy is a reasonable alternative to 5-FU and leucovorin in the metastatic setting. However, caution should be taken when prescribing capecitabine to patients with end-stage renal disease, and capecitabine should be held if the creatinine clearance is lower than 30 mL/min. Furthermore, it is of note that patients in the United States do not tolerate the capecitabine doses used in Asian and European trials, perhaps because of the higher nutritional folate intake in the United States.[129] Thus, we commonly dose-reduce capecitabine by about 20% without any apparent decrease in efficacy but with greatly improved tolerance.

IRINOTECAN

Irinotecan, an inhibitor of topoisomerase I, is a component of frontline therapy in patients with metastatic CRC (mCRC). Two large, randomized trials were conducted in the United States and Europe comparing 5-FU and leucovorin with 5-FU, leucovorin, and irinotecan as first-line treatment of patients with mCRC.[130,131] Both studies demonstrated that the response and OS rates for the group treated with triple-drug therapy were superior to those for the group treated with 5-FU and leucovorin. These results prompted the FDA in 2000 to approve the use of these irinotecan-based combinations for first-line treatment of patients with CRC.

Oxaliplatin

Oxaliplatin is a third-generation platinum derivative that has shown additive or synergistic antitumor activity in combination with a variety of antineoplastic agents, including 5-FU; oxaliplatin is ineffective without 5-FU.[132] In 2000, de Gramont and colleagues[133] reported the results of a phase III trial of infusional 5-FU–leucovorin and oxaliplatin (FOLFOX4) versus 5-FU–leucovorin alone as first-line treatment in patients with advanced CRC. PFS and response rates were significantly better for the FOLFOX arm compared with the 5-FU–leucovorin arm (9.0 months and 50% vs 6.2 months and 22%, respectively). Even though the FOLFOX arm experienced more grade 3 and 4 neutropenia, diarrhea, and neurosensory toxicity, this did not impair quality of life.

Goldberg and associates[134] subsequently compared the activity and toxicity of three different drug combinations in untreated patients with mCRC. A total of 795 patients were randomized to receive IFL, FOLFOX, or IROX (irinotecan + oxaliplatin). The results favored FOLFOX for all endpoints, including time to progression, response rate, and OS. Median survival times in the FOLFOX, IFL, and IROX groups were 19.5, 15.0, and 17.4 months, respectively.

Tournigand and colleagues[135] answered the important question of how to sequence these regimens. They reported the results of a phase III study investigating 5-FU, leucovorin, and irinotecan (FOLFIRI) followed by FOLFOX6 (Table 32–3) on progression of disease versus the opposite sequence (FOLFOX6 followed by FOLFIRI). The two sequences were equivalent in terms of PFS and OS, although the toxicity profiles were different. The median survival times were 21.5 months in the FOLFIRI-FOLFOX arm ($n = 109$) and 20.6 months in the FOLFOX-FOLFIRI arm ($n = 111$) ($P = .99$).

TABLE 32–3 Summary of Common Chemotherapy Regimens Used at MD Anderson Cancer Center for Patients with Colorectal Cancer

Adjuvant Chemotherapy
Capecitabine: 1000 mg/m^2 by mouth twice daily on days 1–14 (3-week cycle, total eight cycles)
5-FL–leucovorin: leucovorin 400 mg/m^2 IV on day 1; 5-FU 400 mg/m^2 IV bolus on day 1 followed by 5-FU 2400 mg/m^2 IV continuous infusion over 46 hours (2-week cycle, total 12 cycles)
Modified FOLFOX 6: oxaliplatin 85 mg/m^2 IV on day 1; leucovorin 400 mg/m^2 IV on day 1; 5-FU 400 mg/m^2 IV bolus on day 1 followed by 5-FU 2400 mg/m^2 IV continuous infusion over 46 hours (2-week cycle, total 12 cycles)
CAPOX: oxaliplatin 130 mg/m^2 on day 1; capecitabine 850 mg/m^2 by mouth twice a day on days 1–14 (3-week cycle, total eight cycles)
Therapy for Metastatic Disease
Capecitabine: 1000 mg/m^2 by mouth twice a day on days 1–14 (3-week cycle)
• With or without bevacizumab (7.5 mg/kg IV every 3 weeks)

(*Continued*)

TABLE 32–3 Summary of Common Chemotherapy Regimens Used at MD Anderson Cancer Center for Patients with Colorectal Cancer *(Cont.)*

5-Fluorouracil–leucovorin: leucovorin 400 mg/m^2 IV on day 1; 5-FU 400 mg/m^2 IV bolus on day 1 followed by 5-FU 2400 mg/m^2 IV continuous infusion over 46 hours (2-week cycle)
• With or without bevacizumab (5 mg/kg IV every 2 weeks)
Modified FOLFOX 6: oxaliplatin 85 mg/m^2 IV on day 1; leucovorin 400 mg/m^2 IV on day 1; 5-FU 400 mg/m^2 IV bolus on day 1 followed by 5-FU 2400 mg/m^2 IV continuous infusion over 46 hours (2-week cycle)
• With or without bevacizumab (5 mg/kg IV every 2 weeks)
• With or without cetuximab[a] (400 mg/m^2 IV first infusion followed by 250 mg/m2 IV weekly or 500 mg/m2 IV every 2 weeks) or panitumumaba (6 mg/kg IV every 2 weeks)
CAPOX: oxaliplatin 130 mg/m^2 on day 1; capecitabine 850 mg/m^2 by mouth twice a day on days 1–14 (3-week cycle)
• With or without bevacizumab (7.5 mg/kg IV every 3 weeks)
• With or without cetuximaba (400 mg/m2 IV first infusion followed by 250 mg/m2 IV weekly or 500 mg/m2 IV every 2 weeks) or panitumumab[a] (9 mg/kg IV every 3 weeks)
Modified FOLFIRI: irinotecan 180 mg/m^2 IV on day 1; leucovorin 400 mg/m^2 IV on day 1; 5-FU 400 mg/m^2 IV bolus on day 1 followed by 5-FU 2400 mg/m^2 IV continuous infusion over 46 hours (2-week cycle)
• With or without bevacizumab (5 mg/kg IV every 2 weeks)
• With or without cetuximaba (400 mg/m^2 IV first infusion followed by 250 mg/m^2 IV weekly) or panitumumab[a] (6 mg/kg IV every 2 weeks)
Irinotecan: 180 mg/m^2 IV on day 1 (2-week cycle) or 300–350 mg/m^2 IV on day 1 (3-week cycle)
Cetuximab[a]–irinotecan
• Cetuximab[a] 400 mg/m^2 IV first infusion followed by 250 mg/m^2 IV weekly plus irinotecan 350 mg/m^2 IV on day 1 (3-week cycle) or 180 mg/m^2 IV on day 1 (2-week cycle)
• Cetuximaba 500 mg/m^2 IV every 2 weeks ± irinotecan 180 mg/m^2 IV every 2 weeks
Panitumumab[a]: 6 mg/kg IV every 2 weeks or 9 mg/kg IV every 3 weeks
FOLFOXIRI: oxaliplatin 85 mg/m^2 IV on day 1; irinotecan 165 mg/m^2 IV on day 1; leucovorin 400 mg/m^2 IV on day 1; followed by 5-FU 2400 mg/m^2 IV continuous infusion over 46 hours (2-week cycle)
• With or without bevacizumab (5 mg/kg IV every 2 weeks)
• With or without cetuximab[a] (400 mg/m^2 IV first infusion followed by 250 mg/m^2 IV weekly or 500 mg/m^2 IV every 2 weeks) or panitumumab[a] (6 mg/kg IV every 2 weeks)
Trifluridine–tipiracil: trifluridine–tipiracil 35 mg/m^2 (trifluridine component) orally twice daily on days 1–5 *and 8–12 (28-day cycle)*
Regorafenib: regorafenib 160 mg once daily for 21 days; then 1 week off (28 day cycle). Recommend starting with 80 to 120 mg once daily for 21 days; then 1 week off for first cycle to determine tolerability
Pembrolizumab[b]: pembrolizumab 2 mg/kg IV every 3 weeks (21-day cycle); or pembrolizumab 200 mg IV every 3 weeks (21-day cycle); or pembrolizumab 400 mg IV every 6 weeks (6-week cycle)
Nivolumab[b]: nivolumab 3 mg/kg IV on day 1 every 14 days (14-day cycles); or nivolumab 240 mg IV on day 1 (14-day cycle); or nivolumab 480 mg IV on day 1 every 28 days (28-day cycle)
Nivolumab–ipilimumab[b]: nivolumab 3mg/kg (30-minute IV infusion) on day 1; ipilimumab 1 mg/mg (30-minute IV infusion) on day 1 (21-day cycle) for four doses; then nivolumab 3 mg/kg IV every 14 days or nivolumab 240 mg IV every 14 days or nivolumab 480 mg IV every 28 days
Cetuximab–encorafenib[c]: cetuximab 400 mg/m^2 IV first infusion followed by 250 mg/m^2 IV weekly; encorafenib 300 mf PO daily; binimetinib 45 mg PO twice daily (28-day cycle)
Pertuzumab–trastuzumab[d]: pertuzumab 840 mg IV loading dose cycle 1 day 1, with subsequent doses 420 mg IV every 21 days; trastuzumab 8 mg/kg IV loading dose cycle 1 day 1, with subsequent doses 6 mg/kg IV every 21 days (21-day cycle)
Larotrectinib[e]: 100 mg PO twice daily (28-day cycle)
Entrectinib[e]: 600 mg PO once daily (28-day cycle)

[a]Cetuximab and panitumumab are indicated only in patients with *RAS* wild-type tumors.
[b]Pembrolizumab, nivolumab, and ipilimumab are only indicated in patients with deficient mismatch repair (dMMR)/microsatellite instability–high tumors.
[c]The combination of cetuximab and encorefenib is only indicated in patients with BRAF V600E mutated tumors.
[d]The combination of pertuzumab and trastuzumab is only indicated for HER2 amplified tumors that are *RAS* and *BRAF* wild type.
[e]Larotrectinib and entrectinib are only Indicated In patients with an NTRK gene fusion.
Concurrent chemotherapy and radiation therapy (rectal cancer):
Continuous infusion of *5-fluorouracil (5-FU)*: 250–300 mg/m^2 IV daily (Monday–Friday on days of radiation therapy only).
Capecitabine: 825 mg/m^2 by mouth twice a day (Monday–Friday on days of radiation therapy only)
FOLFOX, 5-fluorouracil, leucovorin calcium, and oxaliplatin; FOLFIRIIV, 5-FU, leucovorin, irinotecan, oxaliplatin; intravenous; PO, oral; CAPOX, capecitabine and oxaliplatin.

An aggressive approach is the combination of oxaliplatin, irinotecan, and 5-FU–leucovorin (FOLFOXIRI).[136] In the randomized phase III TRIBE study, upfront use of FOLFOXIRI plus bevacizumab resulted in an improvement in RR, PFS, and OS compared with FOLFIRI plus bevacizumab (OS, 29.8 months vs 25.8 months). In the *RAS/RAF* wild-type (WT) population, there was an even greater benefit, with an OS of 37.1 months compared with 25.6 and 13.4 months in the *RAS* MT and *BRAF* MT populations treated with FOLFOXIRI plus bevacizumab, respectively.[137] Concerns about this regimen are largely due to discussion of limited options for second-line therapy if the patient's disease progresses. However, this was disproven in the TRIBE2 trial that evaluated upfront FOLFOXIRI plus bevacizumab followed by the preplanned reintroduction of the same agents after progressive disease. This approach was shown to provide statistically significant, and clinically relevant PFS and OS benefits compared with the preplanned sequential administration of FOLFOX plus bevacizumab and FOLFIRI plus bevacizumab (PFS, 19.1 months vs 16.4 months; $P = .002$; and OS, 27.6 months vs 22.6 months; $P = .033$, respectively).[138]

Regorafenib

Regorafenib, a small-molecule inhibitor of multiple kinases that are involved with various processes, including tumor growth and angiogenesis, has documented efficacy in a salvage therapy setting in advanced CRC. The phase III CORRECT trial randomized 760 patients who progressed on standard therapy to best supportive care (BSC) or regorafenib. The trial met its primary endpoint of OS (6.4 months vs 5.0 months for regorafenib and placebo, respectively; HR, 0.77; $P = .005$). PFS was also significantly but modestly improved (1.9 months vs 1.7 months; $P < .001$).[139] Unfortunately, although response rates to regorafenib are low, adverse events are high. The most common severe toxicities observed with regorafenib were hand-foot skin reaction, fatigue, diarrhea, and hypertension. In a meta-analysis of four studies, the incidence of all-grade hand-foot skin reactions in 500 patients with CRC was 46.6%.[140] To address this, the phase II ReDOS trial investigated the use of an alternative dosing schedule to reduce the toxicities related to regorafenib treatment. Rates of several of the most common adverse events were lower among the dose-escalation group compared with the standard dosing group. Based on these results, the dose-escalation strategy is an appropriate alternative approach for regorafenib dosing.[141]

Trifluridine–Tipiracil (TAS-102)

Trifluridine–tipiracil is an oral combination drug consisting of a cytotoxic thymidine analog trifluridine and a TP inhibitor, tipiracil hydrochloride, which prevents the degradation of trifluridine. Results of the double-blind, randomized, controlled, international phase III RECOURSE trial were published in 2015 followed shortly thereafter by approval of TAS-102 by the FDA.[142] The primary endpoint of OS was met in 800 patients receiving TAS-102 in the third-line setting versus placebo (7.1 months vs 5.3 months, respectively; $P < .001$). Improvement, albeit slight, was also seen in the secondary endpoint of PFS (2.0 months vs 1.7 months; HR, 0.48; $P < .001$). The most common adverse events were grade 3/4 neutropenia (38%) and leukopenia (21%).

Thus, TAS-102 and regorafenib, are reasonable salvage therapies, FDA approved in mCRC to be used after failure of 5-FU, oxaliplatin, irinotecan, VEGF inhibitor, and an anti-EGFR monoclonal antibody (mAb) in *RAS* WT.

Common chemotherapy regimens for both colon and rectal carcinoma are listed in Table 32–3.

Monoclonal Antibodies

Cetuximab

Cetuximab is a chimeric immunoglobulin G1 (IgG1) mAb directed against the epidermal growth factor receptor (*EGFR*). Compared with BSC in a treatment-refractory patient population, single-agent cetuximab resulted in superior OS (6.1 months vs 4.6 months) and quality of life. Two phase III randomized trials subsequently confirmed the efficacy of cetuximab in combination with irinotecan in previously treated patients, with response rates of approximately 20%.[143,144] Improvement in OS versus BSC has since been validated in heavily pretreated patients.[145]

However, anti-EGFR mAbs do not benefit patients with mCRC with oncogenic *RAS* mutations.[146,147] *KRAS* mutations initially identified in codons 12 and 13 of exon 2 result in constitutive activation of the RAS-RAF-MEK-ERK (mitogen-activated protein kinase [MAPK]) pathway.[148–150] Activating mutations in *KRAS* are detected in approximately 40% of mCRC cases[151,152] with good concordance between primary tumors and distant metastases.[153] Expanded *RAS* mutations in *KRAS* exon 3 or 4 or in *NRAS* exon 2, 3, or 4 have also been noted to predict a lack of benefit from anti-EGFR mAbs, increasing the prevalence of all innate *RAS* mutations to 50% to 55%.[148,154,155]

The phase III trial CRYSTAL randomized nearly 1200 patients with untreated mCRC to FOLFIRI with or without cetuximab. Median PFS (8.9 months vs 8.0 months) and RR (47% vs 39%) were modestly improved with cetuximab. Unplanned retrospective analyses showed that clinical benefit was limited to patients with *KRAS* WT tumors. In this group of patients, cetuximab improved the RR from 43% to 59%, median PFS from 8.7

months to 9.9 months, and OS from 20.0 months to 23.5 months.[149,156] In addition, OPUS, a randomized phase II trial in treatment-naïve patients, compared FOLFOX4 plus cetuximab with FOLFOX4 alone and showed improvement in response rate and PFS with cetuximab. Again, analysis revealed that this benefit was restricted to patients without *KRAS* mutations.[157]

The most significant toxicities associated with cetuximab include diarrhea, hypomagnesemia, hypocalcemia, and an acneiform rash. Traditionally, the risk of an allergic hypersensitivity reaction is reported to be less than 5%. However, life-threatening anaphylactic hypersensitivity reactions have been reported in up to 30% of patients residing in select geographic locations.[158]

Cetuximab is currently FDA approved with FOLFIRI in first line, in combination with irinotecan after progression of disease (although it is routinely used in combination with FOLFOX as well), as monotherapy for patients with mCRC who are intolerant of irinotecan-based regimens, and in combination with irinotecan after progression of disease.

Panitumumab

Panitumumab is a fully human IgG2 mAb directed against *EGFR*. In a randomized phase III trial, patients with refractory metastatic disease received BSC with or without panitumumab. The RR and SD rate with panitumumab were 10% and 27% compared with 0% and 10%, respectively, with BSC alone. An OS difference could not be demonstrated in this trial, likely because of crossover from the BSC group.[159] Subsequent analysis revealed that only patients with *KRAS* WT tumors benefited from panitumumab.[146] Although cetuximab and panitumumab have not been compared head to head, they appear to have similar efficacy and toxicity in patients. Infusion reactions are uncommon with panitumumab because it is a fully human mAb. A large randomized phase II trial (ASPECCT) (n = 1010) found that panitumumab is noninferior to cetuximab (Z score, -3.19; P = .0007) and that these agents provide similar OS benefit in patients with chemotherapy-refractory disease (10.0 months vs 10.4 months, respectively). Thus, it is now FDA approved as a single agent for patients failing irinotecan- and oxaliplatin-based chemotherapy. Two phase III trials have also been reported of FOLFOX or FOLFIRI with or without panitumumab for both treatment-naïve and previously treated patients, respectively.[160,161] Both studies reported superior response and PFS for the combination and resulted in approval in combination with chemotherapy in the front- and second-line settings.

Anti-EGFR Antibody Rechallenge

Among patients with mCRC who initially respond to EGFRi, acquired abnormalities eventually develop and result in secondary resistance. Growing use of plasma ctDNA testing has allowed for the noninvasive detection of heterogeneous molecular alterations underlying the evolution of resistance to targeted therapies in advanced CRC.[162,163] Such analyses have uncovered the role of acquired *RAS* mutations in resistance to anti-EGFR mAbs but have also implicated subclonal mutations in the *EGFR* ectodomain in the development of acquired resistance to anti-EGFR therapy.[164]

Several groups have shown that in the absence of continued selective pressure from EGFR inhibition, the prevalence of *RAS* and *EGFR* mutant clones declines with a half-life of approximately 4 months.[165,166] These data are consistent with several prospective trials demonstrating clinical benefit with anti-EGFR rechallenge. In the CRICKET single-arm phase 2 study, patients with tissue-based *RAS* and *BRAF* WT tumors with a PR and PFS of at least 6 months to first-line cetuximab plus irinotecan were studied and found to have RR, SD, and DCR rates of 21%, 32%, and 54%, respectively, to anti-EGFR rechallenge. There was a statistically significant correlation between benefit from the first anti-EGFR therapy and rechallenge.[167] All patients achieving a PR were ctDNA *RAS* WT before rechallenge with EGFRi, and these patients experienced a significantly longer PFS compared with patients with ctDNA *RAS* MT (4 months vs 1.9 months). There are several large-scale clinical trials currently ongoing that will hopefully better inform the rechallenge practice.

Tumor Sidedness

Primary tumor location in mCRC is now considered a clear prognostic and predictive tool to guide management. Right-sided tumors are defined as those that arise in the cecum to the hepatic flexure, and left-sided tumors represent those from the splenic flexure to the rectum. The initial indication that sidedness impacted clinical outcomes were noted in a first-line chemotherapy trial highlighting right-sided tumors exposed to 5-FU–based chemotherapy had worse survival than left-sided tumors, with a difference of at least 5 months.[168] More recently, these findings have been further supported by analysis of two randomized phase III clinical trials using front-line chemotherapy with bevacizumab for treatment-naïve mCRC, AVF2107g and NO16966. Interestingly, right-sided tumors were identified as negative prognostic indictors regardless of mutational status or tumor histology.[169] Furthermore, post-hoc analysis of FIRE-3, PEAK, PRIME, and CRYSTAL all found that OS and PFS benefit from anti-EGFR therapy for *RAS* WT mCRC was limited to left-sided tumors alone.[169–172] To date, CALGB/SWOG 80405 represents the most compelling evidence for predicting the lack of

response to anti-EGFR therapy in relation to tumor sidedness.[173] In this trial, among patients with *RAS* WT tumors treated with chemotherapy and cetuximab, a statistically significant reduction in OS of 13.6 months for right-sided cancers was noted compared with 39.3 months for left-sided cancers ($P = .001$; HR, 0.55). Of note, this stark difference was not appreciated for bevacizumab exposure, consistent with an agnostic impact on survival outcomes between *RAS* WT left-sided versus right-sided tumors ($P = .50$) with anti-VEGF therapy.

because of the retrospective analysis of CALGB 80405 highlighting sidedness as a biomarker of response and selection criteria for EGFR inhibition, both the NCCN and ESMO guidelines support deferring anti-EGFR therapy for patients with *RAS* WT right-sided tumors in the first-line setting. To date, there is no clear consensus on therapy after the front-line setting; however, one trial, CO.17, solidified a lack of benefit with cetuximab compared with best supportive care for refractory *KRAS* mutant tumors. Patients with right-sided tumors had no statistically significant benefit with cetuximab compared with left-sided tumors.[174] Additional studies are needed to determine whether patients with *RAS* WT right-sided tumors can glean any benefit from EGFR inhibition in subsequent lines of therapy.

Bevacizumab

Bevacizumab is a humanized mAb that binds all isoforms of circulating VEGF, thereby inhibiting permeability and angiogenesis mediated by this factor.

In the phase II TREE-2 study, Hochster and colleagues[175] demonstrated the safety and efficacy of bevacizumab in combination with oxaliplatin-based chemotherapy (mFOLFOX6, bFOL, or CAPOX). This trial was not powered for direct comparisons among the three arms, but time to progression (9.9 and 10.3 months, respectively) and OS (26.1 and 24.6 months, respectively) were virtually identical in the mFOLFOX6 and CAPOX arms. In the NO16966 trial, untreated patients were randomized in a 2 × 2 design to FOLFOX4 or CAPOX (noninferiority) with or without bevacizumab.[176] The pooled analysis revealed superior median PFS (9.4 months vs 8.0 months; $P = .002$) in the bevacizumab-containing groups, but a difference in response and OS did not achieve statistical significance. Surprisingly, when PFS was stratified by chemotherapy regimen, the CAPOX regimen fared better. In both of these trials, bevacizumab did not increase the toxicities of chemotherapy. The most significant adverse events associated with bevacizumab were hypertension; proteinuria; thrombosis; and rare instances of bleeding (mostly epistaxis), delayed wound healing, and GI perforation.

The efficacy of bevacizumab as an adjunct to chemotherapy has been validated in the second-line setting as well. ECOG 3200 randomized more than 800 patients with mCRC previously treated with 5-FU and irinotecan (but not oxaliplatin or bevacizumab) to one of three arms: FOLFOX4, bevacizumab, or the combination.[177] The arm receiving bevacizumab as monotherapy was closed to accrual after an interim analysis revealed inferior outcomes compared with the other two arms. Ultimately, the addition of bevacizumab to chemotherapy resulted in improved PFS (median, 7.3 months vs 4.7 months; $P < .0001$) and OS (median, 12.9 months vs 10.8 months; $P = .0011$).

Bevacizumab is now FDA approved for use in combination with fluorouracil-based regimens as a first- or second-line treatment for patients with mCRC.

Two large phase III trials (CAIRO2 and PACCE) examined the efficacy of dual biologic therapy (bevacizumab with anti-EGFR antibody and chemotherapy) in mCRC. Both trials unexpectedly showed worse outcomes with the combination approach.[178,179] In light of these data, dual VEGF and *EGFR* inhibition currently has no role in the treatment of patients with CRC and should not be pursued outside a clinical trial.

Ramucirumab

Ramucirumab, another antiangiogenic agent, is a human mAb that blocks VEGF signaling. In the multicenter, phase III RAISE trial, 1072 patients with mCRC whose disease progressed on first-line therapy with 5-FU, oxaliplatin, and bevacizumab were randomized to FOLFIRI with either ramucirumab or placebo. The primary endpoints of OS were met at 13.3 months and 11.7 months in the ramucirumab and placebo groups, respectively ($P = 0.02$). PFS was also improved slightly with the addition of ramucirumab (5.7 months vs 4.5 months, $P < .0005$).[180]

Aflibercept

Aflibercept is a recombinant fusion protein of portions of human VEGFR 1 and 2 extracellular domains fused to the Fc portion of human IgG1. In the phase III VELOUR trial, 1226 patients with oxaliplatin-refractory mCRC were randomly assigned to aflibercept or placebo plus FOLFIRI. Median OS, the primary endpoint was significantly longer in patients treated with aflibercept irrespective of prior bevacizumab exposure (13.5 months vs 12.1 months).[181]

Considering the results of the RAISE and VELOUR trials, ramucirumab or aflibercept are second-line treatment options in combination with FOLFIRI or irinotecan after progression on therapy not containing irinotecan and are FDA approved for this indication.

Biomarkers and Targeted Therapy for Colorectal Cancer Management

Microsatellite Instability–High Metastatic Colorectal Cancer

Deficient mismatch repair (dMMR) or MSI-H account for only 4% to 5% of all patients with mCRC but represent a unique cohort with a distinct prognosis and treatment option in the form of immunotherapy (Table 32–4).[182]

Considering the hypermutated phenotype of dMMR tumors, the use of checkpoint inhibitors has offered an exciting new treatment strategy for patients with advanced CRC. Targeting programmed death ligand 1 (PD-L1) on tumor cells or programmed cell death protein 1 (PD-1) on T-cells has dramatically impacted patient outcomes. Pembrolizumab and nivolumab are two IgG4 mAbs that target PD-1, both FDA approved for patients with MSI-H mCRC after demonstrating durable clinical activity. The CheckMate-142 study investigated the use of nivolumab alone or in combination with ipilimumab, a fully human IgG1 mAb that targets cytotoxic T-cell lymphocyte antigen-4 (CTLA-4). The overall response rate (ORR) was 31.3% with nearly 70% of patients achieving disease control at 12 weeks and a median OS of 73% at 1 year for the monotherapy arm.[183] In the doublet arm, although grade 3 and 4 treatment-related adverse events were increased to 32%, the ORR was 55% with a disease-control rate of 80% and a 1-year OS of 85%.[184] Single-agent data for pembrolizumab was first reported in a landmark phase II study investigating its efficacy among 41 patients with advanced CRC with or without mismatch-repair deficiency.[182] Both immune-related ORR and PFS were noted to be 40% and 78%, respectively, among patients with dMMR mCRC compared with 0% and 11% for those with pMMR mCRC. At the time of the report, the median PFS and OS were not reached for the dMMR cohort and were 2.2 and 5.0 months for the pMMR cohort, respectively.

Based on this data, MSI status is a definitive predictive biomarker for response to immune checkpoint blockade (Figs. 32–4 and 32–5). NCCN has included single-agent pembrolizumab, nivolumab, or nivolumab plus ipilimumab as viable treatment options for patients with dMMR mCRC in a second- or third-line setting as well as those deemed "not appropriate for intensive therapy."[58]

Of note, the randomized open-label international phase III KEYNOTE-177 trial comparing the anti–PD-1 antibody pembrolizumab with investigator's choice standard chemotherapy in combination with biologic therapy (anti-EGFR or anti-VEGF) for 307 patients with treatment-naïve MSI-H mCRC has been presented.[185] The study met its primary endpoint of PFS with a statistically significant improvement to 16.5 months with pembrolizumab compared with 8.2 months with chemotherapy (HR, 0.60; P = .0002). ORR was also improved to 43.8% with the pembrolizumab arm compared with 33.1% with chemotherapy (P = .0275). OS analysis is pending. Based on these results, the FDA has now approved pembrolizumab for patients with unresectable or metastatic MSI-H/dMMR CRC as first-line treatment.

TABLE 32–4 Prognostic and Predictive Biomarkers in Metastatic Colorectal Cancer

Biomarker	Prognostic	Predictive
dMMR/MSI-H	+	+
Tumor sidedness	+	+ (for left-sided RAS WT)
RAS^{WT}	+	+
RAS $_{mutant}$	-	+
BRAF^{V600E}	+	+
HER2 amplification	-	+
NTRK fusions	Unknown	+
Atypical non-*V600 BRAF*	Unknown	Unknown
POLE	Unknown	Likely

dMMR, deficient mismatch repair; MSI-H, microsatellite instability–high; WT, wild type.

BRAF^{V600E} Mutation

BRAF is a serine threonine kinase that is downstream of RAS in the MAPK pathway and is predominantly mutually exclusive from concurrent *RAS* mutations. The most common BRAF mutation occurs at codon 600 with a valine to glutamic acid change (c.1799T>A or p.V600E) producing a constitutively active protein. In clinical practice, approximately 7% to 14% of all patients with mCRC carry a *BRAF*^{V600E} mutation, and this portends a poor prognosis.[186] Patients with *BRAF*^{V600E} mCRC have a distinct clinical presentation accompanied with hallmark pathologic features that include older women, right-sided T4 tumors, high-grade mucinous histology, sporadic MSI-H phenotype, and predominantly distal nodal involvement with peritoneal disease.[187]

BRAF^{V600E} mCRC is associated with tumorigenesis via the serrated/methylated pathway traditionally through a serrated adenoma precursor. This results in a hypermethylated phenotype with subsequent inactivation of MLH1 yielding sporadic MSI-H/dMMR.[188] Therefore, it is critical to be aware of the MMR status of all patients with *BRAF*^{V600E} because of can have clear clinical implications regarding sequencing of their cancer therapy. Additionally, BRAF mutational status

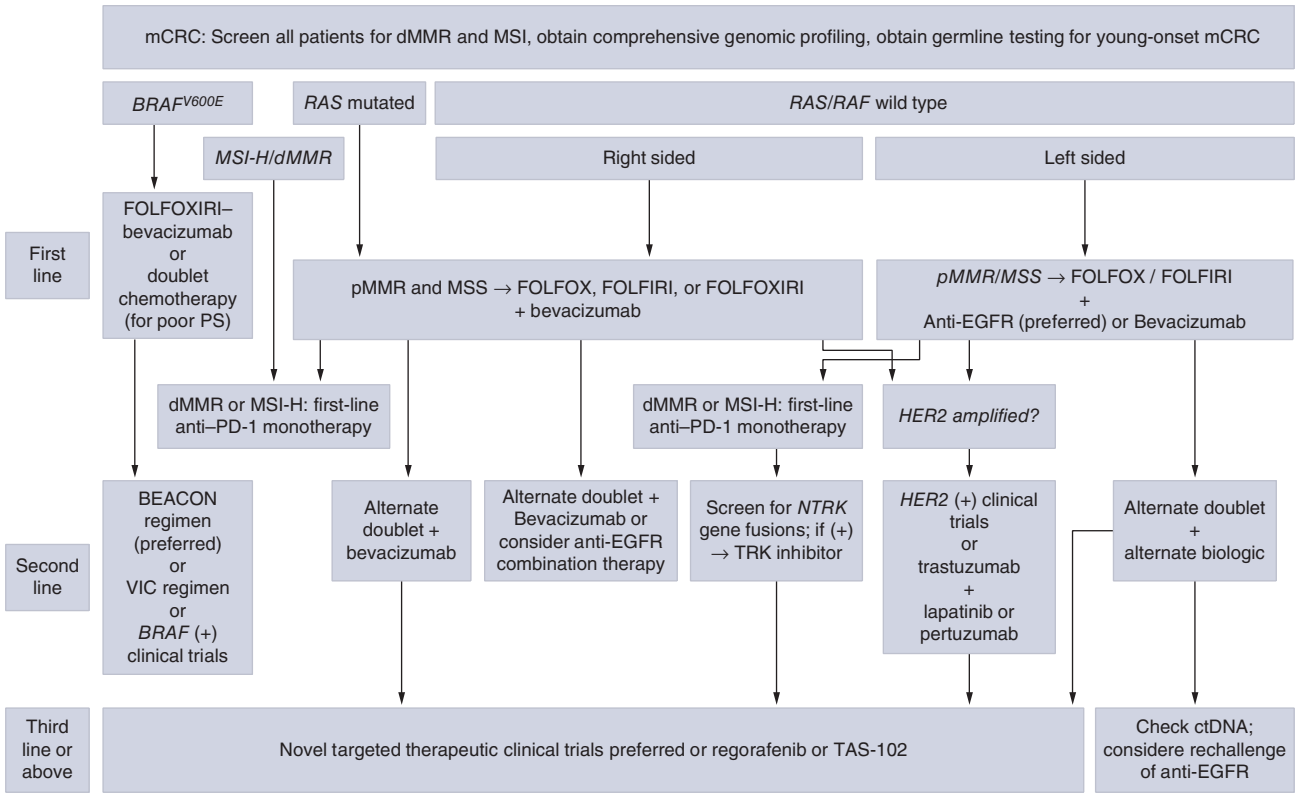


FIGURE 32–4 Biomarker-based decision algorithm for systemic therapy in metastatic colorectal cancer. BEACON; ctDNA, circulating tumor DNA; dMMR, deficient mismatch repair; EGFR, epidermal growth factor receptor; FOLFIRI, ????; FOLFOX, 5-fluorouracil, leucovorin calcium, and oxaliplatin; FOLFOXIRI, ????; mCRC, metastatic colorectal cancer; MSI, microsatellite instability; MSI-H, microsatellite instability–high; PD-1, programmed cell death protein; pMMR, proficient mismatch repair; PS, performance status; TAS-102, trifluridine–tipiracil; VIC, vemurafenib, irinotecan, cetuximab.

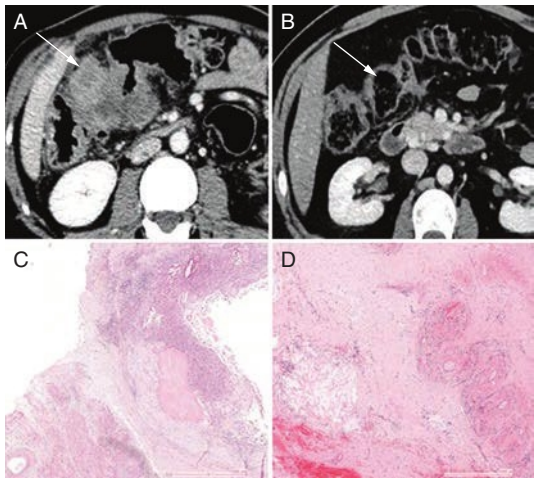


FIGURE 32–5 Radiographic and pathologic response of a microsatellite instability–high colon tumor treated with immunotherapy. **A.** Pretreatment computed tomography (CT) image of the abdomen with arrow depicting a bulky right colon mass (*arrow*). **B.** CT image obtained after 26 months of therapy with ipilimumab and nivolumab demonstrating complete radiographic resolution of the colonic tumor (*arrow*). **C.** Photomicrograph of a right hemicolectomy specimen resected after immunotherapy. The normal muscularis propria bundles are interrupted by fibroelastic tissue containing areas of eosinophilic necrosis, as well as a polymorphic inflammatory infiltrate including cholesterol clefts surrounded by giant resorptive cells (×25 magnification). **D.** The fibrous scar contained many vessels, some with associated thrombosis. Acellular mucin was also visible. (Reproduced with permission from Ludford K, Cohen R, Svrcek M, et al: Pathological Tumor Response Following Immune Checkpoint Blockade for Deficient Mismatch Repair Advanced Colorectal Cancer, *J Natl Cancer Inst* 2021 Feb 1;113(2):208-211.)

remains a prognostic factor in terms of OS in both the early-stage and advanced settings.[189] In the metastatic setting, patients with a *BRAF*^{V600E} mutation are refractory to traditional chemotherapy with an OS of only 10 to 12 months.[186,190]

Considering this, initial therapeutic decisions are paramount for patients presenting with metastatic disease. There are data to support the use of triplet chemotherapy in combination with bevacizumab for *BRAF*^{V600E} mCRC based on the TRIBE study, which compared FOLFOXIRI–bevacizumab versus FOLFIRI–bevacizumab for treatment-naïve patients with mCRC.[137] In this study, the primary endpoint of PFS was met with an improvement of 2.4 months for all patients who received the triplet regimen compared with doublet. Specifically regarding *BRAF*,^{V600E} 28 patients were included in this trial of which 16 were randomized to the triplet arm. Subgroup analysis revealed that the triplet regimen resulted in improvement of OS to 19 months compared with 10.7 months with the doublet regimen for *BRAF*^{V600E} patients. Therefore, in the first-line setting for *BRAF*^{V600E} mCRC patients with adequate performance status, FOLFOXIRI in addition to bevacizumab is a reasonable treatment choice. Of note, in this same study, the RAS/RAF WT cohort that received triplet therapy had a median OS of nearly 42 months, highlighting the innate aggressiveness of *BRAF*^{V600E} mCRC.

In addition to its underlying resistance to standard chemotherapy, the use of anti-EGFR therapy for *BRAF*^{V600E} mCRC is no longer recommended as monotherapy or in combination with chemotherapy because of a lack of benefit. This is based on the collective assessment of multiple studies because individual studies were limited by retrospective nature and small numbers.[191] A meta-analysis of nine phase III and 1 phase II trial (six first-line studies, two second-line studies, and two chemotherapy-refractory studies) evaluated 463 *BRAF*^{V600E} patients to address the impact of EGFR mAbs. This revealed that when anti-EGFR therapy was added to chemotherapy or best supportive care, there was no improvement in PFS, OS, or response rate compared with control regimens.[192] Based on these available data, NCCN, ESMO, and ESMO Asia all recommend the use of EGFR antibodies exclusively for RAS/BRAF WT mCRC patients.

In light of the limitations of chemotherapy and EGFR inhibition for *BRAF*^{V600E} mCRC, the need to develop effective targeted therapies against the mutated protein itself was clear. Unfortunately, although exciting results for *BRAF*^{V600E} mutant metastatic melanoma was achieved with BRAF inhibition, this success was not realized with either vemurafenib or encorafenib in early-phase studies for mCRC, with response rates of 5% and 0%, respectively.[193] Distinct from melanoma, reactivation of EGFR signaling is the most prominent mechanism of resistance in mCRC after single-agent BRAF inhibition supporting the development of rational combination therapies.[194,195] Initial clinical studies exploring the efficacy of BRAF and EGFR targeted therapies revealed disease response in 52% and 67% of treatment-refractory patients.[196,197] Most notably, when this dual targeted approach was combined with chemotherapy (vemurafenib, irinotecan, cetuximab) in the SWOG 1406 study, superior PFS (4.4 months vs 2.0 months) and ORR (16% vs 4%) were achieved among patients exposed to the three-drug combination arm compared with those who received irinotecan and cetuximab alone, supporting its initial insertion into treatment guidelines.[198,199]

MEK is a downstream effector of BRAF, and initial efforts exploring dual BRAF and MEK inhibition reported modest efficacy with response rates of 12% and one complete response (CR) in a cohort of 43 treated patients.[200] The first randomized phase III trial for previously treated *BRAF*^{V600E} mCRC, known as the BEACON CRC study, has been completed and published with updated survival data reported.[201] This pivotal trial evaluated the efficacy of a BRAF inhibitor encorafenib plus cetuximab with or without the MEK inhibitor binimetinib compared the control arm of irinotecan–FOLFIRI plus cetuximab. Initial safety lead-in data reported an ORR of 48% with good tolerability among 29 patients who received the triplet regimen.[202] Interestingly, updated survival data revealed that the doublet regimen (encorafenib–cetuximab) was no less efficacious than the triplet regimen. The doublet arm revealed an improved median OS of 8.4 months compared with 5.4 months for the control arm (HR, 0.60; P = .0003) as well as an improved median PFS of 4.2 months compared with 1.5 months for control (HR, 0.40; P <.0001). Additionally, ORR was noted to be 20% for the doublet arm compared with 2% for the control arm (P <.0001). Based on these data, FDA approval was granted for the doublet regimen on April 8, 2020. Considering these data, the NCCN has recommended the BEACON regimen of encorafenib in combination with cetuximab for previously treated patients with *BRAF*^{V600E} mCRC, reflecting the first time a completely targeted therapeutic approach is available for these high-risk patients.

HER2 Amplification

Human epidermal growth factor receptor (HER2) is a member of the EGFR receptor family and aberrant signaling is known to occur via genomic amplifications promoting upregulation of phosphoinositide 3-kinase (PI3K) and MAPK pathways. In CRC, *HER2* amplification is noted in 3% to 5% of patients, mutually exclusive from *RAS/RAF* mutations and may be associated with de novo resistance to EGFR mAbs. In breast

cancer, HER2 amplifications occur at an increased frequency and has been a focus of therapeutic targeting via mAbs trastuzumab and pertuzumab. Serving as a precedent, this approach was pursued in CRC trials with success. The HERACLES trial accrued patients with CRC with HER2 positivity defined as 3+ HER2 score in greater than 50% of tumor cells by immunohistochemistry (IHC) or with 2+ HER2 score and a HER2:CEP17 ratio greater than 2 in more than 50% of cells by fluorescence in situ hybridization (FISH). In this study, trastuzumab in combination with lapatinib (an oral dual HER2–EGFR kinase inhibitor) was used to treat 27 patients with refractory HER2 mCRC. Nearly 30% of patients had an objective response with 1 patient developing a CR.[203] In the phase II MyPathway study, 57 refractory HER2-amplified patients with mCRC were treated with a combination dual-HER2 targeted approach of pertuzumab and trastuzumab, revealing a 32% ORR and 1 patient with a CR.[204] Considering these two positive landmark studies, the NCCN has added HER2 targeted therapy with trastuzumab and lapatinib or trastuzumab and pertuzumab as viable options for patients with refractory HER2-amplified mCRC. Based on early reports of HER2 amplification representing a negative predictive biomarker for EGFR mAbs, we await results from the ongoing phase II SWOG 1613 study (NCT03365882) evaluating patients with chemotherapy-refractory, anti-EGFR-naïve, HER2-amplified, RAS/RAF WT mCRC randomizing to trastuzumab and pertuzumab versus cetuximab and irinotecan.

The DESTINY-CRC01 trial evaluated trastuzumab deruxtecan (T-DXd), an antibody–drug conjugate consisting of an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase I inhibitor, in 78 patients with previously treated unresectable or mCRC that was HER2 expressing and *RAS/BRAF* WT mCRC with a primary endpoint of RR. Patients with HER2-positive with IHC scoring 3+ or IHC 2+/in situ hybridization+ had RR of 45.3% and stable disease in another 37.7%. Median PFS was 6.9 months in cohort A, and median OS was not reached. Of note, interstitial lung disease is an important adverse event with T-DxD noted in 6.4% of patients in this trial.[205]

NTRK Fusions

Neurotrophic receptor tyrosine kinase fusion (NTRK) genes encode for TrkA, TrkB, and TrkC receptor tyrosine kinases that are responsible for baseline function in human neuronal tissue with activation via MAPK and PI3K pathways. Fusions can be aberrant resulting in oncogenic addiction with a rare prevalence of 0.2% to 2.4% of all CRC with data suggesting higher yield (approaching 3%) in the MSI-H subpopulation.[206] In a landmark study, 55 adult and pediatric patients with NTRK fusions achieved an ORR of 75% with 55% of patients remaining progression-free at 1 year. Among three patients enrolled with CRC, two achieved an objective response.[207] These data have resulted in FDA accelerated tissue agnostic approval to use larotrectinib for all patients with refractory solid tumors and an NTRK fusion. The NCCN has since recommended testing for NTRK gene fusions in mCRC and supports the administration of larotrectinib for this rare cohort of patients.

Evolving Biomarkers of Interest in Metastatic Colorectal Cancer

BRAF$^{non\text{–}V600}$ Mutation

Atypical, non-V600 BRAF mutations are an increasingly recognized molecular subset, representing nearly 2.2% of all patients with mCRC.[208] Unlike *BRAF*,^{V600E} patients with atypical BRAF mCRC have a distinct clinicopathologic profile with most patients having microsatellite stable (MSS) disease, left-sided primary tumors, lower grade histology, and nonperitoneal disease and are commonly co-mutated with RAS. Patients with atypical BRAF mCRC have been reported to have an improved median OS of 60.7 months compared with 11.7 months for those with traditional *BRAF*^{V600E} mutations.[208] Furthermore, preclinical data have described BRAF mutations as unique classes based on their underlying signaling biology. Whereas class I reflects traditional *BRAF*^{V600E} mutations that signal via BRAF monomers with high kinase activity and are non–RAS dependent, atypical non-*V600 BRAF* mutations signal via BRAF dimerization and have been categorized into class II and III subtypes.[209,210] Whereas class II mutations have intermediate to high kinase activity without RAS dependency, class III mutations have low kinase activity and are RAS dependent.

Currently, there are no guidelines to direct the management of patients with atypical *BRAF* mutations with clinical trials recommended after failure of standard cytotoxic chemotherapy. Regarding biologic therapy, although there have been some data to suggest class III mutations may benefit from EGFR inhibition, additional studies have been less convincing.[210,211]

POLE Mutations

The *POLE* gene is located in 12q24.33 and encodes the proofreading exonuclease domain of polymerase epsilon.[212] Somatic mutations in *POLE* are a rare event in CRC, estimated at less than 1%.[213] However, *POLE* mutations are important to highlight considering patients with these mutations have an increased rate of hypermutated tumors with higher neoantigen load, thereby potentially representing a predictive biomarker to immunotherapy in a non–MSI-H setting,

although deciphering between passenger and driver *POLE* mutations is of importance in regards to predicting successful outcomes with checkpoint inhibition.[214,215] Although an evolving area in CRC, there are no guidelines because of limited data to date. However, in clinical practice, identifying the presence or absence of these mutations reflects a potential therapeutic target in the refractory setting.

DECISION MAKING FOR POTENTIAL SURGICAL RESECTION IN PATIENTS WITH METASTATIC COLORECTAL CANCER

Despite therapeutic advances, the estimated 5-year OS for patients unable to be surgically resected remains less than 15%. Although randomized data are limited, retrospectively, surgery has shown 5-year OS in excess of 30%.[216,217] Therefore, multidisciplinary discussions for surgical resection in mCRC should be initiated early if there is a potential for surgery with curative intent. Diagnostic imaging (MRI, PET-CT, and volumetric) has an important role when considering surgical resection. The use, choice, and duration of neoadjuvant chemotherapy should be determined by the treating medical oncologist and surgeon in a multidisciplinary fashion and is typically limited to less than 3 months. Patients who have response or stable disease on neoadjuvant therapy fare better than those with progression.[218] Perioperative and adjuvant therapy (5-FU-based) versus observation has shown a trend toward improved DFS but not OS with hepatic resection.[219–221] This benefit comes at risk of increased postoperative complications from chemotherapy-induced steatohepatitis and hepatic sinusoidal injury.[219,222] Additionally, although bevacizumab is used, we do not use anti-EGFR mAbs in perioperative setting because of inferior OS and PFS seen with the EPOC study.[223] Others challenges are the timing and role of radiotherapy and surgery in patients with metastatic disease in the presence of a primary rectal cancer. At MDACC, our approach is to perform liver metastasectomy first after a course of neoadjuvant chemotherapy followed by chemoradiation and then primary resection.

Follow-up for Patients with Resected Metastatic Colorectal Cancer

After metastasectomy, patients are followed closely with physician visits, CEA level, and diagnostic imaging every 3 to 4 months for the first 3 years, every 6 months for the following 2 years, and annually thereafter. Colonoscopy should continue to be completed every 3 years thereafter (or more frequently based on endoscopic findings). CT (or MRI) is the standard recommended cross-sectional imaging modality. PET-CT may be used for inconclusive findings or if a rising CEA level is noted without measurable disease on CT or MRI. All patients are encouraged to maintain a relationship with a primary care physician for optimal surveillance and health care.

CHALLENGING CLINICAL MANAGEMENT PROBLEMS

Management of the Older Adult Population and Colorectal Cancer

Age-related decline in organ functions and reserves, medical comorbidities, and quality of life considerations often complicate management of older adult patients with CRC. Although essential principles of management in CRC do not vary with age, increased risks of chemotherapy in older adult patients, sometimes perceived and sometimes palpable, may alter the approach to these patients. Despite their underrepresentation in clinical trials, a systematic review of phase III randomized trials (n = 345) for older adult patients (65 years of older) demonstrated that appropriately selected patients can derive equivalent benefits from therapy without a substantial increase in toxicity.[224]

The AVEX study in older adult patients (aged 70 years and older) with untreated mCRC, deemed not to be candidates for aggressive chemotherapy showed that combination bevacizumab and capecitabine was effective (significantly longer median PFS, 9.1 months vs 5.1 months) and well tolerated (treatment-related adverse events of grade 3 or worse, 40% vs 22%) compared with capecitabine alone.[225] Treatment of patients with CRC should be based on a comprehensive assessment of risk–benefit encompassing performance status, comorbidities, and consideration of toxicities rather than age alone. Special emphasis should also be placed on defining molecular subsets such as dMMR mCRC, wherein targeted therapies can provide clinical benefit with lower toxicity compared with conventional cytotoxic chemotherapy.

Malignant Polyps

On occasion, an endoscopically removed polyp may demonstrate invasive adenocarcinoma within a villous or tubular adenoma. Treatment recommendations in this situation should be individualized based on features, including negative margins, no evidence of invasion beyond the submucosa, well- or moderately differentiated adenocarcinoma, and no evidence of lymphatic or vascular invasion. In this setting, the risk of lymph node metastases is low (5%), and follow-up with periodic colonoscopic examinations is reasonable. Unfortunately, retrieval of a sessile or bulky polyp

distorts the depth of invasion or margin status. Furthermore, if pathology demonstrates poor differentiation, invasion into the muscularis, or lymphovascular invasion, surgical resection is advised. In particular, T2 tumors have a 20% likelihood of lymph node metastases, so continued endoscopic follow-up without further surgical intervention is not appropriate.

A malignant polyp in the distal or midrectum is often not amenable to further local staging because endoscopic rectal polypectomy leads to unreliable EUS imaging. Definitive surgical resection should be considered for a resected rectal polyp without clear margins or with adverse pathologic features. If margins are equivocal without muscle invasion, transanal excision may be feasible. Even when laparotomy is considered, a sphincter-preserving procedure is usually possible. Occasionally, an adequately informed patient will refuse surgery, or medical comorbidities preclude surgery as an option. In these special circumstances, nonstandard combined-modality chemoradiation is an alternative to definitive resection.

Nonsurgical Options for Partially Obstructing Tumors

Bowel resection or diverting ostomy may be appropriate, but in patients with poor performance status, nonsurgical management should be considered, which includes expandable metal stents, especially in the rectosigmoid region. Obstructing sites higher in the colon can pose technical barriers to stent insertion. An endoscopically placed colonic decompression tube *proximal* to the obstruction may provide temporary relief. Endoscopic electrosurgical procedures, including argon plasma coagulation, may recanalize the lumen. External-beam radiotherapy may then prevent complete obstruction while alleviating partial obstruction. Patients with impending bowel obstruction are hospitalized for bowel rest, nasogastric tube decompression, and intravenous hydration followed by multidisciplinary evaluation by a gastroenterologist, surgical oncologist, medical oncologist, and radiotherapist.

Multidisciplinary Management of Poor Bowel Function After Curative Treatment

Segmental bowel resections leads to permanent alterations in the frequency and character of bowel movements. Loss of the rectal vault and radiotherapy lead to compromised stool storage and stricture formation at the anastomotic site, and sphincter function may not return to baseline, leading to functional and mechanical dysfunction manifesting as small, frequent bowel movements, with episodic fecal incontinence.

In general, patients are advised that bowel habits may improve for up to 1 year from the time of surgery or up to 6 months after completion of all adjuvant therapy. For patients with more chronic and severe problems (innumerable small bowel movements or fecal incontinence), a multidisciplinary team of surgeons, gastroenterologists, and enterostomal nursing staff recommends a personalized detailed bowel regimen that, with adequate adherence, can improve quality of life and satisfaction with sphincter preservation. On rare occasions, when a sphincter-preserving procedure leads to unbearable dissatisfaction with bowel function, a colostomy or ileostomy may be recommended to improve functional status and quality of life.

MD ANDERSON PRACTICE TIPS

- It is difficult to articulate a general treatment algorithm for patients with metastatic disease, but individual consideration of each patient's case is always considered. Whenever possible, patients with good performance status should be offered therapy as part of a clinical trial.
- Previous analyses have suggested a survival advantage for patients treated with all three active conventional cytotoxic agents (5-FU, irinotecan, and oxaliplatin) during the course of their treatment.[226] Tumor mutation status has become a core part of treatment decision making and should be performed in all patients with metastatic disease. At MDACC, if tumor tissue is unavailable or not amenable for biopsy, ctDNA-based profiling is done to guide therapy.
- Broad principles have emerged as the foundation for therapeutic decisions at MDACC:
- *Asymptomatic patients with metastatic disease are usually offered systemic therapy*. With advent of newer, more efficacious agents, frontline therapy is better tolerated and more likely to be beneficial in asymptomatic patients with good performance status. An exception to this principle is patients with known metastatic disease that is either not evaluable or extremely low volume. In these cases, close follow-up with frequent imaging may be an appropriate initial strategy. Therapy is then initiated when measurable disease is evident or, in the oncologist's judgment, further expectant follow-up is likely to lead to symptoms. Patients with a rising serum CEA level are usually not recommended to undergo treatment in the absence of clear clinical or radiographic evidence of metastatic disease and are followed closely.

MD ANDERSON PRACTICE TIPS

- *The initial treatment for patients with metastatic disease may depend on the timing and residual toxicities of prior adjuvant therapy.* Many patients who develop metastatic disease have received prior adjuvant therapy consisting of oxaliplatin. When patients relapse, they should be considered refractory to this combination if fewer than 12 months have elapsed since the completion of adjuvant therapy. Irinotecan often becomes the primary cytotoxic agent in the treatment of patients with relapsed disease after recent adjuvant therapy.
- *Patients should be treated to maximal benefit or until therapy becomes intolerable.* When patients are receiving systemic therapy for metastatic disease, we usually continue treatment until progression, unacceptable toxicity, or patient's deferment of therapy. Patients receiving oxaliplatin in conjunction with capecitabine or 5-FU, as part of a FOLFOX or CAPOX regimen, may develop unacceptable peripheral neuropathy. In such cases, there is no disadvantage to discontinuation of oxaliplatin, provided maintenance therapy continues. Oxaliplatin may be reintroduced as a component of the regimen when neuropathic symptoms subside or the tumor starts to progress.[227]
- *The benefit of maintenance therapy must be weighed against potential toxicity, and patient preference must be considered as well.* Therefore, a chemotherapy treatment holiday may be appropriate for select patients after prolonged response or stability of disease.
- *The need for local control should always be considered.* Recent experience with combination therapies suggested that the primary tumor may respond well to systemic therapy in some cases, obviating the need for local therapies. As a rule, however, locally recurrent tumor at a site of previous surgery or radiotherapy is not particularly responsive to systemic therapy. Therefore, oncologists must continuously reassess whether local tumor control should take priority over treatment for disseminated disease. Such decisions are usually made with input from a multidisciplinary team.
- *Whenever feasible a multidisciplinary approach should be considered, including role of surgical resection in metastatic disease:* Surgical resection appears to confer a significant survival benefit compared with systemic therapy alone in appropriately selected patients. When possible, a curative-intent metastasectomy (especially liver and lung) should be incorporated in the treatment plan with early discussion between surgical and medical oncologists.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70:7-30.
2. Guinney J, Dienstmann R, Wang X, et al. The consensus molecular subtypes of colorectal cancer. *Nat Med*. 2015;21:1350-1356.
3. Lenz HJ, Ou FS, Venook AP, et al. Impact of consensus molecular subtype on survival in patients with metastatic colorectal cancer: results from CALGB/SWOG 80405 (Alliance). *J Clin Oncol*. 2019;37:1876-1885.
4. Fuchs CS, Giovannucci EL, Colditz GA, et al. Dietary fiber and the risk of colorectal cancer and adenoma in women. *N Engl J Med*. 1999;340:169-176.
5. Moore LL, Bradlee ML, Singer MR, et al. BMI and waist circumference as predictors of lifetime colon cancer risk in Framingham Study adults. *Int J Obes Relat Metab Disord*. 2004;28:559-567.
6. Yuhara H, Steinmaus C, Cohen SE, et al. Is diabetes mellitus an independent risk factor for colon cancer and rectal cancer? *Am J Gastroenterol*. 2011;106:1911-1921; quiz 1922.
7. Stoffel EM, Murphy CC. Epidemiology and mechanisms of the increasing incidence of colon and rectal cancers in young adults. *Gastroenterology*. 2020;158:341-353.
8. Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Screening for colorectal cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2016;315:2564-2575.
9. Towler B, Irwig L, Glasziou P, et al. A systematic review of the effects of screening for colorectal cancer using the faecal occult blood test, hemoccult. *BMJ*. 1998;317:559-565.
10. Lieberman DA, Weiss DG, Bond JH, et al. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. *N Engl J Med*. 2000;343:162-168.
11. Kaminski MF, Bretthauer M, Zauber AG, et al. The NordICC Study: rationale and design of a randomized trial on colonoscopy screening for colorectal cancer. *Endoscopy*. 2012;44:695-702.
12. Bretthauer M, Kaminski MF, Løberg M, et al. Population-based colonoscopy screening for colorectal cancer: a randomized clinical trial. *JAMA Intern Med*. 2016;176:894-902.
13. Lindor NM. Hereditary colorectal cancer: MYH-associated polyposis and other newly identified disorders. *Best Pract Res Clin Gastroenterol*. 2009;23:75-87.
14. Xicola RM, Llor X, Pons E, et al. Performance of different microsatellite marker panels for detection of mismatch repair-deficient colorectal tumors. *J Natl Cancer Inst*. 2007;99:244-252.
15. Giardiello FM, Hamilton SR, Krush AJ, et al. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. *N Engl J Med*. 1993;328:1313-1316.
16. Steinbach G, Lynch PM, Phillips RK, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N Engl J Med*. 2000;342:1946-1952.
17. Burn J, Gerdes AM, Macrae F, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. *Lancet*. 2011;378:2081-2087.
18. Giovannucci E, Egan KM, Hunter DJ, et al. Aspirin and the risk of colorectal cancer in women. *N Engl J Med*. 1995;333:609-614.
19. Giovannucci E, Rimm EB, Stampfer MJ, et al. Aspirin use and the risk for colorectal cancer and adenoma in male health professionals. *Ann Intern Med*. 1994;121:241-246.
20. Sandler RS, Halabi S, Baron JA, et al. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. *N Engl J Med*. 2003;348:883-890.
21. Baron JA, Cole BF, Sandler RS, et al. A randomized trial of aspirin to prevent colorectal adenomas. *N Engl J Med*. 2003;348:891-899.
22. Meyerhardt JA, Shi Q, Fuchs CS, et al. Celecoxib in addition to standard adjuvant therapy with 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX) in stage III colon cancer: results from CALGB/SWOG 80702. *J Clin Oncol*. 2020;38:4003.
23. Luna-Perez P, Rodriguez-Ramirez SE, De la Barrera MG, et al. Multivisceral resection for colon cancer. *J Surg Oncol*. 2002;80:100-104.
24. Lehnert T, Methner M, Pollok A, et al. Multivisceral resection for locally advanced primary colon and rectal cancer: an analysis of prognostic factors in 201 patients. *Ann Surg*. 2002;235:217-225.
25. Rowe VL, Frost DB, Huang S. Extended resection for locally advanced colorectal carcinoma. *Ann Surg Oncol*. 1997;4:131-136.
26. Nakafusa Y, Tanaka T, Tanaka M, et al. Comparison of multivisceral resection and standard operation for locally advanced colorectal cancer: analysis of prognostic factors for short-term and long-term outcome. *Dis Colon Rectum*. 2004;47:2055-2063.
27. Lopez MJ. Multivisceral resections for colorectal cancer. *J Surg Oncol*. 2001;76:1-5.
28. Fleshman J, Sargent DJ, Green E, et al. Laparoscopic colectomy for cancer is not inferior to open surgery based on 5-year data from the COST Study Group trial. *Ann Surg*. 2007;246:655-662; discussion 662-664.
29. Clinical Outcomes of Surgical Therapy Study Group, Nelson H, Sargent DJ, et al. A comparison of laparoscopically assisted and open colectomy for colon cancer. *N Engl J Med*. 2004;350:2050-2059.
30. McCombie AM, Frizelle F, Bagshaw PF, et al. The ALCCaS trial: a randomized controlled trial comparing quality of life following laparoscopic versus open colectomy for colon cancer. *Dis Colon Rectum*. 2018;61:1156-1162.
31. Lacy AM, Delgado S, Castells A, et al. The long-term results of a randomized clinical trial of laparoscopy-assisted versus open surgery for colon cancer. *Ann Surg*. 2008;248:1-7.
32. Kuhry E, Schwenk WF, Gaupset R, et al. Long-term results of laparoscopic colorectal cancer resection. *Cochrane Database Syst Rev*. 2008;CD003432.
33. Jayne DG, Thorpe HC, Copeland J, et al. Five-year follow-up of the Medical Research Council CLASICC trial of laparoscopically assisted versus open surgery for colorectal cancer. *Br J Surg*. 2010;97:1638-1645.
34. Jackson TD, Kaplan GG, Arena G, et al. Laparoscopic versus open resection for colorectal cancer: a metaanalysis of oncologic outcomes. *J Am Coll Surg*. 2007;204:439-446.
35. Zarak A, Castillo A, Kichler K, et al. Robotic versus laparoscopic surgery for colonic disease: a meta-analysis of postoperative variables. *Surg Endosc*. 2015;29:1341-1347.
36. Trastulli S, Cirocchi R, Desiderio J, et al. Robotic versus laparoscopic approach in colonic resections for cancer and benign diseases: systematic review and meta-analysis. *PLoS One*. 2015;10:e0134062.
37. Lim S, Kim JH, Baek SJ, et al. Comparison of perioperative and short-term outcomes between robotic and conventional laparoscopic surgery for colonic cancer: a systematic review and meta-analysis. *Ann Surg Treat Res*. 2016;90:328-339.
38. Chang YS, Wang JX, Chang DW. A meta-analysis of robotic versus laparoscopic colectomy. *J Surg Res*. 2015;195:465-474.
39. Lieu C, Kennedy EB, Bergsland E, et al. Duration of oxaliplatin-containing adjuvant therapy for stage III colon cancer: ASCO clinical practice guideline. *J Clin Oncol*. 2019;37:1436-1447.
40. Kuebler JP, Wieand HS, O'Connell MJ, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. *J Clin Oncol*. 2007;25:2198-2204.
41. de Gramont A, Van Cutsem E, Schmoll H-J, et al. Bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer (AVANT): a phase 3 randomised controlled trial. The *Lancet Oncol*. 2012;13:1225-1233.

42. Cutsem EV, Labianca R, Bodoky G, et al. Randomized phase III trial comparing biweekly infusional fluorouracil/leucovorin alone or with irinotecan in the adjuvant treatment of stage III colon cancer: PETACC-3. *J Clin Oncol*. 2009;27:3117-3125.
43. André T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med*. 2004;350:2343-2351.
44. Alberts SR, Sargent DJ, Nair S, et al. Effect of oxaliplatin, fluorouracil, and leucovorin with or without cetuximab on survival among patients with resected stage III colon cancer: a randomized trial. *JAMA*. 2012;307:1383-1393.
45. Schmoll HJ, Twelves C, Sun W, et al. Effect of adjuvant capecitabine or fluorouracil, with or without oxaliplatin, on survival outcomes in stage III colon cancer and the effect of oxaliplatin on post-relapse survival: a pooled analysis of individual patient data from four randomised controlled trials. *Lancet Oncol*. 2014;15:1481-1492.
46. Schmoll HJ, Tabernero J, Maroun J, et al. Capecitabine plus oxaliplatin compared with fluorouracil/folinic acid as adjuvant therapy for stage III colon cancer: final results of the NO16968 randomized controlled phase III trial. *J Clin Oncol*. 2015;33:3733-3740.
47. Haller DG, Tabernero J, Maroun J, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. *J Clin Oncol*. 2011;29:1465-1471.
48. Grothey A, Sobrero AF, Shields AF, et al. Duration of adjuvant chemotherapy for stage III colon cancer. *N Engl J Med*. 2018;378:1177-1188.
49. Sobrero AF, Andre T, Meyerhardt JA, et al. Overall survival (OS) and long-term disease-free survival (DFS) of three versus six months of adjuvant (adj) oxaliplatin and fluoropyrimidine-based therapy for patients (pts) with stage III colon cancer (CC): final results from the IDEA (International Duration Evaluation of Adj chemotherapy) collaboration. *J Clin Oncol*. 2020;38:4004-4004.
50. Comparison of fluorouracil with additional levamisole, higher-dose folinic acid, or both, as adjuvant chemotherapy for colorectal cancer: a randomised trial. QUASAR Collaborative Group. *Lancet*. 2000;355:1588-1596.
51. Sargent D, Sobrero A, Grothey A, et al. Evidence for cure by adjuvant therapy in colon cancer: observations based on individual patient data from 20,898 patients on 18 randomized trials. *J Clin Oncol*. 2009;27:872-877.
52. Gill S, Loprinzi CL, Sargent DJ, et al. Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? *J Clin Oncol*. 2004;22:1797-1806.
53. Figueredo A, Charette ML, Maroun J, et al. Adjuvant therapy for stage II colon cancer: a systematic review from the Cancer Care Ontario Program in evidence-based care's gastrointestinal cancer disease site group. *J Clin Oncol*. 2004;22:3395-3407.
54. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. *Lancet*. 1995;345:939-944.
55. Tournigand C, Andre T, Bonnetain F, et al. Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly patients (between ages 70 and 75 years) with colon cancer: subgroup analyses of the Multicenter International Study of Oxaliplatin, Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer trial. *J Clin Oncol*. 2012;30:3353-3360.
56. Shah MA, Renfro LA, Allegra CJ, et al. Impact of patient factors on recurrence risk and time dependency of oxaliplatin benefit in patients with colon cancer: analysis from modern-era adjuvant studies in the adjuvant colon cancer end points (ACCENT) database. *J Clin Oncol*. 2016;34:843-853.
57. Yothers G, O'Connell MJ, Allegra CJ, et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. *J Clin Oncol*. 2011;29:3768-3774.
58. Benson AB, Venook AP, Al-Hawary MM, et al. NCCN guidelines insights: colon cancer, version 2.2018. *J Natl Compr Canc Netw*. 2018;16:359-369.
59. Iveson T, Sobrero AF, Yoshino T, et al. Prospective pooled analysis of four randomized trials investigating duration of adjuvant (adj) oxaliplatin-based therapy (3 vs 6 months {m}) for patients (pts) with high-risk stage II colorectal cancer (CC). *J Clin Oncol*. 2019;37:3501.
60. Sargent DJ, Marsoni S, Monges G, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. *J Clin Oncol*. 2010;28:3219-3226.
61. Ribic CM, Sargent DJ, Moore MJ, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *N Engl J Med*. 2003;349:247-257.
62. Klingbiel D, Saridaki Z, Roth AD, et al. Prognosis of stage II and III colon cancer treated with adjuvant 5-fluorouracil or FOLFIRI in relation to microsatellite status: results of the PETACC-3 trial. *Ann Oncol*. 2015;26:126-132.
63. Hutchins G, Southward K, Handley K, et al. Value of mismatch repair, KRAS, and BRAF mutations in predicting recurrence and benefits from chemotherapy in colorectal cancer. *J Clin Oncol*. 2011;29:1261-1270.
64. Sinicrope FA, Mahoney MR, Smyrk TC, et al. Prognostic impact of deficient DNA mismatch repair in patients with stage III colon cancer from a randomized trial of FOLFOX-based adjuvant chemotherapy. *J Clin Oncol*. 2013;31:3664-3672.
65. Kim JE, Hong YS, Kim HJ, et al. Defective mismatch repair status was not associated with DFS and OS in stage II colon cancer treated with adjuvant chemotherapy. *Ann Surg Oncol*. 2015;22(suppl 3):S630-S637.
66. Bertagnolli MM, Redston M, Compton CC, et al. Microsatellite instability and loss of heterozygosity at chromosomal location 18q: prospective evaluation of biomarkers for stages II and III colon cancer—a study of CALGB 9581 and 89803. *J Clin Oncol*. 2011;29:3153-3162.
67. Ychou M, Raoul JL, Douillard JY, et al. A phase III randomised trial of LV5FU2 + irinotecan versus LV5FU2 alone in adjuvant high-risk colon cancer (FNCLCC Accord02/FFCD9802). *Ann Oncol*. 2009;20:674-680.
68. Van Cutsem E, Labianca R, Bodoky G, et al. Randomized phase III trial comparing biweekly infusional fluorouracil/leucovorin alone or with irinotecan in the adjuvant treatment of stage III colon cancer: PETACC-3. *J Clin Oncol*. 2009;27:3117-3125.
69. Saltz LB, Niedzwiecki D, Hollis D, et al. Irinotecan fluorouracil plus leucovorin is not superior to fluorouracil plus leucovorin alone as adjuvant treatment for stage III colon cancer: results of CALGB 89803. *J Clin Oncol*. 2007;25:3456-3461.
70. Taieb J, Tabernero J, Mini E, et al. Oxaliplatin, fluorouracil, and leucovorin with or without cetuximab in patients with resected stage III colon cancer (PETACC-8): an open-label, randomised phase 3 trial. *Lancet Oncol*. 2014;15:862-873.
71. Dasari A, Messersmith WA. Should we perform a new adjuvant trial with bevacizumab? *Curr Colorectal Cancer Rep*. 2011;7:218.
72. Allegra CJ, Yothers G, O'Connell MJ, et al. Bevacizumab in Stage II-III colon cancer: 5-year update of the National Surgical Adjuvant Breast and Bowel Project C-08 trial. *J Clin Oncol*. 2013;31:359-364.
73. Seymour MT, Morton D. FOxTROT: an international randomised controlled trial in 1052 patients (pts) evaluating neoadjuvant chemotherapy (NAC) for colon cancer. *J Clin Oncol*. 2019;37:3504-3504.

74. Wan JCM, Massie C, Garcia-Corbacho J, et al. Liquid biopsies come of age: towards implementation of circulating tumour DNA. *Nat Rev Cancer*. 2017;17:223-238.
75. Tie J, Cohen JD, Wang Y, et al. Circulating tumor DNA analyses as markers of recurrence risk and benefit of adjuvant therapy for stage III colon cancer. *JAMA Oncol*. 2019;5(12):1710-1717.
76. Tie J, Cohen JD, Wang Y, et al. Serial circulating tumour DNA analysis during multimodality treatment of locally advanced rectal cancer: a prospective biomarker study. *Gut*. 2019;68:663-671.
77. Tie J, Wang Y, Tomasetti C, et al. Circulating tumor DNA analysis detects minimal residual disease and predicts recurrence in patients with stage II colon cancer. *Sci Transl Med*. 2016;8:346ra92.
78. Tie J Cohen J, Wang Y, Lee M, et al. Serial circulating tumor DNA analysis as a prognostic marker and a real-time indicator of adjvuvant chemotherapy efficacy in stage III colon cancer. Presented at: the American Society of Clinical Oncology Annual Symposium; Chicago, IL; June 1-5, 20, 2018.
79. Tan G, Chu C, Gui X, et al. The prognostic value of circulating cell-free DNA in breast cancer: a meta-analysis. *Medicine (Baltimore)*. 2018;97:e0197.
80. Dasari A, Grothey A, Kopetz S. Circulating tumor DNA-defined minimal residual disease in solid tumors: opportunities to accelerate the development of adjuvant therapies. *J Clin Oncol*. 18;36(35):JCO2018789032.
81. Morris V, Dasari A, Kopetz S. Can circulating tumor DNA in early-stage colorectal cancer be more than a prognostic biomarker? *JAMA Oncol*. 2019 May 9. Epub ahead of print.
82. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med*. 2004;351:1731-1740.
83. Willeke F, Horisberger K, Kraus-Tiefenbacher U, et al. A phase II study of capecitabine and irinotecan in combination with concurrent pelvic radiotherapy (CapIri-RT) as neoadjuvant treatment of locally advanced rectal cancer. *Br J Cancer*. 2007;96:912-917.
84. Saha A, Ghosh SK, Roy C, et al. A randomized controlled pilot study to compare capecitabine-oxaliplatin with 5-FU-leucovorin as neoadjuvant concurrent chemoradiation in locally advanced adenocarcinoma of rectum. *J Cancer Res Ther*. 2015;11:88-93.
85. Rodel C, Liersch T, Becker H, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. *Lancet Oncol*. 2012;13:679-687.
86. Rodel C, Graeven U, Fietkau R, et al. Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): final results of the multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2015;16:979-989.
87. O'Connell MJ, Colangelo LH, Beart RW, et al. Capecitabine and oxaliplatin in the preoperative multimodality treatment of rectal cancer: surgical end points from National Surgical Adjuvant Breast and Bowel Project trial R-04. *J Clin Oncol*. 2014;32:1927-1934.
88. Navarro M, Dotor E, Rivera F, et al. A phase II study of preoperative radiotherapy and concomitant weekly irinotecan in combination with protracted venous infusion 5-fluorouracil, for resectable locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys*. 2006;66:201-205.
89. Jiao D, Zhang R, Gong Z, et al. Fluorouracil-based preoperative chemoradiotherapy with or without oxaliplatin for stage II/III rectal cancer: a 3-year follow-up study. *Chin J Cancer Res*. 2015;27:588-596.
90. Haddad P, Miraie M, Farhan F, et al. Addition of oxaliplatin to neoadjuvant radiochemotherapy in MRI-defined T3, T4 or N+ rectal cancer: a randomized clinical trial. Asia Pac *J Clin Oncol*. 2017;13:416-422.
91. Gollins S, Sun Myint A, Haylock B, et al. Preoperative chemoradiotherapy using concurrent capecitabine and irinotecan in magnetic resonance imaging-defined locally advanced rectal cancer: impact on long-term clinical outcomes. *J Clin Oncol*. 2011;29:1042-1049.
92. Gerard JP, Azria D, Gourgou-Bourgade S, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. *J Clin Oncol*. 2010;28:1638-1644.
93. Gerard JP, Azria D, Gourgou-Bourgade S, et al. Clinical outcome of the ACCORD 12/0405 PRODIGE 2 randomized trial in rectal cancer. *J Clin Oncol*. 2012;30:4558-4565.
94. Deng Y, Chi P, Lan P, et al. Neoadjuvant modified FOLFOX6 with or without radiation versus fluorouracil plus radiation for locally advanced rectal cancer: final results of the Chinese FOWARC trial. *J Clin Oncol*. 2019;37:3223-3233.
95. Aschele C, Cionini L, Lonardi S, et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. *J Clin Oncol*. 2011;29:2773-2780.
96. Allegra CJ, Yothers G, O'Connell MJ, et al. Neoadjuvant 5-FU or capecitabine plus radiation with or without oxaliplatin in rectal cancer patients: a phase III randomized clinical trial. *J Natl Cancer Inst*. 2015;107(11):djv248. Erratum in: *J Natl Cancer Inst*. 2016;108(4).
97. Willett CG, Duda DG, di Tomaso E, et al. Efficacy, safety, and biomarkers of neoadjuvant bevacizumab, radiation therapy, and fluorouracil in rectal cancer: a multidisciplinary phase II study. *J Clin Oncol*. 2009;27:3020-3026.
98. Uehara K, Hiramatsu K, Maeda A, et al. Neoadjuvant oxaliplatin and capecitabine and bevacizumab without radiotherapy for poor-risk rectal cancer: N-SOG 03 phase II trial. *Jpn J Clin Oncol*. 2013;43:964-971.
99. Landry JC, Feng Y, Prabhu RS, et al. Phase II trial of preoperative radiation with concurrent capecitabine, oxaliplatin, and bevacizumab followed by surgery and postoperative 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX), and bevacizumab in patients with locally advanced rectal cancer: 5-year clinical outcomes ECOG-ACRIN Cancer Research Group E3204. *Oncologist* 2015;20:615-616.
100. Fernandez-Martos C, Pericay C, Losa F, et al. Effect of aflibercept plus modified FOLFOX6 induction chemotherapy before standard chemoradiotherapy and surgery in patients with high-risk rectal adenocarcinoma: the GEMCAD 1402 randomized clinical trial. *JAMA Oncol*. 2019;5(11):1566-1573.
101. Crane CH, Eng C, Feig BW, et al. Phase II trial of neoadjuvant bevacizumab, capecitabine, and radiotherapy for locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys*. 2010;76:824-830.
102. Stephens RJ, Thompson LC, Quirke P, et al. Impact of short-course preoperative radiotherapy for rectal cancer on patients' quality of life: data from the Medical Research Council CR07/National Cancer Institute of Canada Clinical Trials Group C016 randomized clinical trial. *J Clin Oncol*. 2010;28:4233-4239.
103. Sebag-Montefiore D, Stephens RJ, Steele R, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet*. 2009;373:811-820.
104. Quirke P, Steele R, Monson J, et al. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. *Lancet*. 2009;373:821-828.

105. Birgisson H, Pahlman L, Gunnarsson U, et al. Adverse effects of preoperative radiation therapy for rectal cancer: long-term follow-up of the Swedish Rectal Cancer Trial. *J Clin Oncol*. 2005;23:8697-8705.
106. Peeters KC, van de Velde CJ, Leer JW, et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients--a Dutch colorectal cancer group study. *J Clin Oncol*. 2005;23:6199-6206.
107. Marijnen CA, van de Velde CJ, Putter H, et al. Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: report of a multicenter randomized trial. *J Clin Oncol*. 2005;23:1847-1858.
108. Marijnen CA, Kapiteijn E, van de Velde CJ, et al. Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial. *J Clin Oncol*. 2002;20:817-825.
109. Wiltink LM, Chen TY, Nout RA, et al. Health-related quality of life 14 years after preoperative short-term radiotherapy and total mesorectal excision for rectal cancer: report of a multicenter randomised trial. *Eur J Cancer*. 2014;50:2390-2398.
110. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg*. 2006;93:1215-1223.
111. Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. *J Clin Oncol*. 2012;30:3827-3833.
112. Conroy T, Lamfichekh N, Etienne P-L, et al. Total neoadjuvant therapy with mFOLFIRINOX versus preoperative chemoradiation in patients with locally advanced rectal cancer: final results of PRODIGE 23 phase III trial, a UNICANCER GI trial. *J Clin Oncol*. 2020;38:4007.
113. Hospers G, Bahadoer RR, Dijkstra EA, et al. Short-course radiotherapy followed by chemotherapy before TME in locally advanced rectal cancer: the randomized RAPIDO trial. *J Clin Oncol*. 2020;38:4006.
114. Spiegel DY, Boyer MJ, Hong JC, et al. Long-term clinical outcomes of nonoperative management with chemoradiotherapy for locally advanced rectal cancer in the Veterans Health Administration. *Int J Radiat Oncol Biol Phys*. 2019;103:565-573.
115. Smith RK, Fry RD, Mahmoud NN, et al. Surveillance after neoadjuvant therapy in advanced rectal cancer with complete clinical response can have comparable outcomes to total mesorectal excision. *Int J Colorectal Dis*. 2015;30:769-774.
116. Smith JJ, Strombom P, Chow OS, et al. Assessment of a watch-and-wait strategy for rectal cancer in patients with a complete response after neoadjuvant therapy. *JAMA Oncol*. 2019;5:e185896.
117. Martens MH, Maas M, Heijnen LA, et al. Long-term outcome of an organ preservation program after neoadjuvant treatment for rectal cancer. *J Natl Cancer Inst*. 2016;108(12):djw171.
118. Habr-Gama A, Sao Juliao GP, Gama-Rodrigues J, et al. Baseline T classification predicts early tumor regrowth after nonoperative management in distal rectal cancer after extended neoadjuvant chemoradiation and initial complete clinical response. *Dis Colon Rectum*. 2017;60:586-594.
119. Dossa F, Chesney TR, Acuna SA, et al. A watch-and-wait approach for locally advanced rectal cancer after a clinical complete response following neoadjuvant chemoradiation: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2017;2:501-513.
120. Appelt AL, Ploen J, Harling H, et al. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. *Lancet Oncol*. 2015;16:919-927.
121. van der Valk MJM, Hilling DE, Bastiaannet E, et al. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. *Lancet*. 2018;391:2537-2545.
122. Glimelius B. Adjuvant chemotherapy in rectal cancer: state of the art and future perspectives. *Curr Opin Oncol*.2020;32(4):377-383.
123. Hong YS, Nam BH, Kim KP, et al. Oxaliplatin, fluorouracil, and leucovorin versus fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (ADORE): an open-label, multicentre, phase 2, randomised controlled trial. *Lancet Oncol*. 2014;15:1245-1253.
124. Zhao L, Liu R, Zhang Z, et al. Oxaliplatin/fluorouracil-based adjuvant chemotherapy for locally advanced rectal cancer after neoadjuvant chemoradiotherapy and surgery: a systematic review and meta-analysis of randomized controlled trials. *Colorectal Dis*. 2016;18:763-772.
125. Tepper JE, O'Connell MJ, Niedzwiecki D, et al. Impact of number of nodes retrieved on outcome in patients with rectal cancer. *J Clin Oncol*. 2001;19:157-163.
126. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med*. 2001;345:638-646.
127. Hoff PM, Ansari R, Batist G, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. *J Clin Oncol*. 2001;19:2282-2292.
128. Van Cutsem E, Twelves C, Cassidy J, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. *J Clin Oncol*. 2001;19:4097-4106.
129. Haller DG, Cassidy J, Clarke SJ, et al. Potential regional differences for the tolerability profiles of fluoropyrimidines. *J Clin Oncol*. 2008;26:2118-2123.
130. Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group [see comment]. *N Engl J Med*. 2000;343:905-914.
131. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet*. 2000;355:1041-1047.
132. Rothenberg ML, Oza AM, Bigelow RH, et al. Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: interim results of a phase III trial. *J Clin Oncol*. 2003;21:2059-2069.
133. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol*. 2000;18:2938-2947.
134. Goldberg RM, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol*. 2004;22:23-30.
135. Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol*. 2004;22:229-237.
136. Falcone A, Ricci S, Brunetti I, et al. Phase III trial of Infusional Fluorouracil, Leucovorin, Oxaliplatin, and Irinotecan (FOLFOXIRI) Compared With Infusional Fluorouracil, Leucovorin, and Irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol*. 2007;25:1670-1676.

137. Cremolini C, Loupakis F, Antoniotti C, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. *Lancet Oncol*. 2015;16:1306-1315.
138. Cremolini C, Antoniotti C, Lonardi S, et al. Updated results of TRIBE2, a phase III, randomized strategy study by GONO in the first- and second-line treatment of unresectable mCRC. *J Clin Oncol*. 2019;37:3508-3508.
139. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381:303-312.
140. Belum VR, Wu S, Lacouture ME. Risk of hand-foot skin reaction with the novel multikinase inhibitor regorafenib: a meta-analysis. *Invest New Drugs*. 2013;31:1078-1086.
141. Bekaii-Saab TS, Ou FS, Ahn DH, et al. Regorafenib dose-optimisation in patients with refractory metastatic colorectal cancer (ReDOS): a randomised, multicentre, open-label, phase 2 study. *Lancet Oncol*. 2019;20:1070-1082.
142. Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med*. 2015;372:1909-1919.
143. Sobrero AF, Maurel J, Fehrenbacher L, et al. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. *J Clin Oncol*. 2008;26:2311-2319.
144. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med*. 2004;351:337-345.
145. Jonker DJ, O'Callaghan CJ, Karapetis CS, et al. Cetuximab for the treatment of colorectal cancer. *N Engl J Med*. 2007;357:2040-2048.
146. Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol*. 2008;26:1626-1634.
147. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med*. 2008;359:1757-1765.
148. Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *N Engl J Med*. 2013;369:1023-1034.
149. Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med*. 2009;360:1408-1417.
150. Tabernero J, Van Cutsem E, Díaz-Rubio E, et al. Phase II trial of cetuximab in combination with fluorouracil, leucovorin, and oxaliplatin in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol*. 2007;25:5225-5232.
151. Troiani T, Napolitano S, Della Corte CM, et al. Therapeutic value of EGFR inhibition in CRC and NSCLC: 15 years of clinical evidence. *ESMO Open*. 2016;1(5):e000088..
152. Sforza V, Martinelli E, Ciardiello F, et al. Mechanisms of resistance to anti-epidermal growth factor receptor inhibitors in metastatic colorectal cancer. *World J Gastroenterol*. 2016;22:6345-6361.
153. Peeters M, Kafatos G, Taylor A, et al. Prevalence of RAS mutations and individual variation patterns among patients with metastatic colorectal cancer: a pooled analysis of randomised controlled trials. *Eur J Cancer*. 2015;51:1704-1713.
154. Ciardiello F, Normanno N, Maiello E, et al. Clinical activity of FOLFIRI plus cetuximab according to extended gene mutation status by next-generation sequencing: findings from the CAPRI-GOIM trial. *Ann Oncol*. 2014;25:1756-1761.
155. Sorich MJ, Wiese MD, Rowland A, et al. Extended RAS mutations and anti-EGFR monoclonal antibody survival benefit in metastatic colorectal cancer: a meta-analysis of randomized, controlled trials. *Ann Oncol*. 2015;26:13-21.
156. Van Cutsem E, Lang I, Folprecht G, et al. Cetuximab plus FOLFIRI in the treatment of metastatic colorectal cancer (mCRC): the influence of *KRAS* and *BRAF* biomarkers on outcome: updated data from the CRYSTAL trial. Presented at: 2010 Gastrointestinal Cancers Symposium, San Francisco; 2010.
157. Bokemeyer C, Bondarenko I, Makhson A, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol*. 2009;27:663-671.
158. Chung CH, Mirakhur B, Chan E, et al. Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. *N Engl J Med*. 2008;358:1109-1117.
159. Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol*. 2007;25:1658-1664.
160. Peeters M, Price TJ, Cervantes A, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. *J Clin Oncol*. 2010;28:4706-4713.
161. Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol*. 2010;28:4697-4705.
162. Thierry AR, Pastor B, Jiang ZQ, et al. Circulating DNA demonstrates convergent evolution and common resistance mechanisms during treatment of colorectal cancer. *Clin Cancer Res*. 2017;23:4578-4591.
163. Strickler JH, Loree JM, Ahronian LG, et al. Genomic landscape of cell-free DNA in patients with colorectal cancer. *Cancer Discov*. 2018;8:164-173.
164. Montagut C, Dalmases A, Bellosillo B, et al. Identification of a mutation in the extracellular domain of the epidermal growth factor receptor conferring cetuximab resistance in colorectal cancer. *Nat Med*. 2012;18:221-223.
165. Morelli MP, Overman MJ, Dasari A, et al. Characterizing the patterns of clonal selection in circulating tumor DNA from patients with colorectal cancer refractory to anti-EGFR treatment. *Ann Oncol*. 2015;26:731-736.
166. Parseghian CM, Loree JM, Morris VK, et al. Anti-EGFR-resistant clones decay exponentially after progression: implications for anti-EGFR re-challenge. *Ann Oncol*. 2019;30:243-249.
167. Cremolini C, Rossini D, Dell'Aquila E, et al. Rechallenge for patients with RAS and BRAF wild-type metastatic colorectal cancer with acquired resistance to first-line cetuximab and irinotecan: a phase 2 single-arm clinical trial. *JAMA Oncol*. 2019;5:343-350.
168. O'Dwyer PJ, Manola J, Valone FH, et al. Fluorouracil modulation in colorectal cancer: lack of improvement with N -phosphonoacetyl- l -aspartic acid or oral leucovorin or interferon, but enhanced therapeutic index with weekly 24-hour infusion schedule--an Eastern Cooperative Oncology Group/Cancer and Leukemia Group B Study. *J Clin Oncol*. 2001;19:2413-2421.
169. Loupakis F, Yang D, Yau L, et al. Primary tumor location as a prognostic factor in metastatic colorectal cancer. *J Natl Cancer Inst*. 2015;107(3):dju427.
170. Tejpar S, Stintzing S, Ciardiello F, et al. Prognostic and predictive relevance of primary tumor location in patients with RAS wild-type metastatic colorectal cancer: retrospective analyses of the CRYSTAL and FIRE-3 trials. *JAMA Oncol*. 2017;3:194-201.
171. Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2014;15:1065-1075.

172. Douillard JY, Siena S, Cassidy J, et al. Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. *Ann Oncol*. 2014;25:1346-1355.
173. Venook AP, Niedzwiecki D, Lenz HJ, et al. Effect of First-line chemotherapy combined with cetuximab or bevacizumab on overall survival in patients with KRAS wild-type advanced or metastatic colorectal cancer: a randomized clinical trial. *JAMA*. 2017;317:2392-2401.
174. Brulé SY, Jonker DJ, Karapetis CS, et al. Location of colon cancer (right-sided versus left-sided) as a prognostic factor and a predictor of benefit from cetuximab in NCIC CO.17. *Eur J Cancer*. 2015;51:1405-1414.
175. Hochster HS, Hart LL, Ramanathan RK, et al. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE Study. *J Clin Oncol*. 2008;26:3523-3529.
176. Saltz LB, Clarke S, Díaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol*. 2008;26:2013-2019.
177. Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol*. 2007;25:1539-1544.
178. Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. *N Engl J Med*. 2009;360:563-572.
179. Hecht JR, Mitchell E, Chidiac T, et al. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. *J Clin Oncol*. 2009;27:672-680.
180. Tabernero J, Yoshino T, Cohn AL, et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. *Lancet Oncol*. 2015;16:499-508.
181. Van Cutsem E, Tabernero J, Lakomy R, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol*. 2012;30:3499-3506.
182. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med*. 2015;372:2509-2520.
183. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol*. 2017;18:1182-1191.
184. Overman MJ, Lonardi S, Wong KYM, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. *J Clin Oncol*. 2018;36:773-779.
185. Andre T, Shiu K-K, Kim TW, et al. Pembrolizumab versus chemotherapy for microsatellite instability-high/mismatch repair deficient metastatic colorectal cancer: the phase 3 KEYNOTE-177 Study. *J Clin Oncol*. 2020;38:LBA4-LBA4.
186. Tran B, Kopetz S, Tie J, et al. Impact of BRAF mutation and microsatellite instability on the pattern of metastatic spread and prognosis in metastatic colorectal cancer. *Cancer*. 2011;17(20):4623-4632.
187. Morris V, Overman MJ, Jiang ZQ, et al. Progression-free survival remains poor over sequential lines of systemic therapy in patients with BRAF-mutated colorectal cancer. *Clin Colorectal Cancer*. 2014;13:164-171.
188. Seppälä TT, Böhm JP, Friman M, et al. Combination of microsatellite instability and BRAF mutation status for subtyping colorectal cancer. *Br J Cancer*. 2015;112:1966-1975.
189. Roth AD, Tejpar S, Delorenzi M, et al. Prognostic role of KRAS and BRAF in stage II and III resected colon cancer: results of the translational study on the PETACC-3, EORTC 40993, SAKK 60-00 trial. *J Clin Oncol*. 2010;28:466-474.
190. Stintzing S, Miller-Phillips L, Modest DP, et al. Impact of BRAF and RAS mutations on first-line efficacy of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab: analysis of the FIRE-3 (AIO KRK-0306) study. *Eur J Cancer*. 2017;79:50-60.
191. Rowland A, Dias MM, Wiese MD, et al. Meta-analysis of BRAF mutation as a predictive biomarker of benefit from anti-EGFR monoclonal antibody therapy for RAS wild-type metastatic colorectal cancer. *Br J Cancer*. 2015;112:1888-1894.
192. Pietrantonio F, Petrelli F, Coinu A, et al. Predictive role of BRAF mutations in patients with advanced colorectal cancer receiving cetuximab and panitumumab: a meta-analysis. *Eur J Cancer*. 2015;51:587-594.
193. Kopetz S, Desai J, Chan E, et al. Phase II pilot study of vemurafenib in patients with metastatic BRAF-mutated colorectal cancer. *J Clin Oncol*. 2015;33:4032-4038.
194. Prahallad A, Sun C, Huang S, et al. Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR. *Nature*. 2012;483:100-103.
195. Corcoran RB, Ebi H, Turke AB, et al. EGFR-mediated re-activation of MAPK signaling contributes to insensitivity of BRAF mutant colorectal cancers to RAF inhibition with vemurafenib. *Cancer Discov*. 2012;2:227-235.
196. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. *N Engl J Med*. 2015;373:726-736.
197. Yaeger R, Cercek A, O'Reilly EM, et al. Pilot trial of combined BRAF and EGFR inhibition in BRAF-mutant metastatic colorectal cancer patients. *Clin Cancer Res*. 2015;21:1313-1320.
198. Hong DS, Morris VK, El Osta B, et al. Phase IB study of vemurafenib in combination with irinotecan and cetuximab in patients with metastatic colorectal cancer with BRAFV600E mutation. *Cancer Discov*. 2016;6:1352-1365.
199. Scott Kopetz, Shannon L McDonough, Van Karlyle Morris, et al. Randomized trial of irinotecan and cetuximab with or without vemurafenib in BRAF-mutant metastatic colorectal cancer (SWOG 1406). *J Clin Oncol*. 2017;35:520-520.
200. Corcoran RB, Atreya CE, Falchook GS, et al. Combined BRAF and MEK inhibition with dabrafenib and trametinib in BRAF V600-mutant colorectal cancer. *J Clin Oncol*. 2015;33:4023-4031.
201. Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, binimetinib, and cetuximab in BRAF V600E-mutated colorectal cancer. *N Engl J Med*. 2019;381:1632-1643.
202. Van Cutsem E, Huijberts S, Grothey A, et al. Binimetinib, encorafenib, and cetuximab triplet therapy for patients with BRAF V600E-Mutant metastatic colorectal cancer: safety lead-in results from the phase III BEACON Colorectal Cancer Study. *J Clin Oncol*. 2019;37:1460-1469.
203. Sartore-Bianchi A, Trusolino L, Martino C, et al. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2016;17:738-746.
204. Meric-Bernstam F, Hurwitz H, Raghav KPS, et al. Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. *Lancet Oncol*. 2019;20:518-530.
205. Siena S. A phase II, multicenter, open-label study of trastuzumab deruxtecan (T-DXd; DS-8201) in patients (pts) with HER2-expressing metastatic colorectal cancer (mCRC): DESTINY-CRC01.

Presented at: ASCO Virtual Scientific Program, American Society of Clinical Oncology; 2020.
206. Pietrantonio F, Di Nicolantonio F, Schrock AB, et al. ALK, ROS1, and NTRK rearrangements in metastatic colorectal cancer. *J Natl Cancer Inst*. 2017;109(12).
207. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N Engl J Med*. 2018;378:731-739.
208. Jones JC, Renfro LA, Al-Shamsi HO, et al. (Non-V600) BRAF mutations define a clinically distinct molecular subtype of metastatic colorectal cancer. *J Clin Oncol*. 2017;35:2624-2630.
209. Yao Z, Torres NM, Tao A, et al. BRAF mutants evade ERK-dependent feedback by different mechanisms that determine their sensitivity to pharmacologic inhibition. *Cancer Cell*. 2015;28:370-383.
210. Yao Z, Yaeger R, Rodrik-Outmezguine VS, et al. Tumours with class 3 BRAF mutants are sensitive to the inhibition of activated RAS. *Nature*. 2017;548:234-238.
211. Johnson B, Loree JM, Jacome AA, et al. Atypical, non-V600 BRAF mutations as a potential mechanism of resistance to EGFR inhibition in metastatic colorectal cancer. *JCO Precis Oncol*. 2019;3:PO.19.00102.
212. Palles C, Cazier JB, Howarth KM, et al. Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas. *Nat Genet*. 2013;45:136-144.
213. Domingo E, Freeman-Mills L, Rayner E, et al. Somatic POLE proofreading domain mutation, immune response, and prognosis in colorectal cancer: a retrospective, pooled biomarker study. *Lancet Gastroenterol Hepatol*. 2016;1:207-216.
214. Giannakis M, Mu XJ, Shukla SA, et al. Genomic correlates of immune-cell infiltrates in colorectal carcinoma. *Cell Rep*. 2016;17:1206.
215. Campbell BB, Light N, Fabrizio D, et al. Comprehensive Analysis of Hypermutation in Human Cancer. *Cell*. 2017;171:1042-1056.e10.
216. Okumura T, Boku N, Hishida T, et al. Surgical outcome and prognostic stratification for pulmonary metastasis from colorectal cancer. *Ann Thorac Surg*. 2017;104:979-987.
217. Cummings LC, Payes JD, Cooper GS. Survival after hepatic resection in metastatic colorectal cancer: a population-based study. *Cancer*. 2007;109:718-726.
218. Adam R, Pascal G, Castaing D, et al. Tumor progression while on chemotherapy: a contraindication to liver resection for multiple colorectal metastases? *Ann Surg*. 2004;240:1052-1061; discussion 1061-1064.
219. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2013;14:1208-1215.
220. Kanemitsu Y, Shimizu Y, Mizusawa J, et al. A randomized phase II/III trial comparing hepatectomy followed by mFOLFOX6 with hepatectomy alone for liver metastasis from colorectal cancer: JCOG0603 study. *J Clin Oncol*. 2020(suppl);38:4005.
221. Mitry E, Fields ALA, Bleiberg H, et al. Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. *J Clin Oncol*. 2008;26:4906-4911.
222. Vauthey JN, Pawlik TM, Ribero D, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *J Clin Oncol*. 2006;24:2065-2072.
223. Bridgewater JA, Pugh SA, Maishman T, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis (New EPOC): long-term results of a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2020;21:398-411.
224. Kumar A, Soares HP, Balducci L, et al. Treatment tolerance and efficacy in geriatric oncology: a systematic review of phase III randomized trials conducted by five National Cancer Institute-sponsored cooperative groups. *J Clin Oncol*. 2007;25:1272-1276.
225. Cunningham D, Lang I, Marcuello E, et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. *Lancet Oncol*. 2013;14:1077-1085.
226. Grothey A, Sargent D, Goldberg RM, et al. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. *J Clin Oncol*. 2004;22:1209-1214.
227. Maindrault-Goebel F, Tournigand C, André T, et al. Oxaliplatin reintroduction in patients previously treated with leucovorin, fluorouracil and oxaliplatin for metastatic colorectal cancer. *Ann Oncol*. 2004;15:1210-1214.

This page intentionally left blank

33 Anal Cancer

Emma Holliday
Van Morris
Craig A. Messick

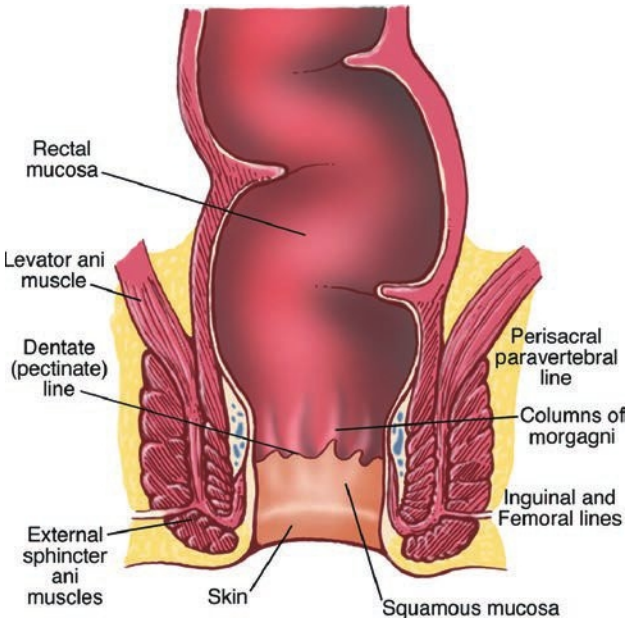
KEY CONCEPTS

- Despite the introduction of a preventive human papillomavirus vaccine, both the incidence of anal cancer and the anal cancer–specific mortality rate continue to rise in the United States.
- Concurrent chemoradiation remains the standard of care for curative-intent therapy for patients with newly diagnosed, locoregional anal cancer.
- To date, there are no data to support benefit with chemotherapy before or after chemoradiation for patients with locoregional anal cancer.
- Salvage surgery with abdominoperineal resection remains the standard of care for patients with nonmetastatic, locoregional anal cancer that recurs after chemoradiation.
- Combination chemotherapy is the current treatment recommendation in the frontline setting for patients with inoperable, metastatic anal cancer.
- Immune checkpoint blockade therapies, either as monotherapy or as a clinical trial option, should be considered for patients with treatment-refractory anal cancer.

Carcinoma of the anal canal is extremely rare, representing approximately 2% to 3% of all gastrointestinal (GI) malignancies. It was estimated that in 2020, 8590 patients (5900 female) would be diagnosed with carcinoma of the anal canal in the United States, resulting in 1350 deaths.[1] The incidence of this disease continues to rise steadily. Over the past 20 years, increasing rates of advanced (metastatic) stage at initial presentation have been reported in the United States and are linked to a rise in cancer-specific mortality rates.[2] Still, a practicing oncologist will evaluate and treat less than one such patient per year. The majority of anal cancer is squamous cell carcinoma (SCC) and typically arises within the anal mucosa.[3] Traditionally, more than 70% of locoregional anal canal caners are cured with the combined modalities of chemoradiation,[4] reserving an abdominoperineal resection (APR) for salvage therapy of patients with persistent or recurrent disease.[5] This chapter focuses on the multimodality treatment of SCC of the anus (SCCA) and the emerging role of immunotherapy in management of patients with this disease.

ANATOMY

Optimal treatment of patients with SCCA requires sound understanding of the anatomy of the anus, which includes the anal canal, anal verge (AV), and anal margin (AM). The anal canal is variable in length and is 2 to 3 cm long in women and 3 to 5 cm in men. The AV is the visible portion of the anus seen with gentle traction applied to the buttocks, and the AM is a region that extends 5 cm radially from the AV around the anal skin (Fig. 33–1). Nomenclature is vital, and accurate description of the tumor location is critical for optimal management. Although classification of these tumors by their histologic definition may offer a more consistent approach to guide diagnosis and treatment,[3] meaningful data suggest such a singular approach to all SCCA may be inadequate, and a tailored approach to these cancers may be more important. For example, malignancies of the AM that do not involve the anal sphincter complex and are smaller than 2 cm are often treated as primary skin cancers, surgically excised with a wide local excision (WLE). This is not to be applied to T2 tumors outright



IGURE 33–1 **Anatomy of the anal canal.**

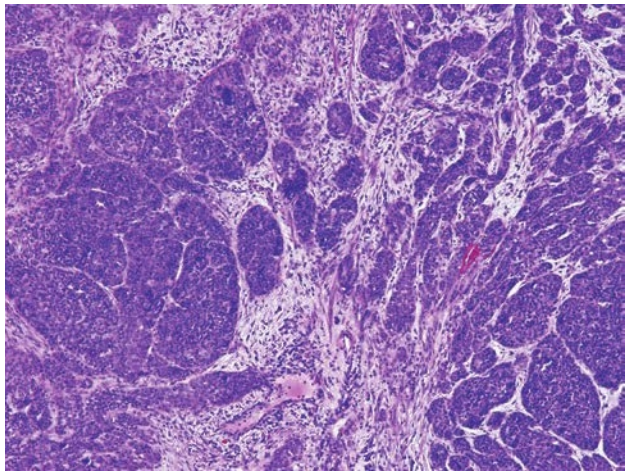


FIGURE 33–2 **Nonkeratinized squamous cell carcinoma of the anal canal.**

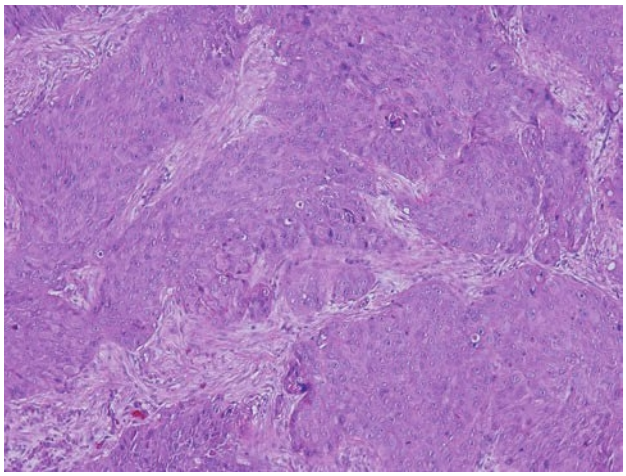


FIGURE 33–3 **Keratinized squamous cell carcinoma of the anal canal.**

CHAPTER 33

and especially those in the anal canal, but T2 tumors that are very small or far away from the sphincters could also conceivably managed with WLE with adequate counseling that T2 tumors may carry up to a 24% risk of positive LN at the time of diagnosis.[6,7]

The anal canal can be divided into two parts by a third part, the anal transition zone (ATZ). The proximal anal canal is composed of rectal mucosa, or columnar epithelium, which transitions to an ill-defined ATZ made of both cuboidal and columnar epithelium (6–12 mm in length) and extends to the dentate line.[8] The dentate line is a visible anatomic site that represents the separation of columnar epithelium (columns of Morgagni) of the proximal half of the anal canal and the squamous epithelium of the distal half of the anal canal extending to the AV. The AV is the convergence of squamous epithelium and the dermis and epidermis of the AM. Importantly, the ATZ mucosa, historically referred to as the cloacogenic mucosa, is the location for approximately 66% of nonkeratinizing SCCAs (Fig. 33–2),[8] whereas tumors distal to the dentate line are keratinizing SCCAs (Fig. 33–3).

The vascular supply of the anal canal consists of the superior, middle, and inferior rectal vessels that originate from the inferior mesenteric, internal iliac, and internal pudendal arteries, respectively. Lymphatic drainage for tumors located cranially to the dentate line is identical to rectal carcinomas draining to the perirectal and paravertebral nodes. Tumors located caudal to the dentate line drain to the inguinal and internal iliac and obturator lymph nodes. A complete physical examination should include examination of the lymph nodes of the groins.

RISK FACTORS

Several risk factors have been previously associated with the development of SCCA. Some of those relate to sexual activity, including a history of more than 10 sexual partners; anal receptive intercourse (especially men having sex with men [MSM]); having a prior sexually transmitted disease, including condyloma acuminata (genital warts, attributed to human papillomavirus [HPV]), gonorrhea, herpes virus, hepatitis, or *Chlamydia trachomatis* infection; and being human immunodeficiency virus (HIV) positive.[9–11] Another well-documented risk factor is immune suppression caused by chronic anti–organ rejection medication as seen in transplant recipient patients. Patients with these risk factors have been designated "high risk" for HPV-related disease development and are the most

commonly screened portion of the population for preinvasive disease. Recently, patients who have been diagnosed with HPV-related disease at a prior organ site (cervix, vagina, vulva, penis, scrotum, or oropharyngeal) are considered to be at greater risk that the general population and have been designated "at risk."[12–14] Although benign conditions such as hemorrhoids, fissures, and anal fistulas are often associated with HPV-related disease of the anus, they have not been determined to be causative.[15] Instead, their associated nonspecific symptoms such as bleeding per rectum, pain, fullness in the anal canal, or incomplete emptying simply overlap with SCCA.

Despite a previous emphasis on HPV being only sexually transmitted, it is now understood that HPV can be transmitted outside of sexual activity. Although transmission remains predominantly through sexual activity and is the most common sexually transmitted infection,[16] acquisition of the virus requires only direct contact with either the virus or viral-laden sloughed squamous cells. Other documented mechanisms of transmission include vertical (maternal–fetal)[17–19] and indirect through fomites.[20] Indirect transmission may be more important because the anus turns over its cellularity every 4 days,[21] one of the fastest in the body, and the body loses approximately 40,000 squamous cells every minute, or roughly 500 million each day, leaving substantial potential for patient exposure. Regardless of mode of transmission, the pathogenic changes leading to SCCA are directly related to the chronic infection with high-risk types, most commonly HPV-16 or HPV-18. Women with a history of cervical, vaginal, or vulvar cancer are three to five times more likely to develop anal cancer as opposed to stomach or colon cancer.[22] Until recently, this relationship was only explained by sexual activity; however, a recent study in women showed significant relationship between front-to-back wiping and HPV local transmission compared with blotting (dabbing) and back-to-front wiping.[23] Although this does not negate the notion of sexual transmission, it offers additional explanation for the large disparity in anal cancer between women and men for women who deny anal receptive intercourse.

Human Papillomavirus

Because HPV is the most common sexually transmitted disease in the United States and strongly associated with the development of anal carcinoma,[16] it is estimated that 75% of men and women of reproductive age have been exposed to HPV at some point in their lives. A well-cited epidemiological study by Giuliano et al[24] in 2008 revealed that in an international cohort of men, who were never received the HPV vaccine, had never practiced anoreceptive intercourse, were HIV-negative, and otherwise not recognized as high risk, the HPV positivity rate was 65.2%. High-risk HPV subtypes (16 and 18) are associated with approximately 85% to 90% of all SCCA case and develop through a precursor lesion termed *high-grade anal squamous cell intraepithelial lesions (HSIL)*. However, HSIL is a premalignant condition for which standard anal screening methods currently have not been universally recommended and have been limited to individuals considered high risk. Two international studies (ANCHOR [NCT02135419] and SPANC [NCT02007421]) are designed to address the question that treating HSIL prevents SCCA development in high-risk patients.

To confirm causation of HPV with SCCA development, a cohort of patients with metastatic SCC of the anal canal at the University of Texas MD Anderson Cancer Center (MDACC) revealed the presence of HPV, via detectable HPV DNA or expression of the protein p16, in 68 (95%) of 72 tumor samples analyzed.[25] Therefore, HPV appears to be found in the vast majority of SCCA regardless of the initial stage of presentation, yet some types are not completely associated with HPV, including basaloid or verrucous types.

The presence of HPV also has been reported to be a positive prognostic biomarker for patients with nonmetastatic SCC of the anal canal. In one study of patients with stages I to III anal cancer, HPV was detected in 120 (88%) of 137 tumors analyzed. In a multivariate analysis, p16 expression was determined to be associated with an improvement both in overall survival (OS) and disease-specific survival relative to patients with HPV-negative tumors.[26]

In 2006 and 2009, introduction of the prophylactic vaccines Gardasil and Cervarix, respectively, directed against primary infection by HPV demonstrated efficacy in reducing precancerous anogenital lesions caused by the high-risk subtypes HPV-16 and -18.[27–29] In late 2014, the U.S. Food and Drug Administration (FDA) approved the introduction of a nonavalent vaccine targeting nine HPV subtypes (6, 11, 16, 18, 31, 33, 45, 52, and 58).[30] A large, double-blind placebo-controlled study in MSM between 16 and 26 years of age demonstrated that use of the quadrivalent vaccine against HPV was both safe and well tolerated but also decreased the incidence HSIL.[29] These findings generated optimism that this preventive approach may decrease the incidence of this disease in the future. Originally approved for use in female adolescents, HPV vaccines have now received extended FDA approval as being "gender neutral" (given to both male and female patients) after their efficacy was shown in both genders, a now very promising primary prevention strategy for SCCA.[30]

Human Immunodeficiency Virus

Although a direct relationship between HIV and SCCA has not been clearly established, a strong correlation exists between HIV and HPV. Compared with

HIV-negative patients, HIV-positive patients are two to six times more likely to be diagnosed with HPV regardless of sexual practices and are also more likely to have a persistent infection.[31,32] HIV-positive men and women exposed to HPV are less likely to "clear" the virus and become HPV-negative.[32,33] For HIV-positive patients, the prevalence of SCCA is greater and presents at a younger age of onset than in HIV-negative patients.[34]

Chronic Immunosuppression

Solid organ transplantation has been associated with a 10-fold increased risk of developing SCCA and a 20-fold increased risk for vulvar and vaginal cancers.[35] A population-based cohort study conducted using the Danish National Patient Registry and the Danish Cancer Registry from 1978 to 2005 found that HIV infection, solid organ transplantation, hematologic malignancies, and a range of specific autoimmune diseases were strongly associated with increased risk of SCCA.[36]

Tobacco Use

Prior case-control studies have indicated that chronic tobacco use may result in a two- to fivefold increased likelihood of developing SCCA.[37] Moreover, tobacco smoking appears to be associated with SCCA recurrence and increased mortality; thus, smoking cessation should be encouraged when a diagnosis of SCCA is confirmed.[38]

PRESENTATION AND DIAGNOSIS

The mean age of diagnosis is approximately 62 years.[39] The most common presenting complaint is rectal bleeding. Other symptoms may include tenesmus, pain, local irritation, discharge, or a change in bowel habits as mentioned earlier. Clinically enlarged inguinal lymph nodes are present in 15% to 25% of patients at presentation.[40] Extreme and late patient presentations may include a fungating perianal mass or a verrucous mass.

A diagnostic evaluation should consist of a complete physical examination, including examination of the inguinal lymph nodes, a digital anorectal examination (DARE), and evaluation of the surrounding mucosa of the anus. Diagnostic studies should include proctosigmoidoscopy (rigid or flexible) or anoscopy (side-viewing or flat, on-end anoscope), chest radiography, and computed tomography (CT) of the chest, abdomen, and pelvis or magnetic resonance imaging (MRI) of the abdomen and pelvis to rule out distant disease. A transrectal or transvaginal ultrasound examination may add benefit in staging.[41–44] Histologic confirmation is required, with a tissue biopsy of the primary site with fine-needle aspiration of any palpable inguinal lymph nodes because this may impact the radiation fields. An HIV test should be considered in all patients, and a one-time test for hepatitis C infection may also be considered for patients born before the year 1965 given the disproportionately high risk of incidence of viral infection for patients in this age range.[45]

STAGING AND PROGNOSIS

The staging classification system for anal cancer was adopted by the American Joint Committee on Cancer (AJCC). The tumor (T) stage, unlike most GI malignancies, is not dependent on the degree of tumor tissue penetration but rather on the size of the primary tumor site. Tumors 2 cm or smaller are considered T1, tumors larger than 2 but 5 cm or smaller are considered T2, tumors larger than 5 cm are considered T3, and locally invasive tumors invading adjacent organs are considered T4. The eighth edition of the AJCC staging guidelines went into effect on January 1, 2018.[46] The T stage did not change, but the nodal (N) staging system changed based on the location of positive nodes. Nodal metastases in primary echelon drainage sites such as the inguinal, mesorectal, or internal iliac basins are considered N1a; nodal metastases in the external iliac basins are considered N1b; and lymph node metastases in both N1a and N1b locations are considered N1c.[46]

Both T and N stage have been significantly associated with response to chemoradiation and OS. Results from Radiation Therapy Oncology Group (RTOG) 8704/Eastern Cooperative Oncology Group (ECOG) 1289 showed patients with tumors 5 cm or larger were more likely to have a positive biopsy 6 weeks after completing chemoradiation (17%) compared with only 7% of patients with a tumor smaller than 5 cm.[47] The RTOG 8314 trial showed a significant difference in 3-year local control rates: 84% in patients with tumors smaller than 3 cm and 62% in patients with tumors 3 cm or larger.[48] In the EORTC phase 3 trial, tumor size was not prognostic for survival or local control, but positive lymph nodes at diagnosis was an independent poor prognostic factor for both local control and OS.[49] Subsequent analysis of the long-term results from RTOG 98-11 showed 5-year locoregional failure ranged from 17% for T2N0 disease to 60% for T4N+ disease. OS at 5 years ranged from 82% for patients with T2N0 disease to 42% for patients with T4N+ disease.[50] Patients with T1N0 tumors were not eligible for enrollment on RTOG 98-11, but small retrospective and population-based studies suggest the local control rates for T1N0 tumors range from 90% to 100%, and the 5-year OS ranges from 80% to 90%.[51,52]

HISTORY OF CHEMORADIATION: THE NIGRO REGIMEN

Before the work published by Nigro and colleagues in the 1970s, the preferred treatment for SCCA was radical surgery (APR) with a permanent colostomy. With this surgical approach alone, the local failure rates were unacceptably high. To improve local control rates, Nigro and colleagues gave chemoradiation to patients in a small pilot study in the preoperative setting. The unexpected result was a complete pathologic response in all three patients. This somewhat anecdotal finding led to the pivotal assertion that surgery may not be necessary for curative intent in the treatment of patients with SCCA.[53] The follow-up study published in 1981 by Dr. Nigro's group outlined the results of 19 further patients treated with a regimen consisting of 30 Gy delivered over 15 days. Radiation delivery consisted of a 15- × 15-cm field centered at the patient's midline with the low edge including the ischial tuberosities. 5-Fluorouracil (5-FU) was given 1000 mg/m^2/24 hours as a continuous infusion on days 1 to 4 of radiation and repeated one month later. Mitomycin C (MMC) was given as a 15 mg/m^2 intravenous bolus on day 1. Surgery occurred 4 to 6 weeks after completion of chemoradiation. Patients were examined preoperatively, and 15 of 19 had no apparent tumor; 12 of 19 had a pathological complete.[54] A subsequent publication of outcomes for a total of 28 patients treated with Nigro and colleagues' protocol reported no serious complications resulted from chemoradiation, though they did experience transient proctitis, leukopenia, and thrombocytopenia. Of the 28 patients, 22 remained tumor free and alive one to 8 years after treatment.[55]

The next series of investigations sought to establish the feasibility of treating SCCA with chemoradiation alone as well as to optimize the treatment regimen, including dose of chemotherapy agent, dose, and duration of radiotherapy. One such early report evaluated patients treated definitively with 30 to 45 Gy of radiation given with two cycles concurrent 5-FU and MMC. John and colleagues[56] reported an 86% complete response rate to this regimen, with all three local failures being successfully salvaged with surgery. The speculations of John et al were (1) the optimal dose of radiation would likely be 41.4 to 50 Gy; (2) radiation was best given continuously, rather than a split course, which may have radiobiological disadvantages; and (3) a second dose of MMC may decrease distant failure rates. Subsequent prospective trials sought to further clarify the added benefit of concurrent chemotherapy to radiation, the optimal concurrent chemotherapy agents to give with radiation, and the preferred dose and fractionation schedule for the radiation itself. Ongoing studies seek to tailor treatment to patients based on known prognostic factors such as T and N stage, escalating therapy for those with higher risk of recurrence and deescalating therapy for those with high cure rates to reduce toxicities.

RADIATION VERSUS CHEMORADIATION: THE ROLE OF MITOMYCIN C

ACT I Trial

To evaluate for a benefit for the addition of cytotoxic chemotherapy to radiation, the phase III Anal Cancer Trial (ACT I) randomized patients to radiation alone (45 Gy) versus continuous infusion 5-FU (1000 mg/m^2 on days 1–4 or 750 mg/m^2 on days 1–5) during the first and last weeks of radiation (45 Gy) with MMC (12 mg/m^2 on day 1).[57] After a median follow-up time of 42 months, the 3-year local failure rate was significantly reduced in the chemoradiation arm versus the radiation-alone arm (39% vs 61%; P <.0001), suggesting an oncologic benefit with multimodality therapy. Here, chemoradiation provided a 46% reduction in local recurrence compared with radiation alone. Notably, the 3-year mortality rate in the radiation-only arm was greater than that of the chemoradiation arm (39% vs 28%). Twenty patients (3%) required a palliative colostomy or anorectal excision because of treatment-related morbidities. Early morbidity was significant in the chemoradiation arm. Subsequently, dose reduction of MMC has been recommended if the patient is 70 years or older or if significant medical comorbidities are present.

EORTC Trial

A smaller study completed by the European Organization for Research and Treatment of Cancer (EORTC) explored the role of chemoradiation and its potential benefit in locoregional control (LRC) and colostomy-free interval.[49] A total of 110 patients were randomized to radiation (45 Gy) with or without continuous infusion 5-FU (750 mg/m^2 on days 1–5 and 29–33) and MMC (15 mg/m^2 on day 1).

Again, event-free survival was superior in the combined-modality arm (P = .03). The overall 5-year survival rate was 56% in this patient population. In contrast to the ACT I study, this clinical trial was limited to patients with more locally advanced anal cancer, specifically, T3 or T4 primary tumors or regional nodal positivity on initial imaging. Chemoradiation contributed 18% actuarial improvement in 5-year LRC and an increase in colostomy-free survival (CFS) (36%). Based on these studies, the phase III UKCCCR and EORTC

studies established combined chemoradiation as superior to radiation alone for LRC and CFS. Most medical oncologists in the United States use 5-FU and MMC as the preferred chemotherapy combination in this setting.

THE INTRODUCTION OF CISPLATIN

Despite the evident benefits of MMC in the treatment of patients with SCCA, potential treatment-related toxicities may include leukopenia, thrombocytopenia, and, rarely, hemolytic uremic syndrome and leukemia. Although a review of prior 5-FU/MMC clinical trials in SCCA suggests the potential for superior results to radiotherapy alone, these often come at the cost of treatment-related morbidity and mortality. Therefore, other agents that may reduce treatment-related toxicities without compromising efficacy would be preferable.

Mitomycin C Versus Cisplatin in Combination with 5-Fluorouracil as a Chemosensitizer (ACT II Trial)

The UK ACT II trial is the largest phase III trial conducted in SCC of the anal cancer and is the most direct analysis of 5-FU–MMC versus 5-FU–cisplatin with concurrent radiation therapy. The ACT II trial also evaluated whether maintenance chemotherapy after completion of chemoradiotherapy reduces recurrence-free survival (RFS).[58] Using a 2 × 2 factorial design, 940 patients with T1 to T4 node-negative and -positive disease were randomly assigned to either 5-FU–MMC or 5-FU–cisplatin administered concurrently with continuous radiotherapy of 50.4 Gy. The second randomization was to two courses of 5-FU–cisplatin (same schedule) consolidation chemotherapy or no further treatment. There was a greater incidence of acute grade 3 or 4 hematologic toxicity in the MMC arm (26% vs 16%; P <.001) but no statistical differences in grade 3 or 4 nonhematologic toxicities (Table 33–1).

Results after a 5-year median follow-up period demonstrated no statistically significant difference for the endpoint of 6-month CR rate for concurrent chemoradiation with 5-FU–MMC versus 5-FU–cisplatin (90.5% vs 89.6%, respectively) and no difference in either RFS or CFS, respectively (Table 33–2).

Although investigators failed to fulfill the primary endpoint of superiority for the cisplatin-based regimen, the results indicate that 5-FU–cisplatin is noninferior to 5-FU–MMC in achieving a CR but is associated with fewer significant hematologic toxicities. Maintenance 5-FU–cisplatin chemotherapy showed no added benefit for RFS or OS. Therefore, at this time, additional chemotherapy after definitive chemoradiation, even for patients with higher risk locally advanced SCCA, is not recommended.

A retrospective analysis in 197 patients with TxNxM0 SCC of the anal canal was completed at

TABLE 33–1 Rates of Grades 3 or 4 Toxicity with 5-Fluorouracil–Mitomycin C versus 5-Fluorouracil–Cisplatin (ACT II)

	5-Fluorouracil–Mitomycin C			5-Fluorouracil-Cisplatin		
	Grade 3, *n* (%)	Grade 4, *n* (%)	Grades 3/4, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)	Grades 3/4, *n* (%)
Gastrointestinal	91 (14)	3 (1)	75 (16)	125 (57)	5 (1)	85 (18)
Nausea	10 (2)	0	10 (2)	25 (5)	0	25 (5)
Vomiting	9 (2)	0	9 (2)	20 (4)	1 (<1)	21 (4)
Diarrhea	43 (9)	1 (<1)	44 (9)	42 (9)	3 (1)	45 (10)
Stomatitis	14 (3)	0	14 (3)	19 (4)	1 (<1)	20 (4)
Skin	193 (41)	35 (7)	228 (48)	201 (43)	21 (4)	222 (47)
Pain	114 (24)	8 (2)	122 (26)	120 (26)	15 (3)	135 (29)
Cardiac	7 (1)	7 (1)	7 (1)	2 (<1)	4 (<1)	6 (<1)
Hematologic	107 (23)	17 (4)	124 (26)[a]	60 (13)	13 (3)	73 (16)[a]
WBC count	103 (22)	13 (3)	112 (24)[a]	48 (10)	8 (2)	55 (12)[a]
Platelets	19 (4)	2 (<1)	21 (4)	2 (<1)	3 (<1)	5 (1)
Hemoglobin	1 (<1)	1 (<1)	2 (<1)	5 (1)	2 (<1)	7 (1)

[a]Denotes statistical significance between two treatment arms.
ACT, Anal Cancer Trial; WBC = white blood cell.
Data from James RD, Glynne-Jones R, Meadows HM, et al: Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2 × 2 factorial trial, *Lancet Oncol* 2013 May;14(6):516-524.

TABLE 33–2 Rates of Treatment Response at Week 26 with 5-Fluorouracil–Mitomycin C versus 5-Fluorouracil–Cisplatin (ACT II)

	5-Fluorouracil–Mitomycin C, *n* (%)	5-Fluorouracil–Cisplatin, *n* (%)
Complete response	391 (91)	386 (90)
Partial response	14 (3)	24 (6)
Stable disease	5 (1)	6 (1)
Progressive disease	22 (5)	15 (4)

ACT, Anal Cancer Trial.
Reproduced with permission from James RD, Glynne-Jones R, Meadows HM, et al: Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2 × 2 factorial trial, *Lancet Oncol* 2013 May;14(6):516-524.

MDACC.[59] Patients received weekly cisplatin (20 mg/m^2 intravenously) and 5-FU (300 mg/m^2/day for 120 consecutive hours weekly as a continuous infusion on days of radiation) for the duration of radiation therapy (55 Gy). The median follow-up period was 8.6 years. Complete responses after chemoradiation were observed in 185 patients (94%). The local recurrence rate was 11% with the use of 5-FU and cisplatin, and all patients with a local recurrence underwent salvage APR or diverting colostomies. Only 16 patients (8%) developed distant metastases. OS at 5 years was 86%. Grade 4 acute toxicities (diarrhea, dehydration, and skin ulceration) were infrequent. Therefore, the use of cisplatin and 5-FU with concurrent radiation is safe and effective in patients with locally advanced SCCA and may be an acceptable alternative to the traditional 5-FU–MMC regimen. Based on the finding from the ACT II trial and MDACC's institutional experience, 5-FU–cisplatin remains a preferred regimen because of its efficacy and decreased myelosuppression relative to 5-FU–MMC. This combination also allows for safer treatment of immunocompromised and older patients who otherwise might not tolerate myelosuppressive combinations.

Neoadjuvant (Induction) Chemotherapy

Another common question for the management of locally advanced anal cancer regards the role of systemic induction treatment before chemoradiation decrease the risk of distant disease development and provide an improvement in OS.

Intergroup/ACCORD 03 Trial

The phase III Intergroup/ACCORD 03 trial created a 2 × 2 factorial design to compare standard-dose (45 Gy/25 fractions, boost of 15 Gy) versus high-dose radiation therapy (boost of 20–25 Gy) and the potential benefits of induction chemotherapy with 5-FU (800 mg/m^2 on days 1–4) and cisplatin (80 mg/m^2 on day 1) for two cycles in locally advanced SCC of the anal canal.[60] Patients were required to have greater than 4-cm primary tumor or node-positive disease. A total of 306 patients were allocated to one of four treatment arms: (1) induction with standard-dose radiation therapy, (2) induction with high-dose radiation therapy, (3) control arm of 5-FU–cisplatin plus standard radiation therapy, and (4) control arm of 5-FU–cisplatin plus high-dose radiation therapy. The results were compared in terms of CFS. After a median follow-up period of 43 months, no statistically significant difference in CFS was noted for the induction arm or with the higher dose radiation therapy arm versus the control arm. Overall, no statistical differences were noted across all arms for local control, CFS, event-free survival, or OS. Therefore, induction chemotherapy does not appear to benefit patients with localized anal cancer intended to be treated with chemoradiation.

RTOG 98-11 Trial

The RTOG 98-11 trial was a large phase III multi-institutional randomized trial for locally advanced SCC of the anal canal[4] that randomized 682 patients with T2 to T4 tumors and any nodal status to receive 5-FU–MMC and concurrent radiation (control arm) or induction 5-FU–cisplatin followed by concurrent 5-FU–cisplatin and radiation. It is important to note the treatment imbalance in the two arms such that whereas patients randomized to the experimental group received induction chemotherapy, those randomized to the control arm did not. All patients received 45 to 50 Gy of radiation, with an additional 10 to 14 Gy in 2-Gy fractions given to patients with residual evidence of disease, tumors larger than 5 cm, or tumor invasion of adjacent organs. From a recent long-term update, improved outcomes were noted in the group randomized to 5-FU–MMC and concurrent radiation. Five-year DFS was significantly better in this group (68% vs 58%) compared with those receiving induction 5-FU–cisplatin followed by concurrent 5-FU–cisplatin and radiation, as was 5-year OS (78% vs 71%). Trends in CFS, LRC, and colostomy failure all favored the 5-FU–MMC arm as well, although none reached statistical significance. Grade 3 or 4 hematologic toxicity was observed more

frequently in patients randomized to the 5-FU–MMC arm (62% vs 42%; $P < .0001$).

Despite the initial appearance that 5-FU–MMC treatment is superior for patients with nonmetastatic SCCA, these findings must be interpreted with caution. This study has since been critiqued for the inequality of the two treatment schedules, making a direct comparison of MMC and cisplatin, in combination with 5-FU, difficult because the confounding factor of induction chemotherapy in the investigational arm.[58] Additionally, administration of induction chemotherapy delayed the time to initiation of curative chemoradiation and thereby prolonged the overall treatment time, a metric that, when extended, has been associated with worse clinical outcomes in clinical trials for SCCA. Nonetheless, based on these findings, induction chemotherapy in patients with early-stage SCC of the anal canal is not routinely administered at MDACC.

RADIATION TECHNIQUE, DOSE, AND FRACTIONATION

Evolution of Radiation Technique

The preferred radiation technique has evolved since the 1970s with advances in technology related to imaging, radiation treatment planning, and radiotherapy delivery. Early radiation therapy was delivered using two simple fields in the anteroposterior and posteroanterior directions on a 6-MeV linear accelerator. The intended target included the anal canal as well as elective nodal coverage of the internal iliac, external iliac, perirectal, presacral, and obturator lymph nodes. For patients who had clinical inguinal nodal involvement, the field was extended laterally to cover the groins, and the surface dose was boosted with supplemental electron beams.[56] Limitations to this technique included high rates of G3 and G4 toxicities, necessitating a treatment break in up to 50% of patients given the volumes of normal bone marrow, bowel, and skin exposed.[61] As radiation techniques moved from the two-dimensional (2D) to the three-dimensional era, radiation to doses of 50 to 54 Gy in 1.8-Gy fractions were able to be given continuously without a planned break and without unplanned breaks because of toxicity. Because of the more conformal dose distribution to the target volume better avoids unnecessary dose to nearby organs and tissues. G3 toxicities for bone marrow, bowel, and skin were shown to be much improved in a phase II study from McGill University[62] and were used in RTOG 9811, UK ACT II, and other contemporary trials.

The next technological improvement in radiation delivery was more conformal technology called intensity-modulated radiation therapy (IMRT). It is a technique that uses multiple radiation beams from various angles in which the intensity of each beam is adapted to match the contours of the radiation target and carve unnecessary dose out of nearby organs. This technique allows for "dose painting," also called a simultaneous integrated boost technique, which allows different targets within the field to receive different doses of radiation per day. IMRT was prospectively testing in a phase 2 study, RTOG 0529. Results showed IMRT was able to significantly reduce acute G2+ hematologic and G3+ dermatologic and GI toxicities compared with historic controls from RTOG 9811.[63] The RTOG 0529 trial established IMRT as the standard of care and it remains today.[64] Current investigations are ongoing into different radiation modalities such as proton beam therapy to see if unnecessary dose to normal tissues in the pelvis can be further reduced.[65]

Radiation Dose and Fractionation

The initial dose and fractionation used in the Nigro protocol was 30 Gy in 15 fractions delivered over 3 weeks.[53] Subsequent studies evaluated doses from 45 to 50.4 Gy delivered over 4 to 5 weeks and showed local failure rates of about 25%.[47] RTOG 92-08 sought to decrease local failure by escalating the radiation dose to 59.6 Gy delivered split course over 8.5 weeks with a planned 2-week rest period to allow for recovery of dermal toxicity. Dose escalation in this study did not show improvement in local control and actually had a higher colostomy rate at 1 and 2 years posttreatment (23% vs 6% and 30% vs 7%) compared with RTOG 87-04, which gave 45 to 50.4 Gy without a planned break.[47] The conclusion of that study was that the split course schedule may have eroded any potential benefit of dose escalation, and the 2-week break may have led to a decrement in tumor control as evidenced by the higher need for colostomy.[66] The RTOG 87-04 and RTOG 92-08 studies both used 2D techniques, which limited the ability to conform the dose away from normal pelvic organs, so the side effects of radiation precluded dose escalation in a continuous fashion without a treatment break. A French randomized phase III study, ACCORD 3, had a 2 × 2 factorial design in which one of the randomizations compared standard-dose boost with high-dose boost given 3 weeks after completion of 45 Gy in 25 fractions. The boost was given with EBRT or brachytherapy with 192-Iridium. There was also no benefit to the higher boost dose in this study, but it should be noted that the schedule for ACCORD 3 was essentially split course with a 3-week break between the end of the initial 45 Gy and the beginning of the boost. It should also be noted that the total dose in the "standard-dose" arm was 60 Gy, and the total dose in the "high-dose" arm was 65 to 70 Gy.[67] The doses delivered on RTOG 0529, which used IMRT technique with a continuous radiation

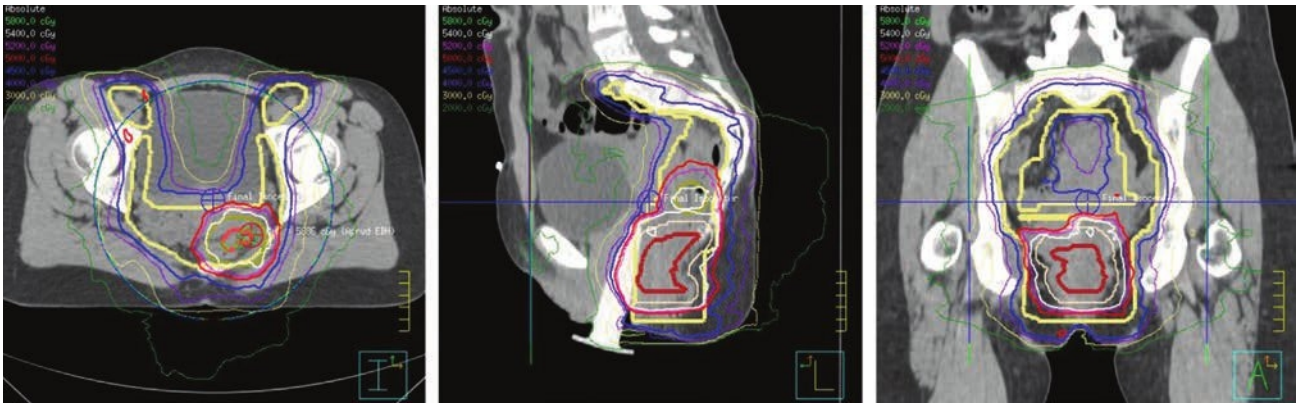


FIGURE 33–4 Representative axial (A), sagittal (B), and coronal (C) slices from a definitive chemoradiation plan for a patient with T2N1a squamous cell carcinoma of the anal canal; 54 Gy in 27 fractions was prescribed to the anal tumor plus margin; 50 Gy in 27 fractions was prescribed to a 1.5-cm presacral lymph node plus margin; and 45 Gy in 27 fractions was prescribed to the elective nodal volume. Note that a vaginal dilator was inserted for planning and daily treatment to displace the anterior vaginal wall and urethra away from the high-dose region.

schedule, depended somewhat on tumor size. T2N0 tumors received a total of 50.4 Gy to the anal tumor with 42 Gy to the elective pelvic lymph nodes in 28 fractions. T3 and T4 tumors received 54 Gy in 30 fractions, and the elective pelvic and inguinal lymph nodes received 45 Gy.[63] Along similar lines, at the MDACC, the current standard uses a moderate dose escalation for T3 and T4 tumors because the analysis of RTOG 98-11 data showed these patients are at highest risk for local recurrence.[50] In total, 50 Gy in 25 fractions for T1 tumors, 54 Gy in 27 fractions for T2 tumors, and 58 Gy in 29 fractions for T3 and T4 tumors are delivered. The doses to the elective pelvic and inguinal nodes are 43 Gy, 45 Gy, and 47 Gy, respectively, in those fractionations. Grossly involved lymph nodes are similarly dosed based on size, with nodes 2 cm or smaller receiving 50 Gy, nodes 2 or larger but 5 cm or smaller receiving 54 Gy, and nodes larger than 5 cm receiving 58 Gy (Fig. 33–4).

With this tailored approach, local recurrence rates have been only 11% despite a disproportionately advanced stage patient population. Furthermore, retrospective multivariate analysis did not show T stage is a poor prognostic factor, potentially because patients with advanced T-stage tumors are treated appropriately more aggressively.[59]

RECURRENT DISEASE

APR is the only effective, definitive treatment option for localized recurrent or residual primary disease after chemoradiation for SCC of the anal canal. Although an often considered aggressive approach to persistence or recurrent disease, APR provides cure in up to 70% of patients.[68–70] In these patients, a typical APR, posterior exenteration or total pelvic exenteration, yields a massive tissue defect that requires reconstruction, and although there are options for tissue rearrangement, a vertical rectus abdominus myocutaneous flap often provides the best reconstruction. There is no role for definitive reirradiation for an in-field recurrence, but neoadjuvant chemoradiation (39 Gy in 26 fractions twice daily with chemotherapy) may be used in cases when there are concerns about the radial margin. When available, consideration of intraoperative radiation may provide an additional option for R1 (tumor 2 mm from margin) disease but has no role if only an R2 (gross tumor at margin) resection is achievable.

The management of patients with nodal recurrences should be individualized based on the extent of disease, prior radiation delivered to the area of recurrence, and performance status of the patient. When patients have been referred to the MDACC with nodal recurrence outside of or at the margin of a prior radiation field, salvage chemoradiation has been effective provided that a full dose of reirradiation is possible. For in-field nodal recurrences, a preoperative chemoradiation to 39 Gy in 26 fractions twice daily followed by surgical resection is typically considered.

METASTATIC ANAL CARCINOMA

Chemotherapy for Metastatic Anal Cancer

Although the majority of patients with SCC of the anal canal will be cured with chemoradiation, a fraction of patients will develop metastatic disease. Median survival from the time of metastatic disease has been estimated between 18 to 24 months.[71] The liver and lymph nodes are among the most common sites for distant

organ involvement, with bone metastases occurring in fewer than 10% of cases.[71] Because of the rarity of metastatic SCCA, a universally accepted treatment approach for the management had been historically based on small case series.[72] However, results from recently completed prospective studies have generated new treatment options for these patients (Table 33–3).

A randomized phase II trial conducted through the National Cancer Institute (NCI)–sponsored International Rare Cancer Initiative (collaboration compared doublet chemotherapy with cisplatin (60 mg/m^2)–5-FU (1000 mg/m^2/day as a continuous infusion for days 1–4) every 21 days or carboplatin (AUC 5)–paclitaxel (80 mg/m^2 on days 1, 8, and 15) every 28 days in patients with previously untreated, unresectable, locally recurrent or metastatic SCCA.[73] In this study (InterAACT) of 91 patients, the primary objective for detecting a 10% difference in response rate was not satisfied. Here, radiographic responses were observed in 57% patients receiving cisplatin–5-FU and in 59% patients receiving carboplatin–paclitaxel. A nonsignificant trend toward improved progression-free survival (PFS) was observed in patients treated with carboplatin–paclitaxel (8.1 months vs 5.7 months; $P = .38$), with an improvement in OS (20 months vs 12 months; $P = .01$). Whereas cisplatin–5-FU had previously been listed as the lone systemic treatment for patients with metastatic SCCA, this study was instrumental in establishing the role of carboplatin–paclitaxel in this setting.

In the InterAACT trial, rates of grade 3 or higher treatment-related adverse events exceeded 70% in both arms, although rates of serious grade 3 or higher adverse events were more common in patients receiving 5-FU–cisplatin every 21 days (62% vs 36%; $P = .02$). Therefore, oncologists should be mindful of anticipated toxicities, especially myelosuppression, nausea and vomiting, and fatigue, when considering these regimens. To mitigate the anticipated treatment-related complications, at our institution, we administer cisplatin (40 mg/m^2) and 5-FU (2400 mg/m^2/day as a continuous infusion over 46 hours) every 14 days. Rates of grade 3 or higher adverse events with this dosing have been reported in single-institution retrospective series to be lower than those noted with the regimens used in the InterAACT trial.[74] This biweekly schedule for cisplatin–5-FU offers a tolerable and effective approach for the treatment of patients with metastatic SCCA.

Recently, the single-arm HPV-EPITOPES-02 trial of docetaxel, cisplatin, and 5-FU for patients with treatment-naïve metastatic anal cancer demonstrated impressive survival outcomes.[75] Here, the overall response rate was reported to be 86% (57 of 66 patients), with complete radiographic responses noted in 44% cases. Median PFS for this regimen was 11 months. As expected for concurrent use of three cytotoxic agents, rates of grade 3 or higher adverse events exceeded 70% but were less common when modified doses were administered every 2 weeks. This regimen appears very effective in the treatment of patients with metastatic SCCA yet should be reserved for patients with a robust performance status who can withstand the likelihood of more pronounced treatment-related toxicity.

Immunotherapy for Metastatic Anal Cancer

Given the paucity of available treatment options for patients with incurable SCCA, the use of immunotherapy is an attractive treatment strategy for this virally driven malignancy. Here, immune checkpoint blockade therapies have been approved for other HPV-associated malignancies, given clinical activity noted in SCC of the head and neck (with or without concomitant chemotherapy)[76–78] and of the cervix.[79]

In the NCI9673 phase II trial of patients with pretreated, unresectable SCCA, radiographic response to the anti–PD-1 (programmed cell death protein 1) antibody nivolumab was observed in 9 of 37 cases (overall response rate, 24%).[80] Including patients with stable disease, the disease control rate with nivolumab was

TABLE 33–3 Clinical Outcomes of Systemic Therapies in Recent Prospective Trials for Metastatic Anal Cancer

Regimen	Trial Name	Line of Treatment	Patients (*n*)	Response Rate (%)	Median PFS (months)	Median OS (months)
Carboplatin–paclitaxel	InterAACT	Frontline	45	59	8.1	20
Cisplatin–5-fluorouracil	InterAACT	Frontline	46	57	5.7	12
Docetaxel–cisplatin/5-fluorouracil	HPV-EPITOPES-02	Frontline	69	86	11	NR
Nivolumab	NCI9673	Refractory	37	24	4.1	12
Pembrolizumab	KEYNOTE-158	Refractory	112	11	2.0	12

NR, not reached; OS, overall survival; PFS, progression-free survival.

72%. Median PFS was 4 months. Nivolumab was well tolerated as a monotherapy in this study. Similarly, the KEYNOTE-158 trial reported an overall response rate of 11% and median PFS of 2 months with single-agent anti–PD-1 antibody pembrolizumab for 112 patients with pretreated metastatic anal cancer.[81] Here, patients who demonstrated a response to pembrolizumab were able to achieve sustained clinical benefit, with PFS exceeding 24 months in more than 90% of this subgroup. Based on these collective findings, nivolumab and pembrolizumab are recommended treatment options for patients with treatment-refractory metastatic SCCA.

Although anti–PD-1 therapies benefit a fraction of patients with incurable SCCA, establishment of a biomarker(s) to identify the subpopulation that derives benefit with this approach is needed. Microsatellite instability and high tumor burden are uncharacteristic of this disease and may not be drivers for response to immune checkpoint blockade.[82] Analysis of pretreatment biopsies from the NCI9673 trial found that higher baseline expression of programmed cell death ligand 1 (PD-L1) on tumor cells and increased numbers of activated cytotoxic T-cells within the tumor microenvironment were both associated with an increased likelihood for response to nivolumab. Coexpression of immune biomarkers LAG-3 and TIM-3 with PD-1 on activated cytotoxic T-cells were also more common for tumors of responding patients. Early results then suggest that immunologically active tumors at baseline may predispose patients with metastatic SCCA to increased benefit of these immunotherapy agents.

Some patients presenting with metastatic disease do achieve excellent long-term survival. For example, a subset of patients at the MDACC with oligometastatic SCCA underwent definitive therapy to limited site(s) of distant metastases, either with surgical resection or with (chemo)radiation. For these patients, OS was prolonged (53 months vs 17 months; $P < .001$), which was likely a reflection of a lower total burden of disease and favorable underlying tumor biology. Consideration of curative-intent surgical resection and/or definitive chemoradiation of oligometastatic SCCA should be considered on an individualized basis through multidisciplinary discussion, most often after demonstration of an upfront response to systemic therapy.

SURVEILLANCE

Although surveillance guidelines are always in flux, current guidelines suggest patients treated with chemoradiation therapy (with curative intent) should be initially evaluated by 3 months upon completion of therapy with an inguinal lymph node examination, DARE, and anoscopy if possible. Review of outcomes from ACT II revealed that 29% of patients without CR by week 11 after completion of definitive chemoradiation did achieve a CR by week 26.[83] Based on these findings, in the presence of improving symptoms or continued tumor regression on evaluation, at the MDACC, patients are allowed 26 weeks to achieve a CR before referral for APR. If clinical progression becomes apparent before this point, then patients are sent promptly for salvage evaluation. After that, routine anal and groin examinations every 3 to 6 months by either the medical, radiation, or surgical oncology providers for 2 years. After 2 years, routine examinations may be performed every 6 months for the remaining 3 years.[84] Biopsy of any scar or questionable residual or recurrent disease before 6 months after chemoradiation is not suggested unless there is clear evidence of residual disease or progression is suspected. If clinical CR is achieved but the posttreatment scar is abnormal yet not suggestive of recurrence, it is important that the surgeon following the patient perform the routine anal examinations to assess for subtle changes and propose biopsy as necessary. Physical examination must include a DARE and assessment for any palpable inguinal lymph nodes. Vaginal dilators may be used three times a week if needed to prevent vaginal strictures. The critical time for the prevention of vaginal stenosis is 3 to 6 months after completion of chemoradiation therapy. Vaginal hormonal creams and suppositories are also useful for treatment of vaginal dryness and dyspareunia. Proctosigmoidoscopy should be performed biannually after a CR for 2 years. Chest radiography and CT of the chest, abdomen, and pelvis or MRI of the abdomen and pelvis should be completed annually for 2 years. Anal cytology collection via a Dacron anal swab (formerly anal pap smears) should continue to be performed annually.

ADENOCARCINOMA OF THE ANAL CANAL

Adenocarcinomas of the anal canal occur less frequently than SCCs and are not to be confused with extramammary Paget disease of the anus.[39] Nonetheless, most of the reports overestimate the incidence of adenocarcinoma of the anal canal because they do not exclude contamination by the more common distal rectal cancer. Its true incidence within all anal cancers is likely less than 10%. The most appropriate management remains to be defined, with no large prospective studies completed to date given its exquisite rarity. The most striking difference between anal adenocarcinoma and SCCA is the high distant metastasis rate in anal adenocarcinoma, which tends to undermine the impact of local tumor control. Retrospective analysis from the MDACC experience with anal adenocarcinoma has suggested a benefit of neoadjuvant chemoradiation

followed by APR (in patients without known metastases) with the consideration of adjuvant chemotherapy analogous to the treatment of rectal cancer.[85]

CONCLUSIONS

Carcinoma of the anus is an uncommon GI malignancy with a rising incidence in the United States despite the introduction of a preventive HPV vaccine. Chemoradiation is provided with curative intent for patients with nonmetastatic disease. Recurrence or persistent disease after curative-intent chemoradiation therapy results in the need for an APR. Hence, it is recommended that all patients diagnosed be initially evaluated at a tertiary cancer center or the equivalent given the rarity of the disease and the potential for permanent loss of sphincter preservation. It is highly recommended that a multidisciplinary team discussion with significant expertise for the most appropriate treatment in this rare malignancy is organized and consulted for management of patients with these diagnoses. Both cytotoxic chemotherapy and immune checkpoint blockade therapies have demonstrated efficacy for patients with metastatic disease. It is expected that the role of immunotherapy will be expanded further in the management of patients with anal cancer in the coming years.

MD ANDERSON PRACTICE TIPS

- Weekly cisplatin and 5-FU is a well-tolerated, clinically efficacious chemosensitizer associated with moderate toxicity for patients with locally advanced anal cancer undergoing chemoradiation.
- For female patients, a vaginal dilator should be used during daily radiation treatments to displace the anterior vaginal wall and urethra from the high-dose region and reduce genitourinary toxicities from treatment. For male patients, the scrotum should be elevated away from the perineum during treatment to reduce skin and testicular toxicity. For both men and women, patients should be treated with a full bladder to displace small bowel from the pelvis and reduce the risk of GI toxicity.
- In the absence of clinical or radiographic progression, patients with locoregional anal cancer can be followed for resolution of their disease up to 26 weeks after completion of chemoradiation. Salvage surgery with APR is reserved for patients with persistent or locally recurrent disease after definitive therapy.
- Patients presenting with oligometastatic anal cancer can be treated successfully with curative intent through multidisciplinary management of the primary tumor and metastatic lesion(s).
- Patients with metastatic anal cancer with/without coexisting altered immunity (eg, HIV/AIDS, concurrent immunosuppressive medications for prior organ transplantation or autoimmune disorder) can safely be treated with a modified, every-14-day regimen of cisplatin–5-FU with a low likelihood for chemotherapy-related myelosuppression.
- At present, immune checkpoint blockade therapies can safely be administered without consideration of tumor mutation burden or PD-L1 status for patients with treatment-refractory metastatic anal cancer, although translational studies seek to characterize biomarkers associated with response to immunotherapy.

ACKNOWLEDGMENTS

The authors acknowledge Dr. Stanley Hamilton and the Department of Pathology at the University of Texas MD Anderson Cancer Center for providing representative pathology slides as a contribution to this chapter.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(1):7-30.
2. Deshmukh AA, Suk R, Shiels MS, et al. Recent trends in squamous cell carcinoma of the anus incidence and mortality in the United States, 2001-2015. *J Natl Cancer Inst*. 2019.
3. Rickert RR, Compton CC. Protocol for the examination of specimens from patients with carcinomas of the anus and anal canal: a basis for checklists. Cancer Committee of the College of American Pathologists. *Arch Pathol Lab Med*. 2000;124(1):21-25.
4. Gunderson LL, Winter KA, Ajani JA, et al. Long-term update of US GI intergroup RTOG 98-11 phase III trial for anal carcinoma: survival, relapse, and colostomy failure with concurrent chemoradiation involving fluorouracil/mitomycin versus fluorouracil/cisplatin. *J Clin Oncol*. 2012;30(35):4344-4351.
5. Bendell JC, Ryan DP. Current perspectives on anal cancer. *Oncology (Williston Park)*. 2003;17(4):492-497, 502-503; discussion 503, 507-509.
6. Papillon J, Chassard JL. Respective roles of radiotherapy and surgery in the management of epidermoid carcinoma of the anal margin. Series of 57 patients. *Dis Colon Rectum*. 1992;35(5):422-429.
7. Khanfir K, Ozsahin M, Bieri S, et al. Patterns of failure and outcome in patients with carcinoma of the anal margin. *Ann Surg Oncol*. 2008;15(4):1092-1098.
8. Gervasoni JE Jr, Wanebo HJ. Cancers of the anal canal and anal margin. *Cancer Invest*. 2003;21(3):452-464.
9. Frisch M, Glimelius B, van den Brule AI, et al. Sexually transmitted infection as a cause of anal cancer. *N Engl J Med*. 1997;337(19):1350-1358.
10. Patel P, Hanson DL, Sullivan PS, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. *Ann Intern Med*. 2008;148(10):728-736.
11. Daling JR, Madeleine MM, Johnson LG, et al. Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. *Cancer*. 2004;101(2):270-280.
12. Nyitray AG, D'Souza G, Stier EA, et al. The utility of digital anal rectal examinations in a public health screening program for anal cancer. *J Low Genit Tract Dis*. 2020;24(2):192-196.
13. Wang M, Sharma A, Osazuwa-Peters N, et al. Risk of subsequent malignant neoplasms after an index potentially-human papillomavirus (HPV)-associated cancers. *Cancer Epidemiol*. 2020;64:101649.
14. Fokom Domgue J, Messick C, Milbourne A, et al. Prevalence of high-grade anal dysplasia among women with high-grade lower genital tract dysplasia or cancer: results of a pilot study. *Gynecol Oncol*. 2019;153(2):266-270.
15. Frisch M, Olsen JH, Bautz A, Melbye M. Benign anal lesions and the risk of anal cancer. *N Engl J Med*. 1994;331(5):300-302.
16. Jay N, Moscicki A-B. Human papillomavirus infection in women. In: Goldman MB, Hatch MC, eds. Women and Health. Academic Press; 2000 [Chapter 25]:324–336. https://doi.org/10.1016/B978-0-12-288145-9.X5000-1.
17. Hahn HS, Kee MK, Kim HJ, et al. Distribution of maternal and infant human papillomavirus: risk factors associated with vertical transmission. *Eur J Obstet Gynecol Reprod Biol*. 2013;169(2):202-206.
18. Koskimaa HM, Waterboer T, Pawlita M, et al. Human papillomavirus genotypes present in the oral mucosa of newborns and their concordance with maternal cervical human papillomavirus genotypes. *J Pediatr*. 2012;160(5):837-843.
19. Trottier H, Mayrand MH, Coutlée F, et al. Human papillomavirus (HPV) perinatal transmission and risk of HPV persistence among children: design, methods and preliminary results of the HERITAGE study. *Papillomavirus Res*. 2016;2:145-152.
20. Roden RB, Lowy DR, Schiller JT. Papillomavirus is resistant to desiccation. *J Infect Dis*. 1997;176(4):1076-1079.
21. Lipkin M, Bell B, Sherlock P. Cell proliferation kinetics in the gastrointestinal tract of man. I. Cell renewal in colon and rectum. *J Clin Invest*. 1963;42(6):767-776.
22. Melbye M, Sprøgel P. Aetiological parallel between anal cancer and cervical cancer. *Lancet*. 1991;338(8768):657-659.
23. Simpson S Jr, Blomfield P, Cornall A, et al. Front-to-back & dabbing wiping behaviour post-toilet associated with anal neoplasia & HR-HPV carriage in women with previous HPV-mediated gynaecological neoplasia. *Cancer Epidemiol*. 2016;42:124-132.
24. Giuliano AR, Lazcano-Ponce E, Villa LL, et al. The human papillomavirus infection in men study: human papillomavirus prevalence and type distribution among men residing in Brazil, Mexico, and the United States. *Cancer Epidemiol Biomarkers Prev*. 2008;17(8):2036-2043.
25. Morris V, Rashid A, Rodriguez-Bigas M, et al. Association of human papillomavirus with unique clinicopathologic features in patients with metastatic squamous cell carcinoma of the anal canal. *J Clin Oncol*. 2014;32:479.
26. Serup-Hansen E, Linnemann D, Skovrider-Ruminski W, et al. Human papillomavirus genotyping and p16 expression as prognostic factors for patients with American Joint Committee on Cancer stages I to III carcinoma of the anal canal. *J Clin Oncol*. 2014;32(17):1812-1817.
27. Kahn JA. HPV vaccination for the prevention of cervical intraepithelial neoplasia. *N Engl J Med*. 2009;361(3):271-278.
28. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med*. 2007;356(19):1928-1943.
29. Palefsky JM, Giuliano AR, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. *N Engl J Med*. 2011;365(17):1576-1585.
30. U.S. Food and Drug Administration. Gardasil 9. https://www.fda.gov/vaccines-blood-biologics/vaccines/gardasil-9
31. Piketty C, Darragh TM, Da Costa M, et al. High prevalence of anal human papillomavirus infection and anal cancer precursors among HIV-infected persons in the absence of anal intercourse. *Ann Intern Med*. 2003;138(6):453-459.
32. Sun XW, Kuhn L, Ellerbrock TV, et al. Human papillomavirus infection in women infected with the human immunodeficiency virus. *N Engl J Med*. 1997;337(19):1343-1349.
33. Critchlow CW, Hawes SE, Kuypers JM, et al. Effect of HIV infection on the natural history of anal human papillomavirus infection. *AIDS*. 1998;12(10):1177-1184.
34. Sobhani I, Vuagnat A, Walker F, et al. Prevalence of high-grade dysplasia and cancer in the anal canal in human papillomavirus-infected individuals. *Gastroenterology*. 2001;120(4):857-866.
35. Adami J, Gäbel H, Lindelöf B, et al. Cancer risk following organ transplantation: a nationwide cohort study in Sweden. *Br J Cancer*. 2003;89(7):1221-1227.
36. Sunesen KG, Nørgaard M, Thorlacius-Ussing O, et al. Immunosuppressive disorders and risk of anal squamous cell carcinoma: a nationwide cohort study in Denmark, 1978-2005. *Int J Cancer*. 2010;127(3):675-684.
37. Daling JR, Sherman KJ, Hislop TG, et al. Cigarette smoking and the risk of anogenital cancer. *Am J Epidemiol*. 1992;135(2):180-189.
38. Ramamoorthy S, Luo L, Luo E, Carethers JM. Tobacco smoking and risk of recurrence for squamous cell cancer of the anus. *Cancer Detect Prev*. 2008;32(2):116-120.
39. Myerson RJ, Karnell LH, Menck HR. The National Cancer Data Base report on carcinoma of the anus. *Cancer*. 1997;80(4):805-815.
40. Khatri VP, Chopra S. Clinical presentation, imaging, and staging of anal cancer. *Surg Oncol Clin North Am*. 2004;13(2):295-308.

41. Cotter SE, Grigsby PW, Siegel BA, et al. FDG-PET/CT in the evaluation of anal carcinoma. *Int J Radiat Oncol Biol Phys*. 2006;65(3):720-725.
42. Mackay SG, Pager CK, Joseph D, et al. Assessment of the accuracy of transrectal ultrasonography in anorectal neoplasia. *Br J Surg*. 2003;90(3):346-350.
43. Tarantino D, Bernstein MA. Endoanal ultrasound in the staging and management of squamous-cell carcinoma of the anal canal: potential implications of a new ultrasound staging system. *Dis Colon Rectum*. 2002;45(1):16-22.
44. Berton F, Gola G, Wilson SR. Perspective on the role of transrectal and transvaginal sonography of tumors of the rectum and anal canal. *AJR Am J Roentgenol*. 2008;190(6):1495-1504.
45. Smith BD, Morgan RL, Beckett GA, et al. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. *MMWR Recomm Rep*. 2012;61(Rr-4):1-32.
46. Amin MB, Edge S, Green F, et al. *AJCC Cancer Staging Manual*. 8th ed. Springer; 2017.
47. Flam M, John M, Pajak TF, et al. Role of mitomycin in combination with fluorouracil and radiotherapy, and salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized intergroup study. *J Clin Oncol*. 1996;14:2527-2539.
48. Sischy B, Doggett RL, Krall JM, et al. Definitive irradiation and chemotherapy for radiosensitization in management of anal carcinoma: interim report on Radiation Therapy Oncology Group study 8314. *J Natl Cancer Inst*. 1989;81:850-856.
49. Bartelink H, Roelofsen F, Eschwege F, et al. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. *J Clin Oncol*. 1997;15(5):2040-2049.
50. Gunderson LL, Moughan J, Ajani JA, et al. Anal carcinoma: impact of TN category of disease on survival, disease relapse, and colostomy failure in the US Gastrointestinal Intergroup RTOG 98-11 phase 3 trial. *Int J Radiat Oncol Biol Phys*. 2013;87(4):638-645.
51. Zilli T, Schick U, Ozsahin M, et al. Node-negative T1-T2 anal cancer: radiotherapy alone or concomitant chemotherapy? *Radiother Oncol*. 2012;102:62-67.
52. Deshmukh AA, Zhao H, Das P, et al. Clinical and economic evaluation of treatment strategies for T1N0 anal canal cancer. *Am J Clin Oncol* 2018;41:626-631.
53. Nigro ND, Vaitkevicius VK, Considine B Jr. Combined therapy for cancer of the anal canal: a preliminary report. *Dis Colon Rectum*. 1974;17(3):354-356.
54. Nigro ND, Vaitkevicius VK, Buroker T, et al. Combined therapy for cancer of the anal canal. *Dis Colon Rectum*. 1981;24(2):73-75.
55. Nigro ND, Seydel HG, Considine B, et al. Combined preoperative radiation and chemotherapy for squamous cell carcinoma of the anal canal. *Cancer*. 1983;51(10):1826-1829.
56. John MJ, Flam M, Lovalvo L, Mowry PA. Feasibility of non-surgical definitive management of anal canal carcinoma. *Int J Radiat Oncol Biol Phys*. 1987;13(3):299-303.
57. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. UKCCCR Anal Cancer Trial Working Party. UK Co-ordinating Committee on Cancer Research. *Lancet*. 1996;348(9034):1049-1054.
58. James RD, Glynne-Jones R, Meadows HM, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2 x 2 factorial trial. *Lancet Oncol*. 2013;14(6):516-524.
59. Eng C, Chang GJ, You YN, et al. Long-term results of weekly/daily cisplatin-based chemoradiation for locally advanced squamous cell carcinoma of the anal canal. *Cancer*. 2013;119(21):3769-3775.
60. Conroy T, Ducreux M, Lemanski C, et al. Treatment intensification by induction chemotherapy (ICT) and radiation dose escalation in locally advanced squamous cell anal canal carcinoma (LAAC): definitive analysis of the intergroup ACCORD 03 trial [abstract]. *J Clin Oncol*. 2009;27(15 suppl):4033.
61. John M, Pajak T, Flam M, et al. Dose escalation without split course radiation for anal cancer: results of a phase II RTOG study. *Int J Radiat Oncol Biol Phys*. 1997;39:203.
62. Vuong T, Devic S, Belliveau P, et al. Contribution of conformal therapy in teh treatment of anal canal carcinoma with combined chemotherapy and radiotherapy: results of a phase II study. *Int J Radiat Oncol Biol Phys*. 2003;56(3):823-831.
63. Kachnic LA, Winter K, Myerson RJ, et al. RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. *Int J Radiat Oncol Biol Phys*. 2013;86(1):27-33.
64. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Anal Carcinoma Version 1.2020. https://www.nccn.org/professionals/physician_gls/default.aspx#site
65. Wo JY, Plastaras JP, Metz JM, et al. Pencil beam scanning proton beam chemoradiation therapy with 5-fluorouracil and mitomycin-C for definitive treatment of carcinoma of the anal canal: a multi-institutional pilot feasibility study. *Int J Radiat Oncol Biol Phys*. 2019;105(1):90-95.
66. John M, Pajak T, Flam M, et al. Dose escalation in chemoradiation for anal cancer: preliminary results of RTOG 92-08. *Cancer J Sci Am*. 1996;2(4):205-2011.
67. Peiffert D, Tournier-Rangeard L, Gérard JP, et al. Induction chemotherapy and dose intensification of the radiation boost in locally advanced anal canal carcinoma: final analysis of the randomized UNICANCER ACCORD 03 trial. *J Clin Oncol*. 2012;30(16):1941-1948.
68. Nilsson PJ, Svensson C, Goldman S, Glimelius B. Salvage abdominoperineal resection in anal epidermoid cancer. *Br J Surg*. 2002;89(11):1425-1429.
69. Tarazi R, Nelson RL. Anal adenocarcinoma: a comprehensive review. *Semin Surg Oncol*. 1994;10(3):235-240.
70. Delhorme JB, Severac F, Waissi W, et al. Surgery is an effective option after failure of chemoradiation in cancers of the anal canal and anal margin. *Oncology*. 2017;93(3):183-190.
71. Eng C, Chang GJ, You YN, et al. The role of systemic chemotherapy and multidisciplinary management in improving the overall survival of patients with metastatic squamous cell carcinoma of the anal canal. *Oncotarget*. 2014;5(22):11133-11142.
72. Eng C, Pathak P. Treatment options in metastatic squamous cell carcinoma of the anal canal. *Curr Treat Options Oncol*. 2008;9(4-6):400-407.
73. Rao S, et al. LBA21-InterAACT: a multicentre open label randomised phase II advanced anal cancer trial of cisplatin (CDDP) plus 5-fluorouracil (5-FU) vs carboplatin (C) plus weekly paclitaxel (P) in patients (pts) with inoperable locally recurrent (ILR) or metastatic treatment naïve disease—An International Rare Cancers Initiative (IRCI) trial. *Ann Oncol*. 2018;29:viii715-viii716.
74. Mondaca S, Chatila WK, Bates D, et al. FOLFCIS treatment and genomic correlates of response in advanced anal squamous cell cancer. *Clin Colorectal Cancer*. 2019;18(1):e39-e52.
75. Kim S, François E, André T, et al. Docetaxel, cisplatin, and fluorouracil chemotherapy for metastatic or unresectable locally recurrent anal squamous cell carcinoma (Epitopes-HPV02): a multicentre, single-arm, phase 2 study. *Lancet Oncol*. 2018;19(8):1094-1106.

76. Burtness B, Harrington KJ, Greil R, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *Lancet*. 2019;394(10212):1915-1928.
77. Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2016;375(19):1856-1867.
78. Chow LQM, Haddad R, Gupta S, et al. Antitumor activity of pembrolizumab in biomarker-unselected patients with recurrent and/or metastatic head and neck squamous cell carcinoma: results from the phase Ib KEYNOTE-012 expansion cohort. *J Clin Oncol*. 2016;34(32):3838-3845.
79. Frenel JS, Le Tourneau C, O'Neil B, et al. Safety and efficacy of pembrolizumab in advanced, programmed death ligand 1-positive cervical cancer: results from the phase Ib KEYNOTE-028 trial. *J Clin Oncol*. 2017;35(36):4035-4041.
80. Morris VK, Salem ME, Nimeiri H, et al. Nivolumab for previously treated unresectable metastatic anal cancer (NCI9673): a multicentre, single-arm, phase 2 study. *Lancet Oncol*. 2017;18(4):446-453.
81. Marabelle A, Cassier PA, Fakih M, et al. Pembrolizumab for advanced anal squamous cell carcinoma (ASCC): results from the multicohort, phase II KEYNOTE-158 study. *J Clin Oncol*. 2020;38(4 suppl):1.
82. Salem ME, Puccini A, Grothey A, et al. Landscape of tumor mutation load, mismatch repair deficiency, and pd-l1 expression in a large patient cohort of gastrointestinal cancers. *Mol Cancer Res*. 2018;16(5):805-812.
83. Glynne-Jones R, Mawdsley S. Anal cancer: the end of the road for neoadjuvant chemoradiotherapy? *J Clin Oncol*. 2008;26(22):3669-3671.
84. Benson AB, Venook AP, Al-Hawary MM, et al. Anal carcinoma, version 2.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Cancer Netw*. 2018;16(7):852-871.
85. Chang GJ, Gonzalez RJ, Skibber JM, et al. A twenty-year experience with adenocarcinoma of the anal canal. *Dis Colon Rectum*. 2009;52(8):1375-1380.

This page intentionally left blank

34 Neuroendocrine Tumors

Jessica E. Maxwell
James C. Yao
Daniel M. Halperin

KEY CONCEPTS

- Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are increasing in incidence, but delay in diagnosis is common. Patients may present with specific symptoms related to a functional tumor or vague gastrointestinal symptoms, emphasizing the importance of maintaining a high index of suspicion for this disease.
- The majority of GEP-NETs arise sporadically. Multiple endocrine neoplasia type 1 is the most common inherited syndrome in which nonfunctional pancreatic neuroendocrine tumors (PNETs) predominate.
- ^{68}Ga tetraazacyclododecanetetraacetic acid-DPhe1-Tyr3-octreotate (^{68}Ga-DOTATATE) has excellent sensitivity and specificity for GEP-NETs. It is used to detect the location of unknown primary tumors and to assess for distant disease. It is not used for routine surveillance.
- Surgical resection is the standard of care for localized GEP-NETs. In advanced disease, surgery may be appropriate when R0 resection can be achieved, or cytoreduction is performed for palliation of symptoms.
- In cases in which hepatic metastases are unresectable, hepatic arterial embolotherapies may be used. Peptide receptor radionuclide therapy is efficacious for hepatic and extrahepatic metastases.
- Systemic therapy for advanced extrapancreatic NETs includes somatostatin analogues and the targeted therapy everolimus. In PNETs, FAS (5-fluorouracil, doxorubicin, and streptozocin), capecitabine and temozolomide, and sunitinib are additional options.

Neuroendocrine tumors (NETs) originate from enterochromaffin cells of the diffuse endocrine system. A diverse set of tumors, they most commonly arise from the gastrointestinal (GI) tract, pancreas, lungs, and bronchi. Less common sites include the thyroid, parathyroid, pituitary gland, adrenal glands, and thymus. This chapter focuses on the low- and intermediate-grade gastroenteropancreatic NETs (GEP-NETs) and lung NETs, leaving small cell carcinomas, medullary thyroid cancer, neuroblastoma, and Merkel cell carcinomas (all technically neuroendocrine neoplasms) to other chapters in this text.

NETs may secrete peptides and neuroamines that cause specific clinical symptoms, although this is not universally present even among tumors originating from the same anatomic site. Localized disease is treated surgically for curative intent. Locoregional or metastatic disease not amenable to surgical resection can be managed with somatostatin analogues (SSAs), peptide receptor radionuclide therapy (PRRT), liver-directed therapy, cytotoxic chemotherapy, or targeted therapies. This chapter discusses current diagnostic and management strategies for lung and GEP-NETs.

EPIDEMIOLOGY AND RISK ASSESSMENT

The Surveillance Epidemiology End Results (SEER) database has catalogued a 6.4-fold increase in the incidence of NETs from 1973 to 2012. This increase was consistent across anatomic site, grade, and stage. Globally, NETs remain relatively rare with an age-adjusted incidence of 6.98 per 100,000 individuals.[1] The disease is slightly more common in women (52.7%) and those 65 years old or older (25.3 per 100,000 persons). Among GEP-NETs, the most common site of origin is the small intestine followed by the rectum and pancreas.[1]

The cause of the increased incidence is unknown but often attributed to greater disease awareness and improved diagnostic capabilities. Common behavioral risk factors such as smoking, obesity, and excessive alcohol use do not appear to play a role in the development of these tumors.[2] Genetic predisposition accounts for approximately 20% of GEP-NETs[3] and is discussed later.

PROGNOSIS

Prognosis varies by stage, primary site, and grade. Considering the 64,971 patients included in the SEER database between 1973 and 2012, median overall survival (OS) ranged from more than 30 years in patients with localized NETs to 10 years in those with regional disease and 1 year in those with distant disease. Examined by grade, low- (G1) and intermediate- (G2) grade NET had median OSs of 16 and 8 years, respectively. High-grade neuroendocrine neoplasms (SEER G3 and G4, corresponding to World Health Organization grade 3 neuroendocrine carcinomas [NECs] in modern nomenclature) had significantly worse survival times, with a median of only 10 months.

Among GEP-NETs, the prognosis is most favorable for appendiceal (>30-year median OS) and rectal NETs (24.6 years) and worst for pancreatic NETs (PNETs; 3.6 years). Survival patterns vary when stage is considered with primary site (Table 34–1). In localized disease, small intestine NETs have an OS of approximately 14 years, and localized appendiceal NETs fare even better with a median OS of more than 30 years. In patients with metastatic disease, small intestine NETs fare best with a median OS of 8.6 years. Patients with metastatic colon NETs have a median OS of only 14 months.[1]

TABLE 34–1 Median Survival of Distant Stage G1-G2 Neuroendocrine Tumors[1]

Organ Site	Median Survival (months)
Appendix	NA
Cecum	98
Colon	14
Lung	24
Pancreas	60
Rectum	33
Small intestine	103
Stomach	29

NA, not available.
Data from analysis of SEER registry, 2000 to 2012.

PATHOGENESIS, MOLECULAR CLASSIFICATION, AND GENETIC PREDISPOSITION

Innovation in the field of molecular biology has expanded our knowledge of the drivers of NET pathogenesis. In PNETs, *MEN1*, *DAXX*, and *ATRX* are frequently mutated. *MEN1* is a tumor suppressor gene that predisposes to multiple endocrine neoplasia type 1 (MEN1) when mutated either sporadically or in the germline. This mutation causes dysregulation of transcription and cell cycle control. Loss of heterozygosity at this locus on chromosome 11q13 is associated with the development of duodenal, gastric, and pancreatic NETs.[4,5] In 2011 Jiao et al. performed exome sequencing on 58 sporadic, resected PNETs. These experiments revealed *MEN1* mutations in 44% of tumors. DAXX and ATRX, two components of a histone chaperone complex important in chromatin remodeling,[6] were also frequently mutated (43%), though in a mutually exclusive fashion. *DAXX/ATRX* mutations drive the alternative lengthening of telomeres (ALT) phenotype,[7,8] which contributes to a neoplastic cell's immortality in a telomerase-independent fashion.[9] Somatic mutations in genes in the mammalian target of rapamycin (mTOR) pathway are found in approximately 15% of PNETs,[10] and loss of heterozygosity of *PHLDA3* (a regulator of the mTOR pathway) at chromosome 1q31 has been found in approximately 70% of studied PNETs.[11] The mutation status of *MEN1*, *DAXX/ATRX*, and the mTOR pathway in PNETs have an indeterminate impact on prognosis and no clear relationship with targeted therapy benefit.[8,10] Thus far, tumor mutational analysis has yet to demonstrate benefit in the selection of targeted agents.[12]

Fewer pathologic genetic alterations have been found in small intestine NETs. Hemizygous loss of chromosome 18 and arm-level gains of chromosomes 4, 5, 14, and 20 are relatively frequent genomic events.[13–15] More recent studies have shown that alterations of the gene *CDKN1B* occur in 7% to 10% of small intestine NETs. This gene is a haploinsufficient tumor suppressor and plays a role in cell cycle progression.[14–17] Clinical trials are ongoing to investigate the safety and efficacy of CDK inhibitors in patients with small intestine NETs (clinical trials.gov; NCT03891784).

MEN1 is the most common inherited cancer syndrome in NETs. This autosomal dominant disorder features the development of PNETs (80%–100%), multigland hyperparathyroidism (95%–100%), and pituitary adenomas (54%–65%). Hereditary PNETs often behave less aggressively than sporadic tumors and are frequently small and multifocal. The majority of MEN1-related PNETs are nonfunctional, although symptomatic gastrinomas are found in 54% and

insulinomas in 18% of patients. Other familial syndromes associated with NETs are neurofibromatosis type I (NF1), tuberous sclerosis, Cowden syndrome, and von Hippel-Lindau syndrome, though these are far less common than MEN1.[18]

PATHOLOGIC CLASSIFICATION

Neuroendocrine neoplasms are categorized as either well- or poorly-differentiated based on the extent to which the neoplastic cells resemble their non-neoplastic counterparts. Well-differentiated NETs are uniform, with characteristic "organoid" arrangements of cells in nesting, trabecular, or gyriform patterns. These cells tend to produce large amounts of neurosecretory granules, which can be detected by immunohistochemical (IHC) staining for common markers such as chromogranin A (CgA) and synaptophysin (Table 34–2). In cases in which the location of the primary NET is unknown, IHC can be used on biopsied metastases to offer some insight into the site of origin.[19,20] Poorly-differentiated NEC have a more sheetlike or diffuse architecture, irregular nuclei, and less cytoplasmic granularity and can take on small cell or large cell morphology in many cases. Expression of common neuroendocrine immunomarkers is often more limited in poorly-differentiated NEC, and thus IHC may be less useful during the diagnostic workup.[21] In cases in which the location of the primary tumor is unknown, IHC can be used on biopsied metastases to elucidate the site of origin.[19,20] Figure 34–1 compares the histologic appearance of a well-differentiated NET versus poorly-differentiated NEC.

Neuroendocrine neoplasms are also described by their grade, which includes three categories (G1–G3) based on proliferation rate. Poorly-differentiated NEC is uniformly grade 3. Grade can be determined either by calculating the mitotic rate (mitoses per 10 high-power fields) or by an IHC method that reports the percentage of neoplastic cells that stain for the proliferation antigen Ki-67. Currently, it is most common for pathologists to define grade via Ki-67. Low-grade (G1) GEP-NETs are defined by a Ki-67 index of 2% or less, intermediate grade (G2) 3% to 20%, and high grade (G3) greater than 20%.[21,22] Regardless of grade, the reproducibility of this test on either biopsy or surgical specimens is greater than 90%.[23]

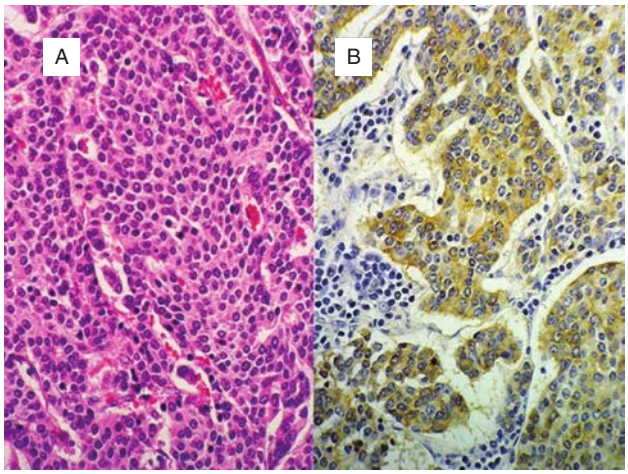


FIGURE 34–1 Histologic appearance of neuroendocrine tumors (NETs). Microscopic appearance of a low-grade NET. A. Standard microscopy showing few mitoses, no necrosis, and a large number of tumor vessels *(arrows)*. B. Immunohistochemical staining for chromogranin A (*brown-colored cells*).

TABLE 34–2 Immunohistochemical Markers of Neuroendocrine Tumors[19]

Marker	Significance
Synaptophysin	Presynaptic vesicle membrane glycoprotein, present on normal and neoplastic neuroendocrine cells
Chromogranin A	Universal marker for neuroendocrine tissue
Cytokeratin(s)	Lack of cytokeratin expression suggests the tumor is either an anaplastic neoplasm or may not be a carcinoma
CDX2 (caudal type homeobox 2)	Transcription factor expressed by epithelial cells of the bowel distal to the stomach; expression is highly sensitive for jejunoileal or appendiceal NET origin
TTF-1 (thyroid transcription factor-1)	Transcription factor critical in lung, thyroid, and brain development; expressed on type II pneumocytes; highly specific marker for lung NET
PAX8 (paired box gene 8)	Expressed in islets of Langerhans and thus useful for identification of PNET
Islet1	Expressed in mesenchymal cells of the dorsal pancreatic bud, in islet cells, chromaffin cells, and in some CNS tissue; positive staining in PNETs and rectal and duodenal NETs

CNS, central nervous system; NET, neuroendocrine tumor; PNET, pancreatic neuroendocrine tumor.

In general, clinical behavior and management are dictated by cellular differentiation and grade. Well-differentiated tumors are typically low or intermediate grade and behave in a more indolent manner. GEP-NETs in this category are typically slower to metastasize, and even in advanced stages patients can live for many years. High-grade tumors, often termed NECs, behave aggressively with an associated poor prognosis.[21,24] Recently, a subset of GEP-NETs with a well-differentiated cellular appearance but high proliferation rate were described. Although series are small, these well-differentiated tumors seem to have a better prognosis compared with poorly-differentiated NEC. In one series of 31 GEP-NETs, median disease-specific survival (DSS) was 55 months, whereas a comparison group of poorly-differentiated G3 tumors demonstrated a DSS of 11 months.[25]

Neuroendocrine neoplasms arising in the lung adhere to different classification and nomenclature standards than those of the GI tract. Whereas typical carcinoids approximate grade 1 GEP-NET and are defined by less than 1 mitosis/2 mm^2 and the absence of necrosis, atypical carcinoids approximate grade 2 GEP-NET and are defined by 2 to 10 mitoses/2 mm^2 or the presence of necrosis. Small cell lung cancer and large cell lung cancer, which are classified morphologically, are equivalent to poorly-differentiated G3 NEC, but well-differentiated G3 NET currently has no analogous entity.[22]

CLINICAL PRESENTATION, DIAGNOSTIC WORKUP, AND CLINICAL STAGING

NETs are best known for their hormonal syndromes, but the pathognomonic triad of diarrhea, wheezing, and flushing is far from universal. More commonly, patients are asymptomatic or develop vague GI symptoms that can be misinterpreted for years before a diagnosis of GEP-NET is confirmed.[26] Timely diagnosis and treatment of GEP-NETs requires a high index of suspicion and referral to a high-volume center with specialized multidisciplinary NET teams.

Laboratory Tests and Biomarkers

Biochemical testing is used in some centers to monitor response to therapy, disease progression, and recurrence. For extrapancreatic GI NETs, both the North American Neuroendocrine Tumor Society (NANETS) and European Neuroendocrine Tumor Society (ENETS) recommend considering measurement of CgA and urine 5-HIAA (u5-HIAA) for these purposes.[27,28] However, the added utility of biomarkers in the era of high-quality cross-sectional imaging remains debated. Furthermore, these tests lack the sensitivity and specificity to be used for diagnosis.

CgA is a 457–amino acid peptide that is widely distributed in neuroendocrine tissues, present in normal islet cells, and co-secreted with serotonin. Its sensitivity and specificity for detection of disease are assay dependent but range between 67% to 93% and 85-% to 96%, respectively. Serum levels of CgA can correlate with tumor burden, and thus this marker is used in some centers to determine the success of debulking procedures, disease recurrence, or progression. Levels can be falsely elevated by SSAs or proton pump inhibitors, or in patients with atrophic gastritis or renal, hepatic, or cardiac dysfunction.

5-HIAA is a metabolite of serotonin that is measured via a 24-hour urine collection or via plasma assays. It has high sensitivity (>95%) but low specificity (35%) for detection of GEP-NETs. Limitations of the test include inconvenience for the patient and false elevations caused by a number of substances—tryptophan-rich foods (cheese, mockernuts, tomatoes, pineapples, spinach), wine, caffeine, and various medications (acetaminophen, monoamine oxidase inhibitors, isoniazid, and 5-fluorouracil [5-FU]). Plasma serotonin levels do not correlate with tumor burden and are not relied on for diagnosis or surveillance.[29]

Some centers use biomarkers such as pancreastatin (a derivative of CgA) and neurokinin A for prognosis, especially in patients undergoing surgery for cytoreductive or curative intent, but supporting data are limited.[30,31]

PNETs may produce insulin, gastrin, glucagon, somatostatin, vasoactive intestinal peptide (VIP), pancreatic polypeptide (PP), or serotonin. Serum measurement of these hormones can aid diagnosis as hypersecretion can produce specific syndromes that are discussed in the sections that follow.

Imaging

Imaging is essential for the diagnostic workup, staging, and surveillance of GEP-NETs. Modalities such as endoscopy, computed tomography (CT), and magnetic resonance imaging (MRI) are used to locate the primary tumor, define resectability, and monitor for progression or recurrence. Nuclear medicine studies (somatostatin-targeted imaging, positron emission tomography [PET]) are used to evaluate tumor functionality and the presence of distant metastases. Complete diagnostic workup typically the requires use of multiple modalities.

Endoscopy

Endoscopic procedures are used to detect primary tumors, for local staging, to provide tissue for diagnosis, and for treatment. Gastric, duodenal, and proximal jejunal tumors can be visualized with

esophagogastroduodenoscopy. Colonic, rectal, and tumors in the terminal ileum can be seen with colonoscopy. Combining an endoscopic procedure with ultrasound (EUS) allows for local staging and tissue diagnosis via fine-needle aspiration. In PNETs, EUS localizes primary tumors with 93% sensitivity and 95% specificity. It is less useful for detecting duodenal NETs with detection rates of 45% to 60%.[32] In cases in which the location of the primary tumor is unknown but the small bowel is suspected, double balloon enteroscopy or capsule endoscopy can be used to visualize the midportion of the small intestine. Unfortunately, with detection rates less than 50%, neither modality is very efficient in this task.[33,34]

Computed Tomography and Magnetic Resonance Imaging

CT is excellent for surgical planning and useful for disease staging and surveillance. Studies examining its utility in detecting primary GEP-NETs report sensitivities ranging from 43% to 90%.[35–37] Regardless of primary tumor site, a multiphase study with intravenous (IV) contrast should be obtained because GEP-NETs are most frequently hypervascular tumors that are best visualized in the early arterial phase of a triple phase scan. A dedicated thin-slice, triphasic (arterial, late arterial, portal venous phases) "pancreas protocol" CT scan can be helpful for locating small, multifocal PNETs and to clearly define the relationship of tumors in the head of the pancreas to mesenteric vascular structures. Detection of small bowel, colon, or rectal NETs can be enhanced with the use of oral or rectal (or both) radiopaque contrast. This modality is also useful for detecting hepatic and soft tissue metastases with detection rates in this context reported at approximately 80%.[36,38,39]

MRI is the favored modality for detailing hepatic metastatic tumor burden (sensitivity, 95.2%)[40] and the pancreatic ductal system before surgery. It is also useful in patients with renal failure or an allergy to iodinated contrast. Optimal imaging requires use of IV gadolinium contrast because most GEP-NET metastases are hyperintense on arterial phases.

Somatostatin Receptor Imaging

Somatostatin is an endogenous peptide with a half-life measured in minutes that inhibits the proliferative and secretory functions target cells throughout the body. There are five subtypes of somatostatin receptors (SSTR1–SSTR5) that are the foundation of somatostatin-targeted imaging and treatment because more than 80% of well-differentiated NETs express a combination of these receptors.[41,42]

Somatostatin receptor scintigraphy (SRS) is a nuclear medicine imaging modality that uses ^{111}In-labeled diethylenetriamine penta-acetic acid octreotide (DTPA-D-Phe^{1}-octreotide) to visualize tumors expressing somatostatin receptors 2 and 5. It is obtained as a full-body scan at 4, 24, and potentially 48 to 72 hours after radionuclide injection and is used for detection of distant metastases. It has a sensitivity of 85% and specificity of 95% for primary GEP-NETs. It has been shown to detect metastases missed by conventional imaging in 30% of cases, but it may miss 17.5% of hepatic metastases otherwise detected by CT or MRI.[40,43]

The development of a positron-emitting ^{68}Ga-labeled radioligand conjugated to SSAs has enhanced the sensitivity (97%) of somatostatin imaging. The PET scan can be fused with CT or MRI, enhancing its anatomic specificity (Fig. 34–2).[44] These studies have improved the detection rate of NETs of the small intestine, including endoluminal tumors as small as 1 cm. False-negative studies are more common with tumors in the head of the pancreas because the uncinate demonstrates a moderate amount of physiologic uptake. As well, subcentimeter multifocal tumors in the small intestine, found in 15% to 30% of patients who are surgically explored, may still be below the limit of resolution.

Fluorodeoxyglucose Positron Emission Tomography

18-Fluorodeoxyglucose PET (FDG-PET) is used for detection of distant metastases in NEC. It has limited utility for staging well-differentiated, low- or intermediate-grade GEP-NETs because these tumors are metabolically inert and thus fail to take up ^{18}FDG well.[45] In high-grade NECs, maximum standardized uptake values (SUV_{max}) exceeding 4.5 are associated with shorter OS and progression-free survival (PFS) compared with GEP-NETs that are not detected.[46]

Other Nuclear Scintigraphy Techniques

Metaiodobenzylguanidine (MIBG) is taken up by some NET cells. ^{131}Iodine-labeled MIBG (^{131}I-MIBG) has an overall sensitivity of 55% to 70% in detecting NETs.[47] Although ^{131}I-MIBG is less sensitive than SRS, it may be used in patients receiving long-acting octreotide, which competitively inhibits uptake of radiolabeled SSAs or for patients whose tumors lack somatostatin receptors.

Clinical Staging

GEP-NETs are staged using the American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) system (Table 34–3 and Table 34-4).[48] The

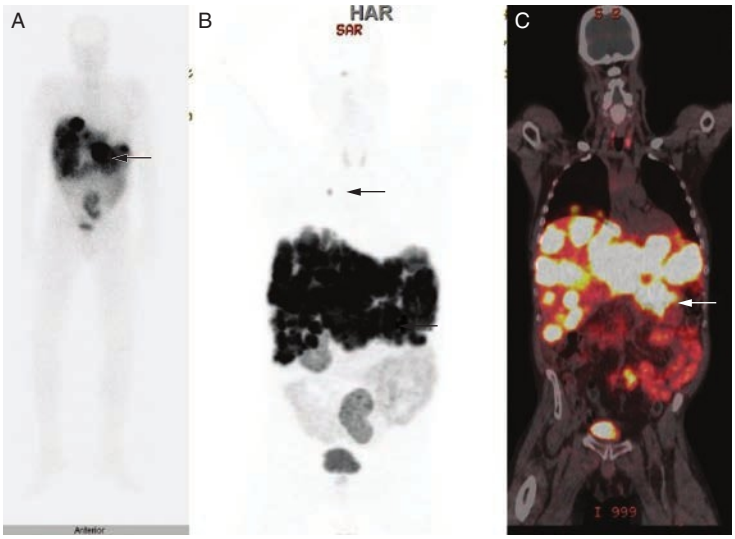


FIGURE 34–2 Somatostatin receptor imaging. All images are of the same patient. Image in **A** was obtained in 2015. Images in **B** and **C** were obtained in 2020. **A.** Octreoscan demonstrating a large pancreatic primary tumor (*arrow*) located in the tail of the pancreas and multiple hepatic lesions. **B.** ^{68}Ga-DOTATATE planar image. This more sensitive imaging technique demonstrates an increased number of hepatic metastases, a pulmonary nodule (*arrow*) and progression of the pancreatic primary tumor. **C.** Fused computed tomography and DOTATATE, coronal image. All images show physiologic uptake in the pituitary, thyroid, uncinate process, spleen, kidneys, and bladder. Note that the patient has a left pelvic kidney.

TABLE 34–3 TNM Staging System for G1/G2 (and rare G3) Well-Differentiated Extrapancreatic Gastrointestinal Neuroendocrine Tumors[a]

		Stomach	Duodenum or Ampulla	Jejunum or Ileum	Appendix	Colon or Rectum
T	TX	Tumor cannot be evaluated				
	T0	No evidence of tumor				
	T1	≤1 cm and extends into lamina propria or submucosa	≤1 cm and only involves mucosa or sphincter of Oddi	≤1 cm and extends into lamina propria or submucosa	≤2 cm	T1a: <1 cm and invades lamina propria or submucosa
						T1b: 1–2 cm and invades lamina propria or submucosa
	T2	>1 cm or extends into the muscularis propria	>1 cm or extends into the muscularis propria	>1 cm or extends into the muscularis propria	>2 cm but ≤4 cm	>2 cm with invasion of the lamina propria or submucosa or invades the muscularis propria
	T3	Invades into but not through subserosa	Invades the pancreas or peripancreatic adipose tissue	Invades into but not through subserosa	>4 cm or with subserosal invasion, or involvement of mesoappendix	Invades into but not through subserosa
	T4	Tumor extends beyond serosa or invades nearby organs				

TABLE 34–3 TNM Staging System for G1/G2 (and rare G3) Well-Differentiated Extrapancreatic Gastrointestinal Neuroendocrine Tumors[a] (Cont.)

		Stomach	Duodenum or Ampulla	Jejunum or Ileum	Appendix	Colon or Rectum
N	NX	Regional lymph nodes cannot be assessed				
	N0	No regional lymph node metastasis				
	N1	Regional lymph node metastasis	Regional lymph node metastasis	Regional lymph node metastases <12 lymph nodes	Regional lymph node metastasis	Regional lymph node metastasis
	N2			Large mesenteric masses (>2 cm) and/or ≥12 nodal deposits, especially those that encase the superior mesenteric vessels		
M	MX	Distant metastases cannot be assessed				
	M0	No distant metastases				
	M1a	Metastases confined to the liver				
	M1b	Metastases in at least one extrahepatic site				
	M1c	Both hepatic and extrahepatic metastases				

	Stage I	Stage II		Stage III		Stage IV
Stomach	T1 N0 M0	T2-3 N0 M0		Any T N1 M0 T4 N0 M0		Any T Any N M1
Duodenum or ampulla						
Jejunum or ileum				Any T N1-2 M0 T4 N0 M0		
Appendix				Any T N1 M0 T4 N0 M0		
Colon or rectum		IIa T2 N0 M0	IIb T3 N0 M0	IIIa T4 N0 M0	IIIb Any T N1 M0	

[a]For any T, add (m) for multiple tumors. For multiple tumors with different Ts, use the highest. Per World Health Organization/American Joint Committee on Cancer guidelines, poorly-differentiated neuroendocrine carcinomas (Ki-67 > 20%) are staged using the staging classifications for adenocarcinomas at the individual primary tumor sites, not as well-differentiated neuroendocrine tumors.
Data from Edge SB, Byrd DR, Byrd DR, et al: AJCC Cancer Staging Manual, 8th ed. New York, NY: Springer; 2017.

system is primary site specific and applies to grade 1 and 2 NETs. This staging is prognostic but not predictive of the benefit with any therapy. At least two staging systems are in use for PNETs. The AJCC TNM PNET staging system derives from the exocrine pancreas adenocarcinoma staging system and describes T stage in terms of resectability. In contrast, the ENETS staging system defines T stage by size and extent of invasion. Regardless of the system used, prognosis and stage maintain an inverse association.[49] High grade NEC are described with a TNM stage according to guidelines for carcinomas of the primary site but are summarized as limited-stage or extensive-stage disease, defined by the ability of the cancer to be treated in a single radiation port, based on the staging of the biologically analogous small cell lung cancer.[47]

CLINICAL FEATURES OF GASTROINTESTINAL NEUROENDOCRINE TUMORS

Gastric Neuroendocrine Tumors

There are three types of gastric NETs. Types I and II arise in response to hypergastrinemia, and type III tumors are sporadic.[50] Type I NETs are most common (75%) and are typically located in the gastric body

TABLE 34–4 Staging System for G1/G2 (and Rare G3) Well-Differentiated Pancreatic Neuroendocrine Tumors[a]

American Joint Committee on Cancer Tumor (T), Node (N), Metastasis (M) Staging System (8th ed, 2017) for G1/G2 (and Rare G3) Well-Differentiated Pancreatic Neuroendocrine Tumors[a] T	TX	Tumor	**Stage I**	**Stage II**	**Stage III**		**Stage IV**
	T1	Limited to the pancreas, <2 cm	T1				
	T2	Limited to the pancreas, 2–4 cm		T2			
	T3	Limited to the pancreas, >4 cm or invading the duodenum or common bile duct		T3			
	T4	Invading adjacent organs or the wall of large vessels			T4	Any T	Any T
N	NX	Regional lymph nodes cannot be assessed					
	N0	No regional lymph node metastasis	N0	N0	N0		Any N
	N1	Regional lymph node metastasis				N1	
M	MX	Distant metastases cannot be assessed					
	M0	No distant metastases	M0	M0	M0		
	M1a	Metastases confined to the liver					M1
	M1b	Metastases in at least one extrahepatic site					
	M1c	Both hepatic and extrahepatic metastases					

[a]Limited to the pancreas means there is no invasion of adjacent organs (stomach, spleen, colon, or adrenal gland) or the wall of large vessels (celiac axis or the superior mesenteric artery). Extension of the tumor into peripancreatic adipose is not a basis for staging. For any T, add (m) for multiple tumors. For multiple tumors with different Ts, use the highest. Per World Health Organization/American Joint Committee on Cancer guidelines, poorly-differentiated pancreas neuroendocrine carcinomas (Ki-67 >20%) are staged using the pancreatic adenocarcinoma guidelines, not as well-differentiated NETs.
Data from Edge SB, Byrd DR, Byrd DR, et al: AJCC Cancer Staging Manual, 8th ed. New York, NY: Springer; 2017.

or fundus. They are associated with chronic atrophic gastritis or pernicious anemia, are frequently subcentimeter and multifocal, and rarely metastasize. The survival rate is estimated at approximately 100% when these tumors are discovered as submucosal lesions amenable to endoscopic resection.[51] Type II tumors arise in the context of pathological hypergastrinemia from Zollinger-Ellison syndrome (ZES; 5%–10%) and are most often (70%) found in patients with MEN1.[51] These are more aggressive than type I tumors because 10% to 30% will metastasize, though usually only to locoregional lymph nodes.[52] Analyzed together, type I and II gastric NETs are associated with an approximate 80% 5-year OS rate.[51] Type III tumors, which arise in a eugastrinemic context and are most similar to NETs arising elsewhere in the body are the most aggressive subtype, with 50% to 100% metastasizing distantly. SEER analysis reveals a median OS of 13 months for patients with metastatic gastric NETs.[53]

Small Intestinal Neuroendocrine Tumors

Sporadic duodenal tumors comprise approximately 3% of all NETs, according to the SEER registry between 1973 and 1999. The vast majority of duodenal tumors arise in D1 and D2, with approximately 20% occurring in the periampullary region. Sporadic duodenal tumors are typically small (<2 cm) single lesions. If multiple tumors are detected, a diagnosis of MEN1 should be considered.[54] Periampullary tumors are typically more aggressive, and these patients may present with obstructive jaundice or cholangitis. Liver metastases occur in fewer than 10% of patients.[51] The most common duodenal NETs are gastrinomas, somatostatinomas, and nonfunctional tumors. Gastrinomas cause symptoms of ZES either sporadically or in the context of MEN1. These patients develop reflux and are at risk for peptic ulcers, GI bleeding, or perforation because of high levels of hydrochloric acid.

NETs of the jejunum and ileum are colloquially referred to as *carcinoid tumors*. These tumors are most often 1 to 2 cm in size and are located within 100 cm of the ileocecal valve.[55] Approximately 41% of patients will have locoregional nodal involvement, and 30% will have distant metastases.[56] In patients who undergo surgical exploration, up to 45% are found to have multiple small-bowel tumors.[57] These tumors are typically subcentimeter and can be missed if patients undergo a minimally invasive operation because of the lack of haptic feedback. Given their small size, they may also be missed on SRS imaging. On CT, an endoluminal tumor may not be obvious, but a calcified mesenteric mass is often seen, which upon surgical exploration approximates the location of the largest primary within the bowel. Before developing distant metastases, patients are either asymptomatic

or describe vague GI symptoms unrelated to the presence or location of the primary tumor. Patients with distant metastases are more likely to present with symptoms related to hormone secretion or from high tumor burden, such as GI bleeding, jaundice, or bowel obstruction. Patients who present with a large mesenteric mass at the takeoff of the superior mesenteric artery may develop chronic mesenteric ischemia. The median survival time of patients with G1 or G2 small intestine NETs is 8.5 years.

Appendiceal Neuroendocrine Tumors

Appendiceal NETs are often discovered incidentally during an appendectomy. Fifty-four percent of patients present with appendicitis, but this is unlikely related to the primary tumor because only one third are located at the base of the appendix.[58] Median OS is more than 30 years when the disease is localized or locally advanced and 2.3 years with distant disease.[53] Still undetermined is whether the disease-specific prognosis is meaningfully different between pediatric and adult patients.

Rectal Neuroendocrine Tumors

Rectal NETs are often found during an evaluation for symptoms related to a benign condition (ie, bleeding, pain, change in bowel habits). Most tumors are 4 to 8 cm from the anal verge, and 80% are localized tumors less than 1 cm in size.[59] Only 4% of patients with rectal NETs present with distant metastases. These tumors appear as a yellow-grey submucosal nodule in the rectal wall. Local excision is adequate for small tumors without high-risk features. Pathologic characteristics that mandate consideration of more extensive surgical resection are perineural or lymphovascular invasion, invasion into the muscularis, or size larger than 2 cm. Tumors with high-risk features carry a 60% to 80% risk of distant metastasis.[59,60] Localized rectal NETs are associated with a median OS of 24.2 years, whereas prognosis for advanced rectal NETs is much poorer at 1.8 years.[53]

CLINICAL FEATURES OF PANCREATIC NEUROENDOCRINE TUMORS

Insulinoma

Insulinoma is the most common type of functional PNET and is characterized by the "Whipple triad" of (1) hypoglycemia; (2) neuroglycopenic symptoms of shakiness, confusion, or sweating; and (3) resolution of these symptoms with eating. These tumors are generally benign (90%), intrapancreatic, solitary, and smaller than 2 cm.[61] Approximately 5% are associated with MEN1; thus, a careful family history must be taken at diagnosis. Measurement of plasma glucose, insulin, C-peptide, and proinsulin during a monitored 72-hour fast confirms the diagnosis. Insulinomas can be difficult to localize in 40% of cases, but combinations of MRI, pancreas protocol CT, and EUS have a sensitivity of 90%. ^{69}Gallium PET imaging may detect lesions missed by other modalities.[62] Patients with lesions that fail to localize on imaging can be discovered intraoperatively using a combination of careful palpation and intraoperative ultrasound to identify the tumor, though this is becoming less common as imaging improves. Portal venous sampling and arterial calcium stimulation are primarily of historical interest.

Gastrinoma

Gastrinomas are located in the duodenum or pancreas in an area called the gastrinoma or Passaro's triangle, which is bound superiorly by the junction of the cystic and common bile ducts, inferiorly at the junction of D2 and D3, and medially by the neck of the pancreas.[63] These tumors cause ZES and patients develop multiple, recurrent peptic ulcers.[64] Twenty percent are found in association with MEN1. Approximately 50% of gastrinomas have distant metastases at diagnosis.[65] Diagnosis requires measurement of fasting serum gastrin and basal gastric acid levels. Duodenal gastrinomas are submucosal and often difficult to detect with EGD. ^{69}Gallium SRS PET can detect 68% of gastrinomas diagnosed biochemically or clinically but missed on conventional imaging.[66]

Glucagonoma

Glucagonoma is a rare but aggressive PNET that typically arises in the tail of the pancreas. Glucagonoma syndrome features necrolytic migratory erythema, diabetes mellitus, stomatitis, anemia, neuropsychiatric disturbances, or diarrhea. The majority of patients present with glucose intolerance, necrolytic migratory erythema, or both. The reddish-brown rash typically involves the face, abdomen, perineum, or extremities. Erythematous areas form bullae that eventually open and encrust. The median time between symptom onset and diagnosis is 39 months, and by this time, 80% of tumors have metastasized. Diagnosis is supported by serum glucagon levels exceeding 1000 pg/mL.[67]

Somatostatinoma

Somatostatinoma is an extremely rare (incidence, 1 in 40 million people) solitary tumor that is found in the pancreas or periampullary duodenum. Functional tumors can cause diabetes, cholestasis, or steatorrhea. Most tumors are malignant (78%), and patients typically present with metastatic disease (70%–92%). Duodenal somatostatinomas are associated with NF1 in approximately 50% of cases and are less likely to

have metastasized at presentation. The 5-year OS for patients with localized disease is 60% to 100%, whereas the 5-year OS for patients with metastatic disease is 15% to 60%.[68]

VIPoma

VIP-secreting tumors (VIPomas) are rare tumors that cause "pancreatic cholera." Confirmed in human participants infused with high concentrations of IV VIP for 10 hours,[69] elevated serum concentrations of VIP cause high-volume (>10–20 L/day) watery diarrhea that results in profound dehydration, hypokalemia, achlorhydria, and paradoxical acidosis. These tumors are located in the pancreatic tail and are typically slow growing with a median OS of 5.9 years. Five percent are seen in patients with MEN1.[70]

Pancreatic Polypeptide–Secreting Tumor

PNETs that hypersecrete PP (PPomas) are exceedingly rare (<1% NET), and although considered a functional PNET, they do not produce a specific clinical syndrome. Secretion of PP is associated with increased satiety, delayed gastric emptying, and inhibition of gallbladder contraction. Some reports suggest an association between PP hypersecretion and glucose intolerance. In patients who present with metastatic disease, this may be the presenting sign.[71–73]

Nonfunctional Pancreatic Neuroendocrine Tumors

Whether sporadic or in the context of MEN1, the majority of PNETs are nonfunctional. These tumors are asymptomatic at presentation unless tumor size or location creates mass effect within the foregut and biliary tree. Their asymptomatic nature contributes to a delay in diagnosis, and 60% to 80% present with metastases.[74] Prospective studies of patients with MEN1 suggest that at least 50% of patients will develop nonfunctional PNET and that these tumors increase in size and number over time, albeit very slowly.[75]

CARCINOID SYNDROME, CARCINOID HEART DISEASE, AND CARCINOID CRISIS

Carcinoid Syndrome

Carcinoid syndrome occurs when metastatic disease, primary tumor location, or tumor volume allows secreted amines to bypass or overwhelm the first-pass effect of the portal circulation. It is most common in extrapancreatic GI NETs, although some cases of "pancreatic carcinoid" have been reported. Common symptoms include flushing, diarrhea, abdominal cramping, and less frequently, wheezing, right-sided heart failure or dysfunction, and pellagra. Symptoms are thought to be caused by circulating serotonin metabolites, kinins, and prostaglandins.

A recent population-based study identified the clinicopathologic factors associated with the presence of carcinoid syndrome at diagnosis. Regionally advanced (22%) and distant metastatic (24.9%) NETs were associated with carcinoid syndrome more frequently than localized NETs (11.9%). Small intestine (32.4%) and cecal (32.2%) NETs were most commonly associated with carcinoid syndrome at diagnosis.[76]

Carcinoid Heart Disease

Carcinoid heart disease is the result of valvular thickening and fibrous plaque formation on the tricuspid and pulmonic valves that results in tricuspid regurgitation and pulmonic valve stenosis. Right ventricular dysfunction or failure suggests long-standing, late-stage disease.[77] A result of sustained release of serotonin, tachykinins, histamine, and prostaglandins, carcinoid heart disease develops in 40% to 70% of patients with carcinoid syndrome.[56,78–80] Patients may be asymptomatic but may also present with exercise intolerance. Florid right heart failure is uncommon. Physical examination and echocardiography aid in diagnosis. Current National Comprehensive Cancer Network guidelines suggest echocardiographic screening for patients with carcinoid syndrome every 2 to 3 years.[81] Screening should also be considered in patients preparing for surgical resection or debulking.[79]

Carcinoid Crisis

Carcinoid crisis is a hemodynamic phenomenon that is the subject of recent controversy. Lacking a consensus definition, it is generally described as a prolonged episode of hemodynamic instability occurring during or in close proximity to an invasive procedure that cannot be ascribed to (peri-) procedural factors such as hypovolemia, medication, hemorrhage, or decreased venous return. Similar to an episode of carcinoid syndrome, patients may develop cutaneous flushing and diarrhea during an event. In part because of the lack of definition, the true prevalence of crisis is unknown but reported between 0% and 35% in patients undergoing surgical resection.[82–86] An episode of crisis is thought to be caused by a massive release of bioactive amines into the systemic circulation, though one recent prospective study did not find elevated levels of serotonin, histamine, kallikrein, or bradykinin during intraoperative crises.[86] Generally recommended treatment consists of bolus injection of 500 to 1000 ug of octreotide

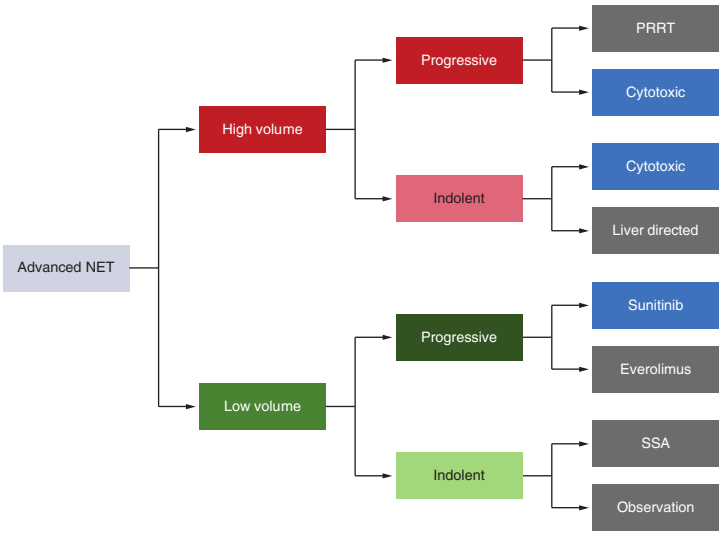


FIGURE 34–3 **Approach to therapy for advanced neuroendocrine tumors. Examples of low-volume metastatic disease are metastases isolated to a single organ or less than 20% liver replacement. PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogue.**

or a continuous infusion of 50 to 100 μg/hour in addition to standard management with antihypertensives or vasopressors. Patients with high-volume metastatic disease or a history of carcinoid syndrome undergoing invasive procedures may be premedicated with bolus injections of octreotide. An intraprocedural continuous infusion of octreotide can be administered as prophylaxis against periprocedural carcinoid crisis. This infusion is tapered over the next 8 to 24 hours. The use of periprocedural SSAs for these purposes is inconsistent among centers and practitioners. Both retrospective and prospective studies question the efficacy of SSA in this context.[83,85] Multi-institutional, prospective studies are required to resolve these issues.

GENERAL APPROACH TO TREATMENT

The dual nature of GEP-NETs—indolent but often discovered after metastatic spread—lies at the core of the challenges that arise during the care of these patients. Considered, deliberate ordering of a variety of treatment modalities is often necessary, which requires that patients obtain treatment at centers equipped to provide specialized, multidisciplinary care. Primary tumor location, stage, and grade dictate management. Regardless of primary site, surgical resection is recommended for G1 and G2 GEP-NETs when clearance of all gross disease can be achieved. Regional therapies for G1 and G2 GEP-NETs are also similar across primary sites, but systemic therapies diverge for pancreatic and extrapancreatic NETs (Fig. 34–3).

Treatment of Resectable Neuroendocrine Tumors

Surgical resection of locoregional disease offers the only chance for cure in patients with GEP-NETs. Appropriate patient selection considers primary site, tumor histology, the extent of detectable disease, and clinical presentation.

Endoscopic resection of types I and II gastric NET is appropriate when tumors are less than 2 cm in size and relatively few in number.[87] If histopathologic analysis reveals high-risk features such as positive resection margins, invasion into the muscularis or lymphovascular invasion, partial gastrectomy and regional lymphadenectomy must be considered. Tumors larger than 3 cm and type III gastric NETs also necessitate consideration of gastrectomy (partial or total, depending on location).[88–90] Endoscopic resection is not appropriate for type III gastric NETs of any size because of their propensity to behave similarly to gastric adenocarcinomas.[91]

Treatment of localized PNETs is dictated primarily by location within the pancreas but also by histology because functional tumors and those diagnosed in the context of MEN1 are often multifocal and theoretically amenable to repeat surgical treatment with parenchymal-sparing techniques. Sporadic tumors located in the head of the pancreas are treated with pancreaticoduodenectomy (Whipple procedure). Tumors in the body or tail can be resected with a distal pancreatectomy. In sporadic, nonfunctional PNETs surgical resection is associated with superior OS (14.3 years vs 3 years),[92]

although tumors smaller than 1 cm can be observed over time because of their low malignant potential. Patients with functional, multifocal tumors present a unique problem because R0 surgical resection may require total pancreatectomy, which is a morbid procedure condemning the patient to brittle diabetes and exocrine insufficiency. Alternatively, patients may be treated with surgical enucleation. This spares parenchyma but increases the risk of pancreatic fistula.[18] Novel technologies such as irreversible electroporation are under investigation for these tumors.[93]

Management of patients with pancreas VIPomas can be especially challenging because the clinical syndrome is commonly associated with advanced disease. Typically, management requires a multimodal approach. Surgical resection of the primary tumor and all metastases is ideal but rarely achieved. Surgical cytoreduction is attempted in some centers to decrease the amount of secreted VIP. Medical therapies may aid in symptom control and in severe cases, infusions of SSAs or glucocorticoid can be helpful to decrease the volume of diarrhea.

Duodenal NETs remote from the ampulla can be resected endoscopically (<2 cm), via transduodenal resection, or with a short-segment resection and anastomosis. Periampullary tumors require a Whipple procedure.[54,89,90] Localized NETs of the jejunum and ileum are treated with segmental resection and regional lymphadenectomy.[94] Regardless of imaging or gross inspection of the bowel intraoperatively, careful palpation of the entire bowel—from the ligament of Treitz to the terminal ileum—is required to ensure identification and resection of all primary tumors because up to 45% of patients have multifocal disease.[57]

For appendiceal NETs, simple appendectomy is appropriate treatment for tumors 1 cm or smaller, with invasion up to the subserosa or with mesoappendiceal invasion 3 mm or less and clear surgical margins. In adult patients, right hemicolectomy is recommended for tumors larger than 2 cm, tumors with deep mesoappendiceal invasion or positive margins, and tumors located at the base of the appendix, although studies have not clearly demonstrated a survival benefit with more extensive surgery.[28]

Colonic NETs are treated via endoscopic snare or partial colectomy and regional mesenteric lymphadenectomy. Small (~1–2 cm) intraluminal tumors that do not invade the muscularis can be excised endoscopically. Attempting removal of larger tumors with these procedures risks piecemeal removal, thus complicating pathologic analysis and increasing the risk of positive margins. Small, submucosal rectal NETs may be treated with local excision. Tumors that invade the muscularis, have high-risk features, or are associated with locoregional spread are treated with segmental resection. Choice of operation in this context parallels that of rectal adenocarcinoma, in which low anterior resection or abdominoperineal resection are options.

Poorly-differentiated grade 3 NEC seldom benefit from surgical resection in isolation because survival is poor regardless of the treatment modality selected. These patients are usually treated with chemotherapy, with radiation added for patients with limited-stage disease and surgical consolidation considered in selected cases.

Treatment of Advanced Neuroendocrine Tumors

The goal of treatment of patients with advanced GEP-NETs is improvement of quality of life and survival. At this stage, treatment is multimodal and can include SSAs, surgery, hepatic metastasis embolization, systemic PRRT, chemotherapy, and systemic targeted therapy. The literature is limited on specific recommendations for the order in which these modalities should be applied, emphasizing the need for specialized, multidisciplinary care.

Somatostatin Analogues

SSAs such as octreotide and lanreotide control symptoms of hormonally active NETs and demonstrate antiproliferative activity for NETs regardless of secretory behavior. These agents are the mainstay of therapy in carcinoid syndrome. Octreotide is an intermediate-acting SSA that can be self-administered subcutaneously every 6 to 12 hours as acute symptoms demand. It provides complete or partial relief of flushing or diarrhea in approximately 85% of patients with carcinoid syndrome and produces a biochemical response rate of up to 72%.[95,96] The dose of octreotide varies from 50 to 500 μg.

Long-acting SSAs have eliminated the need for multiple daily injections in most patients. Depot octreotide (10, 20, or 30 mg) is administered intramuscularly once per month. An intermediate-acting SSA can be used to supplement long-acting agents until steady state is reached. Lanreotide is another SSA in extended-release form, which can be administered subcutaneously monthly in doses of 60, 90, or 120 mg. In 2016, the phase III, randomized ELECT trial showed that treatment with 120 mg of lanreotide every 4 weeks decreased the percentage of days that patients required rescue doses of octreotide[97] and improved control of flushing and diarrhea in these patients.[98]

SSAs have a favorable side effect profile. These drugs can cause sinus bradycardia or cardiac conduction abnormalities; thus, caution is advised in patients with cardiac disease. More commonly, cholestasis and cholelithiasis can result from long-term use,[99] so cholecystectomy should be considered in patients who

undergo resection for their GEP-NETs.[94] Hypoglycemia, or more commonly, hyperglycemia may occur, especially among patients with brittle diabetes. Steatorrhea may also occur but can be managed with pancreatic enzymes taken with food.

SSAs also have anticancer activity. Interim analysis of the phase III randomized trial of depot octreotide 30 mg monthly in untreated metastatic midgut NET (PROMID) demonstrated a significantly longer time to progression with octreotide compared with placebo (PFS hazard ratio [HR], 0.34; P <.001).[100] An international double-blind placebo-controlled phase III trial of lanreotide (120 mg every 28 days) in treatment-naïve patients with nonfunctioning GEP-NET (CLARINET) also demonstrated significantly improved PFS with lanreotide compared with placebo (PFS HR, 0.47; P <.001).[101]

Surgical Resection in the Setting of Advanced Disease

Surgical treatment of advanced GEP-NETs is acceptable either for palliation of symptoms or survival benefit. These operations must be considered carefully and are best performed at high-volume NET centers by experienced surgeons because achieving an R0 resection is only possible in a minority of cases.[102] The risk of surgery must be carefully weighed and expected outcome clearly articulated because surgical complications can impact the survival and quality of life in a group of patients who may otherwise survive many years with their disease left in situ.

Palliative resection of the primary GEP-NET is recommended for patients with functional tumors causing debilitating secretory symptoms or in the setting of obstruction or bleeding. It is unknown whether resection of a nonfunctional tumor is beneficial. A meta-analysis of six studies examining this issue suggested that patients with advanced jejunal, ileal, or pancreatic NETs in the setting of unresectable distant metastatic disease may have a survival benefit with palliative resection of their primary tumors.[103] Studies using propensity matching are mixed. Daskalakis et al[104] compared patients who underwent early "logoregional" surgery for their stage IV small intestinal NETs with those who had surgery at least 6 months after their initial diagnosis. They found no survival difference between groups, but details on the conduct of the operations are not reported; thus, the extent of surgery is unknown. A single-institution series from Frankfurt, Germany, compared patients who had surgery as part of their treatment for hepatic metastases with those who had only nonsurgical interventions. This propensity-matched study showed that there was no survival advantage to incorporating surgery in the matched analysis. The 10-year mortality rate was associated with leaving the primary in situ.[105] Such propensity-matched analyses help minimize selection bias from the retrospective analyses but are not definitive evidence of lack of benefit from early surgical intervention. For now, consideration of surgery in patients with low overall tumor burdens and good functional status is reasonable and offered at the majority of high-volume NET centers.

Metastasectomy is most often performed to treat hepatic metastases and more rarely done for extrahepatic tumor debulking. In the liver, clearance of all hepatic metastases is ideal, although cytoreduction with a goal of clearing a minimum of 70%, and optimally 90% of disease, is considered reasonable in some centers. Anatomic surgical resection or parenchymal-sparing methods such as ablation are acceptable, although recurrence with either strategy is nearly universal. Patients undergoing liver-directed surgery experience superior PFS, OS, symptom control, and have a low postoperative complication rate when carefully selected.[94,106–109] Orthotopic liver transplantation is another investigational surgical approach for treating hepatic metastases and is also associated with OS at 5 and 10 years that is superior to unselected patients.[110] The extent to which this represents an effect of the surgery as opposed to an effect of the selection of patients fit for these interventions is as yet undetermined.

Hepatic Arterial Embolization and Chemoembolization

Liver metastases from NETs receive more than 80% of their blood supply from the hepatic arterial circulation, in contrast to normal liver parenchyma, which receives approximately 70% of its supply from the portal venous system. Thus, embolizing the hepatic artery targets tumor metastases while leaving normal parenchyma relatively unharmed. Three distinct techniques exist for liver-directed embolotherapy, but all rely on selective ischemia of the metastasis for effect. Bland embolization uses embolic particles (Gelfoam powder, polyvinyl alcohol particles, or microembospheres) to cut off the tumor blood supply.[111] The addition of an ethiodized oil emulsion of a chemotherapeutic agent to the embolic material, known as transcatheter arterial chemoembolization (cTACE), or drugs loaded onto embolic microspheres (drug-eluting bead transarterial chemoembolization [DEB-TACE]), allows delivery of relatively larger doses of agents to the tumor, combining local cytotoxicity and ischemia. The most frequently used chemotherapeutic agents for cTACE and DEB-TACE are doxorubicin, epirubicin, cisplatin, gemcitabine, 5-FU, and streptozocin.[112–116]

Benefits of this treatment include symptom relief, slowing progression, and reducing tumor burden before attempting surgical resection or tumor ablation. Many retrospective studies in markedly heterogeneous

populations have shown that these three techniques control symptoms and are associated with favorable PFS and OS. No study has clearly demonstrated one technique to be superior in patients with GEP-NETs, although a randomized trial comparing all three techniques is currently recruiting patients. It should be noted that the DEB-TACE arm of this study closed early because of reports of unacceptable toxicity.[114]

The primary risk of hepatic artery embolization is postembolization syndrome, which is typically self-limited and characterized by pain, GI distress, fever, leukocytosis, and transaminitis. Major complications such as renal failure, gallbladder perforation, cholangitis, peptic ulcer hemorrhage, and abscess formation are rare.[117] Liver necrosis is also uncommon postprocedurally but is associated with previous bile duct dilation and portal vein thrombosis.[118] Embolization has been associated with carcinoid crisis.[119]

In patients with extensive liver tumor burden, multiple embolization sessions may be required, starting with the hepatic lobe with the greatest tumor burden. Embolization of the whole liver in one session runs the risk of prolonged postembolization syndrome or liver failure. The timing of subsequent embolizations is determined primarily by symptoms, tumor behavior, and patient tolerance.

The ordering of hepatic arterial embolization with other regional and systemic therapies in the disease course remains a topic of debate, and specific guidelines from NANETS on this issue do not exist.[18,120] Although some investigators advocate early embolization to reduce tumor burden before initiating systemic therapy, late embolization can also be effective. In a randomized study, patients with NET treated with initial liver embolization followed by interferon therapy had a higher objective response rate after 1 year (86%) than patients who received interferon only (42%), without demonstrating altered survival.[121] In contrast, when embolization or chemoembolization are performed at a median of 37 months after diagnosis, the median survival time after embolization was 80 months, leading the investigators to conclude that later embolization is still effective.[122]

Selective Internal Radiation Therapy

Intra-arterial radioembolization with yttrium-90 (^{90}Y) microspheres is a technique used to treat unresectable liver metastases.[18,120] ^{90}Y is a pure β emitter with a mean soft tissue penetration of 2.5 mm and a maximal depth of 1.1 cm. Great care must be taken with ^{90}Y radioembolization to avoid nontarget delivery of radioactive microspheres to organs such as the lungs and stomach, making an angiogram with selective embolization of all extrahepatic arteries essential before treatment, as well as assessment of lung shunt fraction.

Radioembolization of hepatic metastases has been studied retrospectively as well as prospectively. The study cohorts are heterogeneous, but ^{90}Y radioembolization has been shown to improve symptoms, induce radiographic complete and partial responses, and decrease tumor marker levels and be associated with favorable PFS and OS.[117,123–125] There are no studies that show improved survival benefit with radioembolization compared with other hepatic arterial embolization techniques. This procedure has a favorable safety profile compared with hepatic arterial embolization techniques, with low rates of postembolization syndrome and carcinoid crisis, allowing it to be performed as an outpatient procedure.[119,126] The risk of hepatic cirrhosis is low with this technique but has been reported.[127]

Peptide Receptor Radionuclide Therapy

Radiolabeled SSAs have also been developed, and ^{177}Lu-DOTATATE was approved by the Food and Drug Administration (FDA) in 2018 for use in patients with metastatic GEP-NETs. DOTATATE is a SSA that can be conjugated to the β- and γ-emitter ^{177}lutetium (^{177}Lu).[128] In 2017, the results of the phase 3 trial of ^{177}Lu-DOTATATE for midgut neuroendocrine tumors (NETTER-1) were reported. The trial included 229 patients with well-differentiated, metastatic midgut NETs who were randomized to receive either ^{177}Lu-DOTATATE every 8 weeks or high-dose (60-mg) octreotide LAR. PFS was improved by 79% in the PRRT arm compared with the octreotide arm. The response rate in the ^{177}Lu-DOTATATE group was 18% versus 3% in the octreotide group (P <.001). A preliminary analysis suggested an OS advantage to PRRT, with 14 deaths in the ^{177}Lu-DOTATATE group compared with 26 deaths in the octreotide group (P = .004),[129] but more events are required to confirm this early result. Grade 3 and 4 side effects were rare. The most common in the ^{177}Lu-DOTATATE group were lymphopenia (9%) and thrombocytopenia (2%). A separate report detailed the results of patient quality of life outcomes as assessed with two different quality of life questionnaires administered at baseline and every 12 weeks until tumor progression. Patients treated on the ^{177}Lu-DOTATATE arm had significantly longer time to deterioration for global health status (28.2 months vs 6.1 month) and physical functioning (25.2 months vs 11.5 months).

Chemotherapy

Selection of chemotherapy regimen depends on grade and histology. Well-differentiated extrapancreatic NETs respond poorly to cytotoxic chemotherapy. PNETs respond better. Early randomized studies of streptozocin-based chemotherapy regimens demonstrated biochemical responses and improvements in survival.[130,131] Building on the progress of Moertel et al, a study from

MD Anderson Cancer Center noted radiographic response rates of 39% in a series of 84 patients with PNET using a regimen of 5-FU, doxorubicin, and streptozocin (FAS). The median PFS was an estimated 18 months, with a median OS of 37 months.[132] Temozolomide, an alkylating agent, is an alternative to FAS and has the advantage of being an oral formulation. A randomized trial comparing temozolomide and capecitabine to temozolomide alone in PNET patients demonstrated improved PFS (22.7 vs 14.4 months) and OS (not reached vs 38 months). Poorly-differentiated high-grade NECs are responsive to platinum-based chemotherapy.[133]

Targeted Therapy

The use of targeted therapies in GEP-NETs has greatly expanded in recent years. Building on the observation that increased vascular endothelial growth factor (VEGF) portends poor survival in patients with NET, the VEGF receptor inhibitor sunitinib was tested in a phase III study of 154 patients with PNET with advanced and progressive disease. An interim analysis demonstrated an HR for progression or death of 0.42 favoring sunitinib over placebo (P <.001).[134] This resulted in regulatory approval of sunitinib for the indication. Simultaneously, the mTOR inhibitor everolimus was studied in RADIANT-3. This randomized phase III trial compared everolimus versus placebo in 410 patients with advanced, progressive PNETs. The HR for progression or death was 0.35 (P <.001) favoring everolimus over placebo.[135]

Less progress has been made with targeted agents in extrapancreatic GI NETs. The phase II study of sunitinib showed limited evidence of benefit.[136] The RADIANT-2 study of everolimus in patients with extrapancreatic NET, although limited by randomization imbalance and informative censoring in central radiology review, also failed to demonstrate statistically significant benefit.[137] RADIANT-4, a randomized phase III trial of patients with advanced, progressive, well-differentiated, nonfunctional NETs of the lung or GI tract were assigned to everolimus or placebo in a 2:1 ratio. Everolimus was associated with a 52% decrease in the estimated risk of progression or death (P <.00001).[138] The FDA approved everolimus for well-differentiated, nonfunctional, advanced NETs in 2016.

Surufatinib is the newest targeted agent to be trialed in NETs. This agent targets the VEGF receptor, fibroblast growth factor receptor 1, and colony-stimulating factor 1 receptor. In the phase I/IIb trial, 42 patients with PNET and 39 patients with extrapancreatic NET were treated with 300 mg of oral surufatinib once daily until progression. Radiographic objective response rates were observed in 19% of PNETs and 15% of extrapancreatic NETs. Disease control rates were 91% and 92%, with associated median PFS of 21.2 months and 13.4 months in PNETs and extrapancreatic NETs, respectively.[139] The subsequent phase III trial in advanced extrapancreatic NETs randomized 198 patients (2:1) to 300 mg of surufatinib or placebo. This study was terminated at an interim analysis by the data safety monitoring board because of unequivocal evidence of benefit, with surufatinib significantly prolonging PFS compared with best supportive care (HR, 0.334; 95% confidence interval, 0.223–0.499; P <.0001). The most common severe adverse events were proteinuria (19.4%) and hypertension (36.4%). The disease control rates were 86.5% in the surufatinib group and 65.6% in the placebo group (P = .0022). A phase III trial investigating surufatinib in PNET is ongoing.[140]

Immunotherapy

Currently, there are no checkpoint or immunotherapies approved for use in GEP-NETs. Pembrolizumab, a programmed cell death protein 1 (PD-1) checkpoint inhibitor, may have a role in the treatment of patients with poorly-differentiated NEC because one study showed expression of PD-1 in 16% of GEP NECs.[141]

Additional Symptom Control Methods

Carcinoid symptoms can be exacerbated by epinephrine, exercise, emotions, eating tryptophan-rich foods, and ethanol and may be controlled through modulating these factors or supplementing dietary nicotinamide. Medical management of carcinoid symptoms can include a bronchodilator for bronchospasm and diuretics for fluid overload secondary to valvular dysfunction. A proton pump inhibitor (but not an H2 blocker) can manage gastric hypersecretion in gastrinoma patients. Malignant hypoglycemia in patients with insulinomas can be managed with everolimus.[142]

Elevated levels of serotonin are associated with diarrhea and are not always optimally managed with an SSA. Telotristat ethyl inhibits tryptophan hydroxylase—the rate-limiting step in serotonin synthesis. As such, it has been tested prospectively to determine its efficacy in reducing the frequency of NET-associated diarrhea. In the phase 3 TELESTAR study, patients had a reduction (-2.1 bowel movements per day compared with baseline but only -0.81 bowel movement per day compared with placebo) of the number of bowel movements per day as well as a significant decrease in their u5-HIAA levels.[143] The results of the TELECAST study paralleled those of TELESTAR and showed that telotristat was safe and resulted in a decreased number of bowel movements per day, as well as decreased u5-HIAA levels.[144] Telotristat ethyl is FDA approved for use at a dosage of 250 mg three times per day in patients with NET-related diarrhea that is inadequately controlled by SSA.

CONCLUSION

Multidisciplinary diagnosis and management of patients with GEP-NETs is essential. For localized disease, early and clear communication between the surgeon and the pathologist is required for appropriate prognostication and treatment. Advanced NETs present different challenges, and surgeons, interventional radiologists, medical oncologists, and endocrinologists may all play roles in improving quality and quantity of life for the patient. Despite recent advances in targeted therapy for GEP-NETs, these tumors remain challenging to treat and remain life limiting for many patients. Ongoing studies of targeted agents, PRRT, and immunotherapy will hopefully continue to advance our understanding of the biology of these diverse diseases while bringing needed therapies to this growing patient population.

MD ANDERSON PRACTICE TIPS

- A thin-slice, multiphasic CT scan is required for PNETs being considered for surgical resection.
- Jejunal and ileal NETs are resected using an open approach to allow for careful palpation of the entire small bowel because small, multifocal tumors are common.
- Hepatic metastases are commonly treated with resection when all visible tumors can be safely resected.
- NET growth over time is best gauged with imaging over longer time intervals since the last progression event, such as 6 to 12 months. It is common for studies read with limited comparison to underestimate or overestimate NET growth.
- NEC is fundamentally distinct from NET and requires very different management, principally aggressive chemotherapy.
- With the wide variety of systemic and locoregional treatment options for patients with advanced disease, it is always helpful to ask if the intensity of a proposed approach is appropriate for the pace, volume, and biology of disease.

REFERENCES

1. Dasari A, Shen C, Halperin D, et al. Trends in the Incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol*. 2017;3:1335-1342.
2. Hassan MM, Phan A, Li D, et al. Risk factors associated with neuroendocrine tumors: a U.S.-based case-control study. *Int J Cancer*. 2008;123:867-873.
3. Crona J, Skogseid B. GEP-NETS update: genetics of neuroendocrine tumors. *Eur J Endocrinol*. 2016;174:R275-R290.
4. Lubensky IA, Zhuang Z. Molecular genetic events in gastrointestinal and pancreatic neuroendocrine tumors. *Endocr Pathol*. 2007;18:156-162.
5. Keutgen XM, Kumar S, Gara SK, et al. Transcriptional alterations in hereditary and sporadic nonfunctioning pancreatic neuroendocrine tumors according to genotype. *Cancer*. 2018;124:636-647.
6. Jiao Y, Shi C, Edil B et al. DAXX/ATRX, MEN1 and mTOR Pathway Genes are Frequently Altered in Pancreatic Neuroendocrine Tumors. Science. 2011;331:1199-1203.
7. Heaphy CM, de Wilde RF, Jiao Y, et al. Altered telomeres in tumors with ATRX and DAXX mutations. *Science*. 2011;333:425.
8. Scarpa A, Chang DK, Nones K, et al. Whole-genome landscape of pancreatic neuroendocrine tumours. *Nature*. 2017;543:65-71.
9. Amorim JP, Santos G, Vinagre J, Soares P. The role of ATRX in the alternative lengthening of telomeres (ALT) phenotype. *Genes (Basel)*. 2016;7.
10. Jiao Y, Shi C, Edil BH, et al. DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. *Science*. 2011;331:1199-1203.
11. Ohki R, Saito K, Chen Y, et al. Phlda3 is a novel tumor suppressor of pancreatic neuroendocrine tumors. *Proc Natl Acad Sci U S A*. 2014;111:E2404-E2413.
12. Yao J, Garg A, Chen D, et al. Genomic profiling of NETs: a comprehensive analysis of the RADIANT trials. *Endocr Relat Cancer*. 2019;26:391-403.
13. Kulke MH, Freed E, Chiang DY, et al. High-resolution analysis of genetic alterations in small bowel carcinoid tumors reveals areas of recurrent amplification and loss. *Genes Chromosomes Cancer*. 2008;47:591-603.
14. Banck MS, Kanwar R, Kulkarni AA, et al. The genomic landscape of small intestine neuroendocrine tumors. *J Clin Invest*. 2013;123:2502-2508.
15. Francis JM, Kiezun A, Ramos AH, et al. Somatic mutation of Cdkn1b in small intestine neuroendocrine tumors. *Nat Genet*. 2013;45:1483-1486.
16. Crona J, Gustavsson T, Norlen O, et al. Somatic mutations and genetic heterogeneity at the Cdkn1b locus in small intestinal neuroendocrine tumors. *Ann Surg Oncol*. 2015;22(suppl 3):S1428-S1435.
17. Maxwell JE, Sherman SK, Li G, et al. Somatic alterations of Cdkn1b are associated with small bowel neuroendocrine tumors. *Cancer Genet*. 2015;S2210-7762.
18. Kulke MH, Anthony LB, Bushnell DL, et al. NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. *Pancreas*. 2010;39:735-752.
19. Bellizzi AM. Assigning site of origin in metastatic neuroendocrine neoplasms: a clinically significant application of diagnostic immunohistochemistry. *Adv Anat Pathol*. 2013;20:285-314.
20. Maxwell JE, Sherman SK, Stashek KM, et al. A practical method to determine the site of unknown primary in metastatic neuroendocrine tumors. *Surgery*. 2014;156:1359-1365; discussion 65-66.
21. Klimstra DS, Modlin IR, Coppola D, et al. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. *Pancreas*. 2010;39:707-712.
22. Rindi G, Klimstra DS, Abedi-Ardekani B, et al. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. *Mod Pathol*. 2018;31:1770-1786.
23. Nadler A, Cukier M, Rowsell C, et al. Ki-67 is a reliable pathological grading marker for neuroendocrine tumors. *Virchows Arch*. 2013;462:501-505.
24. Richards-Taylor S, Ewings SM, Jaynes E, et al. The Assessment of Ki-67 as a prognostic marker in neuroendocrine tumours: a systematic review and meta-analysis. *J Clin Pathol*. 2016;69:612-618.
25. Tang LH, Untch BR, Reidy DL, et al. Well-differentiated neuroendocrine tumors with a morphologically apparent high-grade component: a pathway distinct from poorly-differentiated neuroendocrine carcinomas. *Clin Cancer Res*. 2016;22:1011-1017.
26. Vinik AI, Silva MP, Woltering EA, et al. Biochemical testing for neuroendocrine tumors. *Pancreas*. 2009;38:876-889.
27. Vinik AI, Woltering EA, Warner RRP, et al. NANETS consensus guidelines for the diagnosis of neuroendocrine tumor. *Pancreas*. 2010;39:713-734.
28. Pape UF, Perren A, Niederle B, et al. ENETS consensus guidelines for the management of patients with neuroendocrine neoplasms from the jejuno-ileum and the appendix including goblet cell carcinomas. *Neuroendocrinology*. 2012;95:135-156.
29. Maxwell JE, O'Dorisio TM, Howe JR. Biochemical diagnosis and preoperative imaging of gastroenteropancreatic neuroendocrine tumors. *Surg Oncol Clin N Am*. 2016;25:171-194.
30. Sherman SK, Maxwell JE, O'Dorisio MS, et al. Pancreastatin predicts survival in neuroendocrine tumors. *Ann Surg Oncol*. 2014;21:2971-2980.
31. Diebold AE, Boudreaux JP, Wang YZ, et al. Neurokinin a levels predict survival in patients with stage IV well differentiated small bowel neuroendocrine neoplasms. *Surgery*. 2012;152:1172-1176.
32. Anderson MA, Carpenter S, Thompson NW, et al. Endoscopic ultrasound is highly accurate and directs management in patients with neuroendocrine tumors of the pancreas. *Am J Gastroenterol*. 2000;95:2271-2277.
33. Bellutti M, Fry LC, Schmitt J, et al. Detection of neuroendocrine tumors of the small bowel by double balloon enteroscopy. *Dig Dis Sci*. 2009;54:1050-1058.
34. van Tuyl SA, van Noorden JT, Timmer R, et al. Detection of small-bowel neuroendocrine tumors by video capsule endoscopy. *Gastrointest Endosc*. 2006;64:66-72.
35. Sahani DV, Bonaffini PA, Fernandez-Del Castillo C, Blake MA. Gastroenteropancreatic neuroendocrine tumors: role of imaging in diagnosis and management. *Radiology*. 2013;266:38-61.
36. Chiti A, Fanti S, Savelli G, et al. Comparison of somatostatin receptor imaging, computed tomography and ultrasound in the clinical management of neuroendocrine gastro-entero-pancreatic tumours. *Eur J Nucl Med*. 1998;25:1396-1403.
37. Kumbasar B, Kamel IR, Tekes A, et al. Imaging of neuroendocrine tumors: accuracy of helical CT versus SRS. *Abdom Imaging*. 2004;29:696-702.
38. Sundin A, Vullierme MP, Kaltsas G, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: radiological examinations. *Neuroendocrinology*. 2009;90:167-183.
39. Dahdaleh FS, Lorenzen A, Rajput M, et al. The value of preoperative imaging in small bowel neuroendocrine tumors. *Ann Surg Oncol*. 2013;20:1912-1917.
40. Dromain C, de Baere T, Lumbroso J, et al. Detection of liver metastases from endocrine tumors: a prospective comparison of somatostatin receptor scintigraphy, computed tomography, and magnetic resonance imaging. *J Clin Oncol*. 2005;23:70-78.
41. Reubi JC. Somatostatin and other peptide receptors as tools for tumor diagnosis and treatment. *Neuroendocrinology*. 2004;80(suppl 1):51-56.

42. Reubi JC, Krenning E, Lamberts SWJ. Distribution of somatostatin receptors in normal and tumor tissue. *Metabolism*. 1990;39:78-81.
43. Krenning EP, Kwekkeboom DJ, Bakker WH, et al. Somatostatin receptor scintigraphy with [111In-DTPA-D-Phe1]- and [123I-Tyr3]octreotide: the Rotterdam experience with more than 1000 patients. *Eur J Nucl Med*. 1993;20:716-731.
44. Gabriel M, Decristoforo C, Kendler D, et al. 68Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. *J Nucl Med*. 2007;48:508-518.
45. Sundin A, Eriksson B, Bergström M, et al. PET in the diagnosis of neuroendocrine tumors. *Ann N Y Acad Sci*. 2004;1014:246-257.
46. Bahri H, Laurence L, Edeline J, et al. High prognostic value of 18f-FDG PET for metastatic gastroenteropancreatic neuroendocrine tumors: a long-term evaluation. *J Nucl Med*. 2014;55:1786-1790.
47. Kalemkerian GP, Gadgeel SM. Modern staging of small cell lung cancer. *J Natl Compr Canc Netw*. 2013;11:99-104.
48. Edge SB, Byrd DR, Compton CC, et al. *AJCC Cancer Staging Manual*. 7th ed. Springer; 2010.
49. Strosberg JR, Cheema A, Weber J, et al. Prognostic validity of a novel American Joint Committee on Cancer Staging Classification for pancreatic neuroendocrine tumors. *J Clin Oncol*. 2011;29:3044-3049.
50. Carney JA, Go VLW, Fairbanks VF, et al. The syndrome of gastric argyrophil carcinoid tumors and nonantral gastric atrophy. *Ann Intern Med*. 1983;99:761-766.
51. O'Toole D, Delle Fave G, Jensen RT. Gastric and duodenal neuroendocrine tumours. *Best Pract Res Clin Gastroenterol*. 2012;26:719-735.
52. Rindi G, Luinetti O, Cornaggia M, et al. Three subtypes of gastric argyrophil carcinoid and the gastric neuroendocrine carcinoma: a clinicopathologic study. *Gastroenterology*. 1993;104:994-1006.
53. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol*. 2008;26:3063-3072.
54. Jensen RT, Rindi G, Arnold R, et al. Well-differentiated duodenal tumor/carcinoma (excluding gastrinomas). *Neuroendocrinology*. 2006;84:165-172.
55. Keck KJ, Maxwell JE, Utria, et al. The Distal Predilection of Small Bowel Neuroendocrine Tumors. Ann Surg Oncol. 2018;25(11):3207-3213.
56. Strosberg J. Neuroendocrine tumours of the small intestine. *Best Pract Res Clin Gastroenterol*. 2012;26:755-773.
57. Choi AB, Maxwell JE, Keck KJ, et al. Is multifocality an indicator of aggressive behavior in small bowel neuroendocrine tumors? *Pancreas*. 2017;46:1115-1120.
58. Kulke MH. Clinical presentation and management of carcinoid tumors. *Hematol Oncol Clin North Am*. 2007;21:433-55; vii-viii.
59. Hamada Y, Tanaka K, Tano S, et al. Usefulness of endoscopic submucosal dissection for the treatment of rectal carcinoid tumors. *Eur J Gastroenterol Hepatol*. 2012;24:770-774.
60. Bertani E, Ravizza D, Milione M, et al. Neuroendocrine neoplasms of rectum: a management update. *Cancer Treat Rev*. 2018;66:45-55.
61. Okabayashi T, Shima Y, Sumiyoshi T, et al. Diagnosis and management of insulinoma. *World J Gastroenterol*. 2013;19:829-837.
62. Treglia G, Inzani F, Campanini N, et al. Insulinoma detected by 68ga-DOTANOC PET/CT and missed by 18F-Dihydroxyphenylalanine PET/CT. *Clin Nucl Med*. 2013;38:e267-e270.
63. Stabile BE, Morrow DJ, Passaro E. The gastrinoma triangle: operative implications. *Am J Surg*. 1984;147:25-31.
64. Zollinger RM, Ellison EH. Primary peptic ulcerations of the jejunum associated with islet cell tumors of the pancreas. *Ann Surg*. 1955;142:709-723.
65. Fendrich V, Langer P, Waldmann J, et al. Management of sporadic and multiple endocrine neoplasia type 1 gastrinomas. *Br J Surg*. 2007;94:1331-1341.
66. Naswa N, Sharma P, Soundararajan R, et al. Diagnostic performance of somatostatin receptor PET/CT Using 68Ga-DOTANOC in gastrinoma patients with negative or equivocal CT findings. *Abdom Imaging*. 2013;38:552-560.
67. Eldor R, Glaser B, Fraenkel M, et al. Glucagonoma and the glucagonoma syndrome—cumulative experience with an elusive endocrine tumour. *Clin Endocrinol (Oxf)*. 2011;74:593-598.
68. Williamson JM, Thorn CC, Spalding D, Williamson RC. Pancreatic and peripancreatic somatostatinomas. *Ann R Coll Surg Engl*. 2011;93:356-360.
69. Kane MG, O'Dorisio TM, Krejs GJ. Production of secretory diarrhea by intravenous infusion of vasoactive intestinal polypeptide. *N Engl J Med*. 1983;309:1482-1485.
70. Angelousi A, Koffas A, Grozinsky-Glasberg S, et al. Diagnostic and management challenges in vasoactive intestinal peptide secreting tumors: a series of 15 patients. *Pancreas*. 2019;48:934-942.
71. Kuo SC, Gananadha S, Scarlett CJ, et al. Sporadic pancreatic polypeptide secreting tumors (PPomas) of the pancreas. *World J Surg*. 2008;32:1815-1822.
72. Maxwell JE, O'Dorisio TM, Bellizzi AM, Howe JR. Elevated pancreatic polypeptide levels in pancreatic neuroendocrine tumors and diabetes mellitus: causation or association? *Pancreas*. 2014;43:651-656.
73. Quin JD, Marshall DA, Fisher BM, MacCuish AC. Metastatic pancreatic polypeptide producing tumour presenting with diabetes mellitus. *Scott Med J*. 1991;36:143.
74. Kuo JH, Lee JA, Chabot JA. Nonfunctional pancreatic neuroendocrine tumors. *Surg Clin North Am*. 2014;94:689-708.
75. Fendrich V, Bartsch DK. Surgical treatment of gastrointestinal neuroendocrine tumors. *Langenbecks Arch* Surg. 2011;396:299-311.
76. Halperin DM, Shen C, Dasari A, et al. Frequency of carcinoid syndrome at neuroendocrine tumour diagnosis: a population-based study. *Lancet Oncol*. 2017;18:525-534.
77. Rajamannan NM, Caplice N, Anthikad F, et al. Cell proliferation in carcinoid valve disease: a mechanism for serotonin effects. *J Heart Valve Dis*. 2001;10:827-831.
78. Lundin L, Norheim I, Landelius J, et al. Carcinoid heart disease: relationship of circulating vasoactive substances to ultrasound-detectable cardiac abnormalities. *Circulation*. 1988;77:264-269.
79. Castillo JG, Milla F, Adams DH. Surgical management of carcinoid heart valve disease. *Semin Thorac Cardiovasc Surg*. 2012;24:254-260.
80. Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol*. 2008;9:61-72.
81. Kulke MH, Shah MH, Benson AB, et al. Neuroendocrine tumors, version 1.2015: clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2015;13:80-110.
82. Fouche M, Bouffard Y, Le Goff MC, et al. Intraoperative carcinoid syndrome during small-bowel neuroendocrine tumour surgery. *Endocr Connect*. 2018;7:1245-1250.
83. Kinney MAO, Nagorney DM, Clark DF, et al. Partial hepatic resections for metastatic neuroendocrine tumors: perioperative outcomes. *J Clin Anesth*. 2018;51:93-96.
84. Woltering EA, Wright AE, Stevens MA, et al. Development of effective prophylaxis against intraoperative carcinoid crisis. *J Clin Anesth*. 2016;32:189-193.
85. Condron ME, Pommier SJ, Pommier RF. Continuous infusion of octreotide combined with perioperative octreotide bolus does not prevent intraoperative carcinoid crisis. *Surgery*. 2016;159:358-365.
86. Condron ME, Jameson NE, Limbach KE, et al. A prospective study of the pathophysiology of carcinoid crisis. *Surgery*. 2019;165:158-165.

87. Uygun A, Kadayifci A, Polat Z, et al. Long-term results of endoscopic resection for type i gastric neuroendocrine tumors. *J Surg Oncol*. 2013.
88. Boudreaux JP. Surgery for gastroenteropancreatic neuroendocrine tumors (GEPNETS). *Endocrinol Metab Clin North Am*. 2011;40:163-171, ix.
89. Huang LC, Poultsides GA, Norton JA. Surgical management of neuroendocrine tumors of the gastrointestinal tract. *Oncology*. 2011:794-803.
90. Knigge U, Hansen CP. Surgery for GEP-NETS. *Best Pract Res Clin Gastroenterol*. 2012;26:819-831.
91. Rindi G, Azzoni C, La Rosa S, et al. ECL cell tumor and poorly-differentiated endocrine carcinoma of the stomach: prognostic evaluation by pathological analysis. *Gastroenterology*. 1999;116:532-542.
92. Roland CL, Bian A, Mansour JC, et al. Survival impact of malignant pancreatic neuroendocrine and islet cell neoplasm phenotypes. *J Surg Oncol*. 2012;105:595-600.
93. Papamichail M, Ali A, Pizanias M, et al. Irreversible electroporation for the treatment of pancreatic neuroendocrine tumors. *Korean J Hepatobiliary Pancreat*. Surg 2016;20:116-120.
94. Howe JR, Cardona K, Fraker DL, et al. The surgical management of small bowel neuroendocrine tumors: consensus guidelines of the North American Neuroendocrine Tumor Society. *Pancreas*. 2017;46:715-731.
95. Ramage JK, Davies AH, Ardill J, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours. *Gut*. 2005;54(suppl 4):iv1-16.
96. Anthony L, Freda PU. From somatostatin to octreotide LAR: evolution of a somatostatin analogue. *Curr Med Res Opin*. 2009;25:2989-2999.
97. Vinik AI, Wolin EM, Liyanage N, et al. Evaluation of lanreotide depot/autogel efficacy and safety as a carcinoid syndrome treatment (ELECT): a randomized, double-blind, placebo-controlled trial. *Endocr Pract*. 2016;22:1068-1080.
98. Fisher GA Jr, Wolin EM, Liyanage N, et al. Patient-reported symptom control of diarrhea and flushing in patients with neuroendocrine tumors treated with lanreotide depot/autogel: results from a randomized, placebo-controlled, double-blind and 32-week open-label study. *Oncologist*. 2018;23:16-24.
99. Ahrendt SA, McGuire GE, Pitt HA, Lillemoe KD. Why does somatostatin cause gallstones? *Am J Surg*. 1991;161:177-183.
100. Rinke A, Muller HH, Schade-Brittinger C, et al. placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide lar in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID study group. *J Clin Oncol*. 2009;27:4656-4663.
101. Caplin ME, Pavel M, Cwikla JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. 2014;371:224-233.
102. Niederhuber JE, Fojo T. Treatment of metastatic disease in patients with neuroendocrine tumors. *Surg Oncol Clin N Am*. 2006;15:511-533, viii.
103. Almond LM, Hodson J, Ford SJ, et al. Role of palliative resection of the primary tumour in advanced pancreatic and small intestinal neuroendocrine tumours: a systematic review and meta-analysis. *Eur J Surg Oncol*. 2017;43:1808-1815.
104. Daskalakis K, Karakatsanis A, Hessman O, et al. Association of a prophylactic surgical approach to stage IV small intestinal neuroendocrine tumors with survival. *JAMA Oncol*. 2018;4:183-189.
105. Schreckenbach T, Hubert H, Koch C, et al. Surgical resection of neuroendocrine tumor liver metastases as part of multimodal treatment strategies: a propensity score matching analysis. *Eur J Surg Oncol*. 2019;45:808-815.
106. Mayo SC, de Jong MC, Pulitano C, et al. Surgical management of hepatic neuroendocrine tumor metastasis: results from an international multi-institutional analysis. *Ann Surg Oncol*. 2010;17:3129-3136.
107. Maxwell JE, Sherman SK, O'Dorisio TM, et al. Liver-directed surgery of neuroendocrine metastases: what is the optimal strategy? *Surgery*. 2016;159:320-333.
108. Ejaz A, Reames BN, Maithel S, et al. Cytoreductive debulking surgery among patients with neuroendocrine liver metastasis: a multi-institutional analysis. *HPB (Oxford)*. 2018;20:277-284.
109. Akyildiz HY, Mitchell J, Milas M, et al. Laparoscopic radiofrequency thermal ablation of neuroendocrine hepatic metastases: long-term follow-up. *Surgery*. 2010;148:1288-1293; discussion 1293.
110. Mazzaferro V, Sposito C, Coppa J, et al. The long-term benefit of liver transplantation for hepatic metastases from neuroendocrine tumors. *Am J Transplant*. 2016;16:2892-2902.
111. Basuroy R, Srirajaskanthan R, Ramage JK. A Multimodal approach to the management of neuroendocrine tumour liver metastases. *Int J Hepatol*. 2012;2012:819193.
112. Hajarizadeh H, Ivancev K, Mueller CR, et al. Effective palliative treatment of metastatic carcinoid tumors with intra-arterial chemotherapy/chemoembolization combined with octreotide acetate. *Am J Surg*. 1992;163:479-483.
113. Kim YH, Ajani JA, Carrasco CH, et al. Selective hepatic arterial chemoembolization for liver metastases in patients with carcinoid tumor or islet cell carcinoma. *Cancer Invest*. 1999;17:474-478.
114. Chen JX, Wileyto EP, Soulen MC. Randomized embolization trial for neuroendocrine tumor metastases to the liver (RET-NET): study protocol for a randomized controlled trial. *Trials*. 2018;19:390.
115. Suzuki K, Yoneda M, Kobayashi N, Nakajima A. Neuroendocrine tumor treated with arterial chemoembolization using DEB-TACE. *Intern Med*. 2019;58:2895-2896.
116. Bhagat N, Reyes DK, Lin M, et al. Phase II study of chemoembolization with drug-eluting beads in patients with hepatic neuroendocrine metastases: high incidence of biliary injury. *Cardiovasc Intervent Radiol*. 2013;36:449-459.
117. O'Toole D, Ruszniewski P. Chemoembolization and other ablative therapies for liver metastases of gastrointestinal endocrine tumours. *Best Pract Res Clin Gastroenterol*. 2005;19:585-594.
118. Joskin J, de Baere T, Auperin A, et al. Predisposing factors of liver necrosis after transcatheter arterial chemoembolization in liver metastases from neuroendocrine tumor. *Cardiovasc Intervent Radiol*. 2015;38:372-380.
119. Dermine S, Palmieri LJ, Lavole J, et al. Non-pharmacological therapeutic options for liver metastases in advanced neuroendocrine tumors. *J Clin Med*. 2019;8(11):1907.
120. Boudreaux JP, Klimstra DS, Hassan MM, et al. The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the jejunum, ileum, appendix, and cecum. *Pancreas*. 2010;39:753-766.
121. Hanssen LE, Schrumpf E, Kolbenstvedt AN, et al. Treatment of malignant metastatic midgut carcinoid tumours with recombinant human alpha2b interferon with or without prior hepatic artery embolization. *Scand J Gastroenterol*. 1989;24:787-795.
122. Eriksson BK, Larsson EG, Skogseid BM, et al. Liver Embolizations of patients with malignant neuroendocrine gastrointestinal tumors. *Cancer*. 1998;83:2293-2301.
123. Kennedy AS, Dezarn WA, McNeillie P, et al. Radioembolization for unresectable neuroendocrine hepatic metastases using resin 90y-microspheres: early results in 148 patients. *Am J Clin Oncol*. 2008;31:271-279.

124. Paprottka PM, Hoffmann RT, Haug A, et al. Radioembolization of symptomatic, unresectable neuroendocrine hepatic metastases using yttrium-90 microspheres. *Cardiovasc Intervent Radiol*. 2012;35:334-342.
125. Zubiri L, Bilbao JI, Rodriguez J, Sangro B. Selective internal radiation therapy: an effective treatment for hormonal syndromes in pancreatic neuroendocrine tumors. *Hepa Oncol*. 2018;5:ePub.
126. Padia SA. Y90 clinical data update: cholangiocarcinoma, neuroendocrine tumor, melanoma, and breast cancer metastatic disease. *Tech Vasc Interv Radiol*. 2019;22:81-86.
127. Loree JM, Hiruki T, Kennecke HF. Case report of cirrhosis following yttrium-90 radioembolization for pancreatic neuroendocrine liver metastases. *Case Rep Oncol*. 2016;9:76-82.
128. Halperin DM, Dasari A, Yao JC. [177lu-DOTA,TYR]-octreotate in the treatment of midgut neuroendocrine tumors. *Future Oncol*. 2016;12:313-321.
129. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of (177) LU-DOTATATE for midgut neuroendocrine tumors. *N Engl J Med*. 2017;376:125-135.
130. Moertel CG, Hanley JA, Johnson LA. Streptozocin alone compared with streptozocin plus fluorouracil in the treatment of advanced islet cell carcinoma. *N Engl J Med*. 1980;303:1189-1194.
131. Moertel CG, Lefkopoulo M, Lipsitz S, et al. Streptozocin-doxorubicin, streptozocin-fluorouracil, or chlorozotocin in the treatment of advanced islet-cell carcinoma. *N Engl J Med*. 1992;326:519-523.
132. Kouvaraki MA, Ajani JA, Hoff P, et al. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. *J Clin Oncol*. 2004;22:4762-4771.
133. Sorbye H, Welin S, Langer SW, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the Nordic NEC STUDY. *Ann Oncol*. 2013;24:152-160.
134. Raymond E, Dahan L, Raoul J, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364:501-513.
135. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364:514-523.
136. Kulke MH, Lenz HJ, Meropol NJ, et al. Activity of sunitinib in patients with advanced neuroendocrine tumors. *J Clin Oncol*. 2008;26:3403-3410.
137. Pavel ME, Hainsworth JD, Baudin E, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2011;378:2005-2012.
138. Yao JC, Fazio N, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2016;387:968-977.
139. Xu J, Li J, Bai C, Xu N, et al. Surufatinib in advanced well-differentiated neuroendocrine tumors: a multicenter, single-arm, open-label, phase IB/II trial. *Clin Cancer Res*. 2019;25:3486-3494.
140. Xu J, Shen L, Zhou Z, et al. Efficacy and safety of surufatinib in patients with well-differentiated advanced extrapancreatic neuroendocrine tumors: results from the randomized phase Iii study (SANET-EP). Presented at: European Society of Medical Oncology; Barcelona, Spain; 2019.
141. Roberts JA, Gonzalez RS, Das S, et al. Expression of PD-1 and PD-L1 in poorly-differentiated neuroendocrine carcinomas of the digestive system: a potential target for anti-PD-1/PD-L1 therapy. *Hum Pathol*. 2017;70:49-54.
142. Kulke MH, Bergsland EK, Yao JC. Glycemic control in patients with insulinoma treated with everolimus. *N Engl J Med*. 2009;360:195-197.
143. Kulke MH, Horsch D, Caplin ME, et al. Telotristat ethyl, a tryptophan hydroxylase inhibitor for the treatment of carcinoid syndrome. *J Clin Oncol*. 2017;35:14-23.
144. Pavel M, Gross DJ, Benavent M, et al. Telotristat ethyl in carcinoid syndrome: safety and efficacy in the TELECAST phase 3 trial. *Endocr Relat Cancer*. 2018;25:309-322.

Section VII

Breast Cancer

Section Editor: Gabriel N. Hortobagyi

35 Early-Stage and Locally Advanced Breast Cancer

36 Metastatic Breast Cancer

37 Management of Locally Advanced Breast Cancer, Including Inflammatory Breast Cancer

38 Special Situations in Breast Cancer

This page intentionally left blank

35 Early-Stage and Locally Advanced Breast Cancer

Demetria Smith-Graziani
Mariana Chavez-MacGregor

KEY CONCEPTS

- A multidisciplinary approach is of upmost importance, especially with regard to planning and coordinating multimodality therapy. It is important to involve surgical and radiation oncology colleagues early to determine the best treatment plan.
- Choice of systemic therapy is ultimately guided by biomarker status of the patient's tumor.
- Whereas patients with hormone receptor–positive cancers should receive endocrine therapy, those with human epidermal growth factor receptor 2 (HER2)–positive cancers should receive anti-HER2 targeted therapy.
- Genomic assays can help assess the benefit of adjuvant chemotherapy in patients with hormone receptor–positive/HER2-negative breast cancer.
- All women with node-positive disease and a significant percentage of women with node-negative tumors that are hormone receptor negative or larger than 1 cm in size benefit from chemotherapy. Those with HER2-positive breast cancer need to receive anti-Her2 therapy
- Chemotherapy is the cornerstone of treatment for patients with triple-negative breast cancer (TNBC).
- Preoperative or neoadjuvant chemotherapy should be administered in most patients with HER2-positive or TNBC. The presence of a pathological complete response or residual disease has important prognostic implications but now allows us to identify patients that will benefit from additional adjuvant treatment.

EPIDEMIOLOGY

Incidence

Breast cancer is the second most common cause of death for U.S. women with an age-adjusted death rate of 20.3 per 100,000. In 2020, it is estimated that 276,480 American women will be diagnosed with breast cancer and that 42,170 will die from this disease, making breast cancer the third most common cause of cancer-related morality for all people in the United States, with lung cancer being the most common.[1]

In the early 1980s, the rates of breast cancer diagnosis rose sharply, likely related to increased mammographic screening, because it was the incidence of stage 0 and I carcinomas that rose most sharply. Data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute demonstrate that although the incidence of breast cancer later stabilized by the end of the 1980s, there has been an increase in the percentage of breast cancers that are hormone receptor positive. This is thought to be caused by either changes in receptor assays or an increased use of hormone replacement therapy by women.[2,3] The incidence of primary breast cancer then decreased around 2003, shortly after the publication of the Women's Health Initiative (WHI) results, which prompted many healthy postmenopausal women to stop using hormone replacement therapy.[4]

Breast cancer incidence has long varied in different regions of the world. Its incidence is highest in Northern Europe and North America and lowest in Asia and Africa. Data suggest that this variability is caused not only by environmental factors but also to lifestyle. This is supported by the observation that breast cancer incidence is higher in second-generation Asian immigrants in the United States.[5]

Mortality

Breast cancer overall mortality rates had been stable for more than 50 years before 1989. Starting in the 1990s, there has been a steady decrease in breast cancer deaths every year. Mortality rates declined by 1.4% per year from 1989 to 1995 and by 3.2% per year thereafter. This is thought to be due in part to increased use of mammography, resulting in earlier diagnosis, and the use of more effective treatments. Mortality rates continue to be higher for African American women. This is due in part to disparities in health care access that exist both for diagnosis as well as treatment.[6]

RISK FACTORS

The two most important risk factors for breast cancer are female gender and increasing age.[7] However, many additional patient characteristics increase one's risk of breast cancer (Table 35–1).

Hereditary

Family History

Although it is known that family history is an important risk factor for breast cancer, only 15% to 25% of newly diagnosed patients have a positive family history. The Gail model was the first to incorporate the number of first-degree relatives into a comprehensive model of breast cancer risk assessment.[8] Claus et al[9] then assessed the estimated risk of breast cancer based on the number of familial cases and their ages of diagnosis. It is now well known that the risk for each patient with a positive family history is affected by the age of the family member at diagnosis, the total number of first-degree relatives affected, and the patient's age. Based on data from a large meta-analysis, the risk of breast cancer for a patient with one affected first-degree relative increased 1.8-fold; if there were two affected first-degree relatives, that risk increased 2.93-fold. This risk was then further modified by the age of the patient, such that a woman's risk of breast cancer before age 40 years was increased to 5.7-fold if one relative was diagnosed before age 40 years.[10]

Genetic Mutations

The overall prevalence of specific genetic mutations accounting for breast cancer is rare (5%–10% of all cases). Risk can be further subdivided based on a patient's history. The most commonly studied mutations are on the *BRCA1* and *BRCA2* genes, although multiple other mutations exist on genes such as *p53*, *ATM*, *CHEK2*, *PTEN*, *MLH1*, *MSH2*, and *PALB2*.[11] In a study that analyzed 10,000 individuals, excluding those with Ashkenazi ancestry, the prevalence of *BRCA1* and *BRCA2* mutations varied, with a low of 2.9% if the patient and all first- or second-degree relatives had no prior history of breast cancer or ovarian cancer at younger than 50 years of age. A maximum prevalence of 81.3% was noted if the patient and any first- or second-degree relative had breast cancer diagnosed at younger than 50 years of age and ovarian cancer at any age.[12] Because genetic testing often leads to important medical decisions both for the patient and other family members, it is important to determine whom it is most appropriate to screen by taking into account population-dependent positive and negative predictive values of the test, using statistical models, and following current guidelines.

Conditions of the Breast

Ductal Carcinoma in Situ and Lobular Carcinoma in Situ

There has been a rapid increase in the literature concerning the epidemiology, natural history, and treatment of ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS). (See detailed information in Chapter 38.)

With DCIS, the 10-year risk of invasive breast cancer is 5% in the contralateral breast. LCIS has been regarded as a risk factor for ipsilateral and contralateral breast cancer. Recent research supports that LCIS is a direct nonobligatory precursor of both invasive lobular and ductal carcinoma. For patients diagnosed with

Table 35-1 Risk factors for breast cancer. DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ.

Hereditary	Conditions of the breast	Natural hormonal factors	Exogenous hormonal use	Other risk factors
• Family history • Genetic mutations	• DCIS • LCIS	• Age at menarche • Age at first pregnancy • Age at menopause • Pregnancy	• Oral contraceptives • Hormone replacement therapy	• Alcohol consumption • Obesity

LCIS, the risk of developing breast cancer in either breast is 1% a year.[13]

Natural Hormonal Factors

Age at Menarche

A later age of menarche is protective. One study has reported that for every 2-year delay in menarche, there was a 10% reduction in breast cancer risk.[14]

Age at First Pregnancy

There is a favorable risk reduction associated with earlier age of pregnancy. Women who give birth for the first time at age 35 years have a 1.6-fold higher risk of breast cancer compared with women who were 26 to 27 years of age at the time of first birth. Women who are older than age 30 years at the time of first birth are at higher risk than nulliparous women.[15]

Age at Menopause

Late menopause is associated with a higher risk of breast cancer. Oophorectomy before age 40 years decreases the lifetime risk of breast cancer by 50%.[16]

Pregnancy

Breast cancer is the most common cancer associated with pregnancy, with its incidence being 1 in 3000. The incidence of pregnancy-associated breast cancer is likely related to the delay of childbirth until after age 30 years. There are controversial data from two reports suggesting that pregnancy might cause a transient rise in breast cancer risk. However, a clearly documented decreased risk of breast cancer occurs 10 to 15 years after childbirth.[17] (See detailed information in Chapter 38.)

Exogenous Hormonal Use

Oral Contraceptives

Most studies have not shown an increased risk of breast cancer with oral contraceptive use.[18,19] However, a meta-analysis showed a significant but small increase in relative risk of breast cancer.[20] A concern about the meta-analysis is that follow-up was limited.

Hormone Replacement Therapy

The WHI showed that the relative risk of breast cancer was increased to 1.26 for women who took combined treatment with estrogen and progesterone for a mean of 5.2 years compared with placebo.[21] Although long-term hormone replacement therapy was associated with a higher risk of breast cancer, short-term use did not seem to significantly increase the risk of breast cancer.

Other Risk Factors

The risk of breast cancer increases with the amount of alcohol consumed. Compared with women who do not drink any alcohol, consuming one alcoholic drink per day increases breast cancer risk by 7% to 10%. Consuming two or three alcoholic beverages per day is associated with a 20% increase in breast cancer risk.[7]

Obesity has also been linked to breast cancer risk. In postmenopausal women, obesity is more strongly associated with an increased risk of hormone receptor–positive breast cancer. However, weight gain in premenopausal women may increase the risk of triple-negative breast cancer (TNBC).[7]

STAGING OF BREAST CANCER

2017 Tumor, Node, Metastasis Revisions

The 2017 eighth edition of the *Cancer Staging Manual* published by the American Joint Committee on Cancer (AJCC) was modified from the prior staging criteria, published in 2010 (Tables 35–2 and 35–3).[22]

Anatomic Staging

Anatomic stage group should be used only when biomarker analysis is not available. It is based only on the anatomic extent of cancer as defined by the tumor (T), node (N), and metastasis (M) categories.[22]

Prognostic Staging

Prognostic staging is preferred for patient care and should be used for all patients in the United States. When biomarker analysis is available, clinicians should use clinical and pathological prognostic stage groups. The AJCC also recommends that all specimens have a histologic tumor grade and description of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status. Pathologic staging was updated to include genomic profiling to better refine prognostication. Approximately one third of patients' staging is reassigned after pathologic data are obtained. There are currently 122 different staging categories. Please refer to the AJCC eighth edition for more details regarding staging.

PROGNOSTIC FACTORS

There is interest in the assessment of prognostic factors in breast cancer. About 30% of patients with node-negative disease die from a breast cancer–related cause. Thus, there is a great thrust of research to

TABLE 35–2 Tumor, Node, Metastasis Staging System for Breast Cancer

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ (DCIS)
Tis (Paget)	Paget disease of the nipple with no tumor[a]
T1	Tumor ≤20 mm in greatest dimension
T1mi	Microinvasion ≤1 mm in greatest dimension
T1a	Tumor >1 mm but ≤5 mm in greatest dimension
T1b	Tumor >5 mm but ≤10 mm in greatest dimension
T1c	Tumor >10 mm but ≤20 mm in greatest dimension
T2	Tumor >20 mm but ≤50 mm in greatest dimension
T3	Tumor >50 mm in greatest dimension
T4	Tumor of any size with direct extension to
	(a) Chest wall or
	(b) Skin, only as described below
T4a	Extension to chest wall, not including pectoralis muscle adherence or invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma with typical skin changes involving one third or more of the skin of the breast
Regional Lymph Nodes—Clinical (cN)	
cNX	Regional lymph nodes cannot be assessed (eg, previously removed)
cN0	No regional lymph node metastases (by imaging or clinical examination)
cN1	Metastases to movable ipsilateral axillary level I, II axillary lymph node(s)
cN1mi	Micrometastases (~200 cells, >0.2 mm but none >2.0 mm)
cN2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases
cN2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
cN2b	Metastases only in clinically detected ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases
cN3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected[b] ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastases in ipsilateral infraclavicular lymph node(s)
N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastases in ipsilateral supraclavicular lymph node(s)
Regional Lymph Nodes—Pathological (pN)	
pNX	Regional lymph nodes cannot be assessed (eg, previously removed or not removed for pathologic study)
pN0	No regional lymph node metastasis identified or isolated tumor cell clusters (ITCs) only[c]
pN0(i+)	Malignant cells in regional lymph node(s) not > 0.2 mm (detected by H&E or IHC, including ITC)
pN0(mol+)	Positive molecular findings by RT-PCR; no ITCs
pN1	Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by SLNB but not clinically detected

TABLE 35–2 Tumor, Node, Metastasis Staging System for Breast Cancer (*Cont.*)

pN1mi	Micrometastases (>0.2 mm and/or >200 cells but none >2.0 mm)
pN1a	Metastases in 1–3 axillary lymph nodes; at least one metastasis >2.0 mm
pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by SLNB but not clinically detected[b]
pN1c	Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by SLNB but not clinically detected
pN2	Metastases in 4–9 axillary lymph nodes or in clinically detected[d] internal mammary lymph nodes in the absence of axillary lymph node metastases
pN2a	Metastases in 4–9 axillary lymph nodes (at least one tumor deposit >2.0 mm)
pN2b	Metastases in clinically detected[d] internal mammary lymph nodes in the absence of axillary lymph node metastases
pN3	Metastases in ≥10 axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary lymph nodes; or in >3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by SLNB but not clinically detected or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in ≥10 axillary lymph nodes (at least one tumor deposit >2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
pN3b	Metastases in clinically detected[d] ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in >3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by SLNB but not clinically detected
pN3c	Metastases in ipsilateral supraclavicular lymph nodes
Distant Metastases (M)	
M0	No clinical or radiographic evidence of distant metastases
cM0(i+)	No clinical or radiographic evidence of distant metastases but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
cM1	Distant detectable metastases as determined by clinical and radiographic means
pM1	Any histologically proven metastases in distant organs; or if in nonregional nodes, metastases >0.2 mm

[a]Paget disease associated with a tumor is classified according to the size of the tumor.
[b]Not clinically detected is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.
ITCs are defined as small clusters of cells not >0.2 mm, single tumor cells, or a cluster of <200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunohistochemistry (IHC) methods.
[d]*Clinically detected* is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination.
H&E, hematoxylin and eosin; RT-PCR, reverse transcription polymerase chain reaction; SLNB, sentinel lymph node biopsy.
Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the *AJCC Cancer Staging System* (2020).

determine markers that could further identify which patients would benefit most from available adjuvant treatment.

Predictive versus Prognostic Factors

With the growing array of articles in this field, it is important to distinguish predictive from prognostic factors. A predictive factor is one that can provide information on the likelihood of response to a given therapeutic intervention. A prognostic factor is one that can provide information on outcome at the time of diagnosis, independent of treatment.[23] Lymph node status is an example of a prognostic factor; ER and HER2 status are examples of a prognostic and predictive factor.

Pathologic Factors

Prognosis is still determined in large part by histopathology. Multiple studies showed that the most powerful prognostic factor is the extent of disease in the axillary lymph nodes.[24,25] Other important pathologic factors are hormone receptor status, HER2 status, histologic grade, tumor type, and lymphovascular invasion.

Axillary Lymph Nodes

More than 30 years ago, it was established that the number of involved lymph nodes could be used to predict disease-free survival (DFS) and overall survival (OS). In the absence of effective systemic therapy, the

TABLE 35–3 Tumor, Node, Metastasis Anatomic Stage Grouping for Breast Cancer

Stage Grouping			
0	Tis	N0	M0
IA	T1[a]	N0	M0
IB	T0	N1mi	M0
	T1[a]	N1mi	M0
IIA	T0	N1	M0
	T1[a]	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1[a]	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

[a]T1 includes T1mi.
Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging System (2020).

5-year DFSs were 62% with 1 to 3 positive axillary lymph nodes, 58% for 4 to 9 positive lymph nodes, and 29% for 10 or more positive lymph nodes.[25]

Nuclear Grade

Nuclear or histologic grade describes the degree of tumor differentiation and is based on a pathologist's assessment of nuclear size and shape, number of mitoses, and degree of tubule formation. Although a nuclear grade of 1 (most differentiated) to 3 (least differentiated) is reported with every breast cancer pathology report, its use in predicting outcome is still debated.[26] This is in part secondary to interobserver variation in the classification of differentiation. The Nottingham combined grading system seems to be most useful because of its semiquantitative approach and is currently recommended by the College of American Pathologists (CAP).

Hormone Receptor Status

ER and PR positivity correlate with favorable prognosis during the first 3 to 5 years after diagnosis. Immunohistochemical assays have now become the favored approach because they can be used with a variety of specimens. A "positive" specimen is defined as at least 1% of positive cells. The updated American Society of Clinical Oncology (ASCO)/CAP guidelines define cancers with 1% to 10% ER-positive cells as "ER low positive."[27]

Proliferative Rate

This can be evaluated by a variety of methods, including mitotic figure count, S-phase fraction (the fraction of cells synthesizing DNA) as determined by flow cytometry, thymidine labeling index, and monoclonal antibodies to antigens in proliferating cells. A high S-phase fraction is usually associated with poor differentiation and lack of ER positivity. Antibodies to Ki-67 can be used to determine a proliferative rate that corresponds with the S-phase fraction. A recent meta-analysis showed a positive correlation between high Ki-67 and poor prognosis.[28]

HER2/neu Overexpression

The *HER2/neu* oncogene codes for a 185-kDa transmembrane glycoprotein that has intracellular tyrosine kinase activity and is a member of the family of epidermal growth factor receptors. This group of receptors has an important role in the activation of epidermal signal transduction pathways controlling for epithelial growth and differentiation. Overexpression of the *HER2/neu* oncogene is present in up to 30% of invasive breast cancers.

The current standard is to perform either fluorescence in situ hybridization (FISH) by single or dual probe and immunohistochemistry (IHC). The ASCO/CAP guidelines for HER2 testing were updated in 2018. Breast cancer is defined as HER2-positive if IHC is noted to be 3+ or single probe FISH average HER2 copy number is 6.0 or more signals per cell. By dual-probe FISH, the *HER2*/CEP17 ratio should be 2.0 or greater, or the *HER2* copy number should be 6.0 or greater signals per cell regardless of *HER2-to-*CEP17 ratio. Equivocal results include IHC 2+ or dual probe FISH *HER2*/CEP17 ratio less than 2.0 and an *HER2* copy number between 4.0 and 6.0 signals per cell. Equivocal results should be confirmed with the other approved diagnostic tests. If results continue to be equivocal, repeat testing or a new biopsy should be considered.[29]

Before introduction of HER2-targeted therapy, overexpression of *HER2/neu* was associated with shorter DFS and OS.[30] A large single-institution study reviewed all women with T1a and T1b disease diagnosed between 1990 and 2002. Multivariate analysis of 965 patients showed that patients with HER2-positive tumors had 5.09 times the rate of recurrence and 7.81 times the rate of distant recurrence at 5 years compared

TABLE 35–4 Currently Available and Frequently Used Genomic Assays in Estrogen Receptor–Positive Early-Stage Breast Cancer

Assay	Classifiers (*n* genes)	Platform	Binary (High vs Low)	Decentralized Testing	Recommended by ASCO Clinical Practice Guideline (Node Negative)	Validated N0 and N1	Utility in Late Recurrence
Oncotype DX[a]	16	qPCR	No	No	Evidence quality: high Strength recommendation: strong	Yes	Possibly
Prosigna[b]	50	nCounter	No	Yes	Evidence quality: high Strength recommendation: strong	Yes	Yes
MammaPrint[c]	70	Microarray or qPCR	Yes	No	Evidence quality: intermediate Strength recommendation: moderate	Yes	No
EndoPredict[d]	8	qPCR	Yes	Yes	Evidence quality: intermediate Strength recommendation: moderate	Yes	Possibly
Breast Cancer Index[e]	7	qRT-PCR	Yes	No	Evidence quality: intermediate; Strength of recommendation: moderate	Yes	Yes

[a]Genomic Health.
[b]NanoString Technologies.
[c]Agendia.
[d]Myriad Genetics.
[e]bioTheranostics.
ASCO, American Society of Clinical Oncology; qPCR, quantitative polymerase chain reaction; qRT-PCR, quantitative reverse transcriptase polymerase chain reaction.
Modified with permission from Chia SKL. Clinical application and utility of genomic assays in early-stage breast cancer: key lessons learned to date, *Curr Oncol* 2018 Jun;25(Suppl 1):S125-S130.

with patients with hormone receptor–positive, HER2-negative tumors.[31] The predictive response with HER2 has been demonstrated in prospective randomized controlled trials (discussed later in the Systemic Therapy for HER2-Positive Breast Cancer section).[32,33]

Genomic Assays

A number of gene expression assays are now commercially available that can help clinicians determine the patient's individual prognosis and the benefit of the addition of adjuvant chemotherapy to adjuvant endocrine therapy in hormone receptor–positive breast cancer (Table 35–4).

PRINCIPLES OF TREATMENT

At MD Anderson Cancer Center (MDACC), every effort is made to integrate clinical information with imaging, pathologic staging, and molecular characteristics to optimize treatment efficacy and, whenever possible, perform breast-conserving surgery (BCS). A multidisciplinary approach is of upmost importance, especially with regard to planning and combined-modality therapy. It is important to involve surgical and radiation oncology colleagues early to determine the best treatment plan. All patients at MDACC (including those with DCIS) undergo receptor testing for hormone receptor status for ER and PR. In addition, patients with invasive cancers are tested for *HER2/neu* status.

Surgery

Breast-Conserving Therapy

BCS, or segmental resection, has revolutionized patient care for breast cancer over the past three decades. Most women are able to preserve their breasts without a negative effect on survival. Breast-conserving therapy involves the surgical removal of tumor with negative margins followed by radiation therapy to the breast. Multiple studies have shown that patients with

stage I breast cancer treated with BCS have DFS and OS rates similar to patients treated with modified radical mastectomies.[34]

There are only a few true absolute contraindications to BCS, including persistently positive resection margins, multicentric disease, diffuse malignant-appearing microcalcifications, inflammatory breast cancer, a history of prior radiation to the breast or mantle region (for Hodgkin disease), and pregnancy, although it might be possible to perform BCS in the third trimester. Relative contraindications include a history of connective tissue disease suggesting that radiation would be poorly tolerated, centrally located tumors involving the nipple–areolar complex, and a large tumor in a small breast that might lead to a poor cosmetic result. Although the final decision about whether to offer BCS is left to the discretion of surgical colleagues, most patients who do not meet one of the absolute or relative contraindications are offered this surgical approach.

Risk Factors for Ipsilateral Recurrence with Breast-Conserving Surgery

The risk of ipsilateral tumor recurrence ranges from 0.5% to 2.0% per year. Risk factors include age younger than 35 years, an extensive intraductal component, major lymphocytic stromal reaction, peritumoral invasion, positive margins of resection, and presence of tumor necrosis.

Axillary Lymph Node Dissection

Sentinel lymph node biopsy (SLNB) is the standard of care for patients with clinically negative axilla. In accordance with the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial, patients undergoing BCS with T1 or T2 tumors with fewer than three positive sentinel nodes can forgo complete axillary dissection if they are treated with whole-breast irradiation. Otherwise, if a positive sentinel node is identified, complete axillary node dissection should be performed.[35]

Mastectomy

As with stage I disease, multiple studies of patients with T2 tumors treated with either BCS or modified radical mastectomy have documented similar long-term outcomes. Patients with tumors larger than 4 to 5 cm are often not considered to be ideal candidates for BCS because of the potential for residual tumor and poor cosmetic result. These patients are usually treated with neoadjuvant systemic therapy but may still require mastectomy depending on response to treatment.

The historical surgical procedure for locally advanced disease is mastectomy. Clinical trials using neoadjuvant chemotherapy have noted that 50% or more of women with locally advanced breast cancer can be treated with BCS after neoadjuvant therapy.[36] One concern is that women who need to be downstaged with preoperative chemotherapy to be eligible for segmental mastectomy have a higher local failure rate.[37] This can be improved through accurate localization of the tumor using a radiopaque clip, so that the appropriate area of tumor involvement can be resected, even if a complete or near-complete response is achieved with neoadjuvant therapy. Shared decision making is encouraged in which patients understand the outcomes, potential for additional treatment (radiation therapy), and cosmetic implications of each option. Clearly, plastic-reconstructive surgeons are key of the multidisciplinary team, and their early involvement is recommended.

Radiation Therapy

After Breast-Conserving Surgery

Radiation of the breast after this form of surgery is similar in terms of area treated and dose given to the treatment of stage I. Regional nodal irradiation to negative axillary lymph nodes is not routinely given. Some groups recommend irradiation of the supraclavicular fossa or internal mammary chain for those with positive lymph nodes. The American Society of Radiation Oncology (ASTRO) also states that accelerated partial breast irradiation (APBI) may be suitable in carefully selected patients who meet criteria based on age, tumor pathology, and surgical margins.[38]

After Mastectomy

Postmastectomy irradiation should be considered for patients with positive postmastectomy margins, primary tumors larger than 5 cm, or four or more positive lymph nodes. The ASCO clinical care guidelines recommend the routine use of postmastectomy radiation for women with stage III or T3 disease or those with four or more positive lymph nodes.[39] Treatment of the axilla in the absence of gross residual disease, even for patients with multiple positive lymph nodes, is not routinely recommended. At MDACC, high-risk patients who do not fill the postmastectomy radiation criteria are discussed as individual cases in a radiation oncology planning conference to determine the benefit of this approach.

Nodal Disease

Radiation treatment guidelines recommend that patients with locally advanced disease and residual disease in the primary tumor and/or axillary lymph nodes, whether they undergo lumpectomy or mastectomy,

receive comprehensive radiation to the breast and/or chest wall, as well as the internal mammary, axillary apical, and supraclavicular lymph nodes to a total dose of 50 to 60 Gy. Patients who achieve a complete pathological response in the primary tumor and lymph nodes usually receive radiation therapy based on the tumor size and lymph node involvement at presentation; however, given the good outcomes seen in these patients, clinical trials are ongoing to determine the possibility of de-escalation and omitting radiation. The results are eagerly awaited and can be practice changing.

Systemic Therapy

The use of chemotherapy, hormonal therapy, and targeted therapy before or after definitive local therapy has had a significant effect on the management and outcomes of breast cancers. Systemic therapy reduces risk of recurrence and potentially eliminates micrometastatic disease. All women with node-positive disease and a significant percentage of women with node-negative tumors that are hormone receptor negative or larger than 1 cm in size benefit from chemotherapy. The choice of agents to be used for chemotherapy and hormonal therapy should be guided by the patient's age, concomitant medical issues, positive or negative axillary lymph node involvement, and status of the hormone receptors and HER2. Whereas patients with hormone receptor–positive cancers should receive endocrine therapy, those with HER2-positive cancers should receive anti–HER2-targeted therapy. The details of systemic therapy by subtype are discussed later in this chapter.

Selecting the Initial Treatment Strategy

Small node-negative tumors are often treated with upfront surgery followed by adjuvant radiation therapy and/or systemic therapy as indicated. Patients with larger or node-positive tumors often benefit from neoadjuvant systemic therapy.

The concept of giving chemotherapy in the preoperative setting was first evaluated more than 40 years ago for the treatment of patients with locally advanced and inoperable breast cancer. There are multiple possible benefits. One is the ability to downstage a tumor, which would result in making an unresectable tumor operable or enable BCS or segmental mastectomies to be offered to a greater number of patients with operable breast cancer. In addition, there are biological advantages, such as the ability to assess response or resistance to chemotherapy early, delivering the chemotherapy before surgical alterations to the vasculature, and using molecular profiling in conjunction with pathologic response to predict outcomes for patients.

A 1976 study of patients with inflammatory breast cancer showed that two thirds responded to neoadjuvant 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC).[40] In 1978, another study was published addressing the benefit for patients with inoperable breast cancer treated with neoadjuvant chemotherapy. A total of 110 patients were enrolled and were treated with doxorubicin and vincristine. Complete response was seen in 16% of patients, and partial response was seen in 55% of patients. The 36-month survival rates were 53% for the study group and 41% for the historical controls. The positive results of this study led to other trials that confirmed the benefits of the neoadjuvant approach.[41]

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial was the largest to date to investigate neoadjuvant chemotherapy. A total of 1523 patients with T1 to T3 and N0 to N1 disease were randomized to receive preoperative versus postoperative Adriamycin and Cyclophosphamide (AC) for four cycles.[42] Results showed a significant increase in lumpectomies in the neoadjuvant group. Final comparison of the two groups showed no difference in DFS or OS at 5 years. This was true for all groups including tumors larger than 5 cm. In a trial that investigated downstaging of axillary nodal metastases after primary chemotherapy,[43] Cox regression analysis showed that one of the parameters associated with poor distant DFS was persistent nodal involvement after neoadjuvant therapy. Thus, it was concluded that the response of the axillary nodes to neoadjuvant chemotherapy was a better predictor than the response of the primary tumor.

In general, neoadjuvant therapy with either anthracycline- or taxane-containing regimens has been shown in multiple trials to result in an increase in the number of women able to undergo BCS.[44] These responses have been well correlated to DFS and OS, making response to preoperative chemotherapy an important prognostic factor in the treatment of patients with early and locally advanced breast cancer. At this time, the majority of neoadjuvant studies have not yet shown an increase in OS for patients treated with this approach compared with the administration of the same systemic therapy postoperatively.

As part of the initial evaluation at MDACC, a radiopaque marker is placed in the breast before the initiation of systemic therapy. Clinical response is documented by serial physical examinations, mammograms, and ultrasounds of the breast and nodal regions. Overall, the response to neoadjuvant therapy regimens depends on the patient's tumors characteristics and the treatment. The tumor effect on the axillary lymph nodes, rather than the response of the primary tumor itself, may be more important in predicting long-term outcome.[45]

Clinical endpoints have been shown to improve with neoadjuvant therapy involving a combined-modality

approach. Patients who are treated with a multimodality treatment approach can achieve excellent long-term survival rates. However, it is clear that those who do not respond to neoadjuvant therapy have poorer outcomes. Women who fail to respond to neoadjuvant anthracycline-based therapy remain free of distant disease in only 30% of cases.[46] The 2014 Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) meta-analysis found that pathological complete response (pCR), defined as ypT0 ypN0 or ypT0(is) ypN0, is associated with improved survival and that this correlation is strongest among patients with TNBC (OS hazard ratio [HR], 0.16; 95% confidence interval [CI], 0.11–0.25) and hormone receptor–negative/HER2+ tumors (OS HR, 0.08 ; 95% CI, 0.03–0.22).[47]

SYSTEMIC THERAPY FOR HORMONE RECEPTOR–POSITIVE/ HER2-NEGATIVE BREAST CANCER

Node Negative

Multigene assays can help quantify a patient's risk of breast cancer recurrence.[48] Onco*type* DX is a commercially available, validated laboratory test performed on a tumor specimen that analyzes 21 genes associated with receptor expression, proliferation, invasion, and other factors. Calculations based on the expression of these 21 genes result in a recurrence score that relays the likelihood of breast cancer recurrence in the first 10 years after diagnosis if the patient receives 5 years of tamoxifen.[49] These studies found that patients with recurrence scores less than 11 have an excellent prognosis and do not benefit from chemotherapy, but those with high recurrence scores (>25) are likely to benefit from chemotherapy. For women with intermediate recurrence scores, the benefit of chemotherapy was initially uncertain. To elucidate the benefit of systemic cytotoxic therapy for this middle group, the Eastern Cooperative Oncology Group (ECOG) designed a trial known as TAILORx (Trial Assigning Individualized Options for Treatment).[50] This study randomly assigned women with node-negative, HER2-negative, hormone receptor–positive early breast cancer with a midrange recurrence score[11–25] to treatment with either hormonal therapy or chemotherapy followed by hormonal therapy. Among women with intermediate recurrence scores, endocrine therapy was noninferior to chemotherapy followed by endocrine therapy. However, a subgroup analysis showed evidence of some benefit in women 50 years of age or younger with recurrence scores of 16 to 25.[51] An update to TAILORx published in 2019 also incorporated clinical risk as defined by tumor size and histologic grade to guide adjuvant therapy selection. Investigators found no benefit from chemotherapy for women aged 50 or younger with a recurrence score of 16 to 20 and low clinical risk. However, there was a chemotherapy benefit for premenopausal women aged 46 to 50 years and a trend toward benefit in women aged 41 to 45 years. This benefit was thought by some to be due to the -induced menopause; however, the trial was not designed to test this hypothesis.[52] The MammaPrint assay, discussed in more detail later, can also be used to assess risk of recurrence.

Node Positive

Recently, investigators have attempted to use genomic assays to guide adjuvant systemic therapy in patients with limited nodal disease. A comprehensive review of evidence regarding use of Oncotype DX in node-positive hormone receptor–positive, HER2-negative breast cancer found that the testing consistently identifies patients at low risk for recurrence in whom chemotherapy can be avoided without negatively affecting outcomes.[53] In the Microarray in Node-Negative and 1-3 Positive Lymph Node Disease May Avoid Chemotherapy (MINDACT) trial, a randomized phase III study of women with node-negative and node-positive (up to three positive axillary nodes) early-stage breast cancer, the 70-gene signature assay MammaPrint was used in combination with clinical risk to guide adjuvant treatment. Patients with discordant genomic and clinical risk results were randomized to receive chemotherapy or no chemotherapy. Among women with high clinical risk and low genomic risk for recurrence who received chemotherapy, 5-year survival without distant metastasis was 1.5% higher than the 5-year survival among women with a similar risk profile who did not receive chemotherapy.[54] Clinicians should discuss the potential risk and benefits of chemotherapy with patients who fall into this category.

Chemotherapy

Neoadjuvant

As mentioned previously, neoadjuvant chemotherapy in appropriately selected patients can improve surgical outcomes and provide information regarding response to therapy that can be used to assess risk of recurrence. The same chemotherapy regimens used in the adjuvant setting (outlined later) can be used in the neoadjuvant setting. However, the response rates to neoadjuvant chemotherapy are lower among patients with hormone receptor–positive tumors.[47]

Adjuvant

The choice of agents to be used for chemotherapy should be guided by the patient's age, concomitant medical issues, and positive or negative axillary lymph

node involvement. Estimation of risk of recurrence and death should be assessed. As noted in the previous section, Oncotype DX, MammaPrint, and other assays can help stratify risk for hormone receptor–positive patients.[48]

Historical Perspective

Studies in the 1960s and 1970s evaluated whether single-agent chemotherapy after local therapy had any benefit compared with observation alone. Most reports documented that single agents have modest or no effect on DFS. Subsequently, the focus shifted to polychemotherapy, with most trials evaluating variations of the three-drug regimen of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) or similar anthracycline-containing regimens.[55,56]

These polychemotherapy regimens clearly showed a greater benefit in DFS and OS, but it was often unclear to clinicians which regimens were superior or equivalent. The Oxford Overview in 1998 helped clarity this issue by reviewing data from about 18,000 women in 47 trials that compared polychemotherapy or no chemotherapy, about 6000 women in 11 trials that compared longer versus shorter polychemotherapy, and about 6000 women in 11 trials of anthracycline-containing regimens versus CMF.[57] The final interpretation concluded that adjuvant polychemotherapy was more effective than monotherapy, and anthracycline-based regimens reduced risk of recurrence by 12% compared with CMF. Data from the Oxford Overview in subsequent years also demonstrated that the addition of taxanes adds the efficacy of anthracycline-based regimens. However, sequential administration of anthracycline and taxane are better tolerated than concurrent administration.

The ECOG E1199 trial attempted to define the more effective adjuvant taxane and the optimal schedule of administration.[58] All patients received a standard dose and schedule of AC and were randomized to receive paclitaxel (175 mg/m^2) every 3 weeks for four cycles, paclitaxel (80 mg/m^2) every week for 12 doses, docetaxel (100 mg/m^2) every 3 weeks for four cycles, or docetaxel (35 mg/m^2) every week for 12 doses. Weekly paclitaxel compared with every 3 weeks was better, with an odds ratio of 1.27 for DFS (P =.006) and 1.32 for OS (P =.01). No significant difference existed between paclitaxel and docetaxel. Paclitaxel every 3 weeks was no longer recommended after this trial (Fig. 35–1).

The US09735 trial was a randomized study that compared four cycles of standard-dose AC with four cycles of docetaxel (75 mg/m^2) and cyclophosphamide (TC) (600 mg/m^2). Most patients (84.3%) were younger than 65 years old, and 48% had node-negative disease. At a median follow-up of 7 years, there

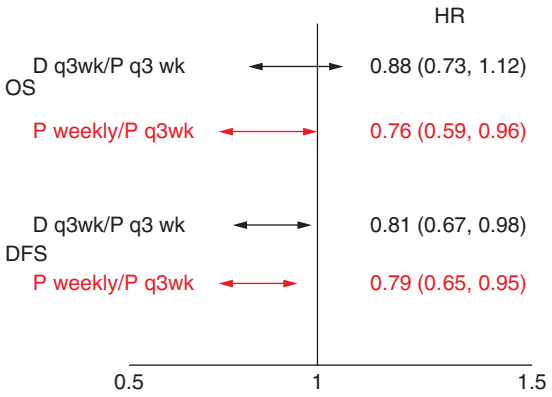


FIGURE 35-1 Results of Eastern Cooperative Oncology Group E1199: optimal adjuvant taxane and optimal schedule of administration. D, docetaxel; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; q, every; P, paclitaxel. (Data from Sparano JA, Wang M, Martino S, et al: Weekly paclitaxel in the adjuvant treatment of breast cancer, *N Engl J Med* 2008 Apr 17;358(16):1663-1671.)

was a significant difference in DFS between TC and AC (81% vs 75%; HR, 0.74). Additionally, there was a significant difference in OS (87% vs 82%). Febrile neutropenia in older patients was 8% with TC and 4% with AC.[59] The Anthracyclines in Early Breast Cancer (ABC) Trials were a series of three trials of women randomized to six cycles of TC or a taxane in addition to AC. Data from these trials showed 88.2% 4-year invasive DFS for women who received TC and 90.7% invasive DFS for those received paclitaxel and AC. Subgroup analysis shows that TC may have more similar efficacy to AC and paclitaxel among patients with hormone receptor–positive tumors. However, there is a definite benefit to AC and paclitaxel among patients with hormone receptor–negative tumors.[60]

Dose Density

One approach to increase response rate to chemotherapy is dose density. This term refers to the administration of chemotherapeutic agents with a shortened interval between treatments based on the knowledge that a given dose always kills a particular fraction of cancer cells. More frequent administration of cytotoxic therapy may thus be more efficacious than dose escalation to reduce tumor burden. Several trials have explored dose-density regimens. The Cancer and Leukemia Group B (CALGB) 9741 trial explored the possible superiority of dose-dense over conventional scheduling of adjuvant chemotherapy for node-positive breast cancer.[61] Patients were randomly assigned to receive AC and paclitaxel (175 mg/m^2) either in 2- or 3-week schedules, with growth factor support provided to the dose-dense schedule. At a median follow-up period of 36 months, dose-dense treatment

improved DFS from 75% in the 3-week arm to 82% in the dose-dense arm (P =.01). OS was also improved (92% with every 2 weeks vs 90% with every 3 weeks; P =.013).

As noted in the Historical Perspective section, E1199 demonstrated a significant improvement of weekly paclitaxel over paclitaxel every 3 weeks.[58] It is not clear whether the benefit demonstrated in CALGB 9741 is from the dose-dense nature of the anthracycline or the taxane schedule. Additionally, NSABP B-38 found no significant difference in outcomes between TAC for six cycles and dose-dense AC with weekly paclitaxel.[62] Last, the SWOG SO0221 trial compared weekly paclitaxel (80 mg/m^2) versus dose-dense paclitaxel (175 mg/m^2) in patients with node-positive breast cancer who had already received AC.[63] The results showed equivalent 5-year PFS between the weekly (82%) and biweekly regimens (81%). The weekly schedule was less toxic and did not require growth factor supplementation.

Endocrine Therapy

The correlation between the endocrine system and breast cancer was first recognized more than 100 years ago. Beatson[64] first described bilateral oophorectomy in treating inoperable cases of breast cancer. However, the true understanding of the biological mechanisms that cause estrogen to stimulate the growth of hormone receptor–positive tumors is more recent. Jensen first identified the ER and led subsequent cloning of ER and PR.[65] This knowledge has enabled the development of multiple therapies. Many of these therapies have varying mechanisms of action. Selective estrogen receptor modulators compete with estrogen for binding ER. Selective estrogen receptor downregulators cause degradation of ER upon binding. Aromatase inhibitors (AIs) inhibit conversion of androgens to estrogens. Ovarian ablation and suppression result in estrogen deprivation. However, all endocrine therapies have the common goal of decreasing estrogen availability for hormone receptor–positive tumors. When selecting an appropriate endocrine therapy for a patient, it is important to know the patient's menopausal status.

Tamoxifen

In the late 1970s, tamoxifen was shown to be effective for the treatment of patients with metastatic breast cancer. This form of treatment was well received because data from trials showed that patients experienced fewer side effects than they did with traditional chemotherapy or with old-fashioned endocrine therapy (high-dose estrogens, androgens, adrenalectomy, or hypophysectomy). The proven efficacy of tamoxifen in the metastatic setting enabled its study for adjuvant use.

Tamoxifen was the first targeted drug to be used as an endocrine treatment for patients with early breast cancer. An early placebo-controlled trial Nolvadex Adjuvant Trial Organization (NATO) of tamoxifen as adjuvant therapy for patients with early breast cancer, NATO, showed that 2 years of tamoxifen treatment reduced treatment failure at 21 months compared with control (14.2% vs 20.5%, respectively).[66] Since then, the efficacy of tamoxifen in the adjuvant treatment of patients with primary breast cancer has been demonstrated repeatedly.

Since tamoxifen became available more than 40 years ago, a large number of trials have investigated its efficacy and tolerability in the treatment of patients with primary breast cancer. Although some individual trials are too small to justify firm conclusions, a meta-analysis has increased confidence in the effectiveness of tamoxifen in improving DFS and OS. Additionally, large cooperative group (NSABP B-14) and international randomized trials (Stockholm and Scottish trials) of tamoxifen versus placebo have demonstrated a clear benefit in DFS and OS.[67–69]

An overview of 55 trials studying adjuvant tamoxifen for 1, 2, or 5 years versus no treatment in patients with primary breast cancer showed that tamoxifen treatment produced highly significant benefits in terms of both recurrence of first events and mortality in the hormone receptor–positive population. The reductions in recurrence were 21%, 28%, and 50%, and the reductions in death rate were 14%, 18%, and 28% for 1, 2, and 5 years of tamoxifen treatment, respectively (P <.00001 for each). Tamoxifen treatment for 1, 2, and 5 years also reduced the incidence of contralateral breast cancer by 13%, 26%, and 47%, respectively.[70] The benefits occurred almost exclusively in the hormone receptor–positive population. Tamoxifen improves the 10-year survival rate of women who have ER-positive or ER-unknown tumors.

As noted in the Chemotherapy section, the addition of chemotherapy in intermediate- or high-risk groups is recommended. It was not until recently that the appropriate sequence of chemotherapy and hormonal therapy was definitively documented. One difficulty was that evidence had existed in experimental systems that tamoxifen could antagonize the cytotoxic effects of particular chemotherapeutic agents.

One particular study was designed to address the specific timing of tamoxifen therapy.[55] Patients were divided among three groups: tamoxifen alone, FAC chemotherapy followed by tamoxifen, and concomitant FAC and tamoxifen. Patients were followed up for a median of 8.5 years. The estimated DFS was 67% in the sequential treatment group compared with 62% in the concurrent treatment group.

Aromatase Inhibitors

First Line

Although tamoxifen has proven efficacy for the treatment of patients with hormone receptor–positive breast cancer both alone and in combination with chemotherapy, its usefulness is in part curtailed by its partial estrogen agonist activity. The documented negative secondary effects of tamoxifen include an increased incidence of endometrial cancer, uterine sarcoma, and thromboembolic disease. Thus, there is great interest in exploring other endocrine therapies.

In women whose ovarian function has ceased, the primary remaining estrogen source is the conversion of adrenal androgens to estrogens in peripheral tissues by the cytochrome P450 enzyme aromatase. AIs reduce the availability of estrogen by inhibiting the aromatase enzyme and are indicated for the treatment of breast cancer in postmenopausal women whose ovarian function has ceased.[71] Selective AIs, including anastrozole, letrozole, and exemestane, are now available for the treatment of metastatic breast cancer and in the adjuvant setting. Common side effects of all AIs include hot flashes, osteoporosis, arthritis, and joint and muscle pains.

Based on the antitumor activity of the third-generation AIs in the setting of metastatic disease, these drugs were evaluated in the adjuvant setting. The ATAC (Arimidex [anastrozole], Tamoxifen, Alone or in Combination) trial was a double-blind, multicenter study of postmenopausal women with invasive operable breast cancer who had completed primary therapy and were eligible for adjuvant treatment. They were randomized to tamoxifen, anastrozole, or a combination of the two.[72] Time to recurrence was significantly longer with anastrozole versus tamoxifen in the overall population, with a larger benefit seen in the hormone receptor–positive population. A reduction in the incidence of contralateral breast cancers favored anastrozole, with statistical significance in the hormone receptor–positive population. The DFS estimates at 4 years were 86.9% and 84.5% for anastrozole and tamoxifen, respectively.[73]

Anastrozole was associated with significantly fewer withdrawals from treatment than tamoxifen (21.9% vs 26.0%; P =.0002) and significantly fewer withdrawals because of adverse events (7.8% vs 11.1%; P <.0001). Anastrozole also resulted in a lower incidence of hot flashes, vaginal discharge, and vaginal bleeding (P <.0001 for each); of ischemic cerebrovascular events and thromboembolic events (P =.0006 for each), including deep venous thrombosis (P =.02); and of endometrial cancer (P =.02). Tamoxifen resulted in a lower incidence of musculoskeletal disorders (including myalgias and arthralgias) and fractures (P <.0001 for both). The tolerability results in the updated analysis showed no major difference from those seen in the first analysis.[74]

A meta-analysis published in 2010 reviewed the use of AIs versus tamoxifen in postmenopausal women with ER-positive tumors. This review compared AIs as initial monotherapy with tamoxifen monotherapy or as a hormone switch after 2 to 3 years of tamoxifen for a total of 5 years. The conclusion was that AI therapy was associated with a lower rate of recurrence when used as an initial monotherapy or after 2 to 3 years of tamoxifen compared with tamoxifen monotherapy.[75]

Sequential

It is postulated that tamoxifen might stop being effective because breast cancer cells develop resistance to tamoxifen, dependence on tamoxifen, or great sensitivity to circulating estrogen. Consequently, the use AIs after tamoxifen was investigated. The MA-17 trial showed that the addition of letrozole after 5 years of tamoxifen resulted in a significant improvement in DFS.[76]

The Breast International Group (BIG) 1-98 trial compared letrozole with tamoxifen in postmenopausal hormone receptor–positive women and was later amended to include two sequential strategies using letrozole either before or after tamoxifen for a total of 5 years. The results showed that upfront AI reduced the risk of recurrence and improved DFS better than upfront tamoxifen and better than either switching strategy.[77,78]

Another double-blind randomized trial investigated the use of exemestane to complete the 5 years of adjuvant endocrine treatment after 2 to 3 years of tamoxifen in postmenopausal women with primary breast cancer.[79] Exemestane demonstrated an absolute benefit in DFS of 4.7%.

Duration of Therapy

In general, outcomes with antiestrogen therapies are hindered by noncompliance, with 20% to 50% nonadherence rates. This is the same difficulty faced in other disease states, and a cancer diagnosis does not necessarily command optimal compliance with oral therapy. Many barriers influence compliance, including medication cost, access to mail-order pharmacies, and a lack of understanding of the benefits of such medicine. A population-based study performed in British Columbia noted that adherence was still difficult even when these oral agents were given free of charge in a country with a national formulary system. Patients who are prescribed oral medication should be followed regularly, and compliance should be reinforced as highly important, as shown in multiple studies, even when drug cost is not a barrier.[80]

Further clarification of the optimal treatment duration of tamoxifen was investigated in two large trials: ATTOM (Adjuvant Tamoxifen Treatment Offers More) and ATLAS (Adjuvant Tamoxifen—Longer Against Shorter). The ATLAS trial enrolled women with early breast cancer who had completed 5 years of tamoxifen and randomly assigned the women to either continue tamoxifen for 10 years or stop at 5 years.[81] The risk of recurrence during years 5 to 14 was 21.4% versus 25.1% for women who continued tamoxifen versus those who did not. The breast cancer mortality rates during years 5 to 14 for women who continued tamoxifen versus the control group were 12.2% and 15.0%, respectively. Pulmonary embolus and endometrial cancer occurred significantly more frequently in the extended tamoxifen group (Fig. 35–2).

The ATTOM trial had a similar design to ATLAS.[82] Women randomized to continue tamoxifen, versus those who stopped tamoxifen, had significantly less breast cancer recurrence (580 of 3468 patients vs 672 of 3,85 patients; P =.003) and significantly decreased breast cancer mortality (392 of 3468 patients vs 443 of 3485 patients; P =.050). Combining the two trials strengthens the statistical significance of recurrence (P <.0001), breast cancer mortality (P =.002), and OS (P =.005).

The MA.17R trial compared extended AI therapy with placebo in 1918 women who had already received 5 years of AI therapy, including those who received prior tamoxifen. Although extended AI therapy was not associated with improved OS, it was significantly associated with improved 5-year DFS (95% vs 91%) and a lower annual incidence of contralateral breast cancer (0.21% vs 0.49%).[82] Current ASCO clinical practice guidelines recommend that women with node-positive breast cancer be offered extended adjuvant endocrine therapy, including an AI, for up to 10 years. These recommendations are based on six studies comparing extended AI treatment with placebo. Clinicians should consider the potential side effects of long-term endocrine therapy, such as decreased bone density, and how individual patients tolerate therapy when deciding whether to continue extended treatment.

Additionally, ASCO recommends that women with node-negative breast cancer should consider extended therapy based on their individual recurrence risk as determined by established prognostic factors.[84]

Ovarian Ablation and Suppression

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overviews in 1990 showed that chemotherapy in combination with tamoxifen had a beneficial effect in premenopausal women. The 1998 EBCTCG overview[70] showed that the benefits of chemotherapy combined with tamoxifen in patients with ER-positive disease occurred irrespective of age or menopausal status. The benefits of chemotherapy in terms of contralateral breast cancer and improved survival also occurred irrespective of age or menopausal status.

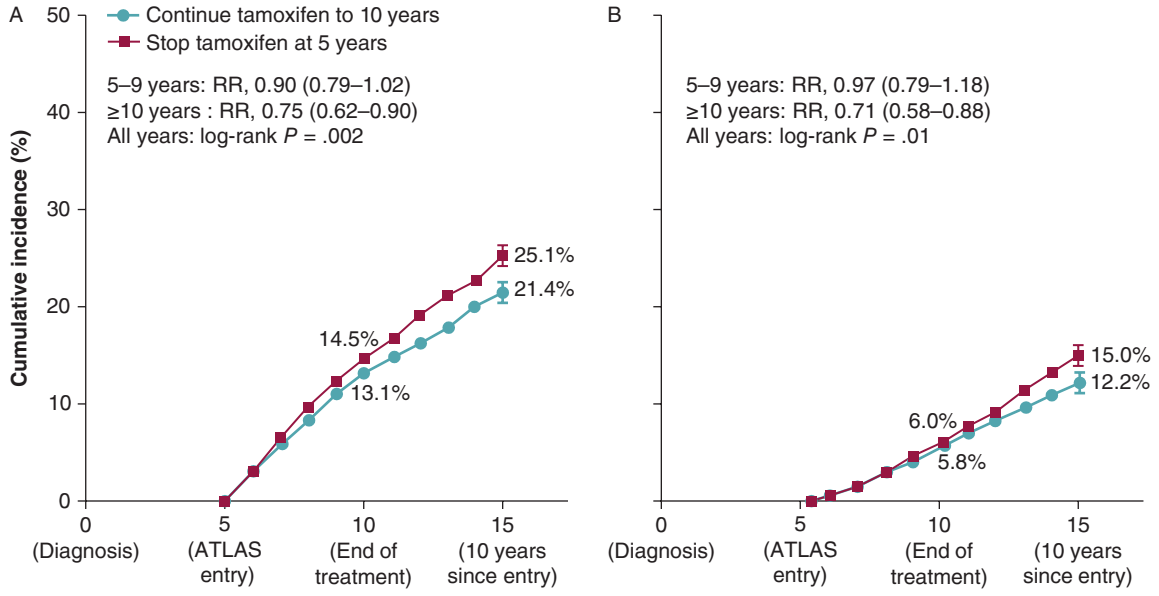


FIGURE 35-2 **ATLAS (Adjuvant Tamoxifen—Longer Against Shorter) trial studying 5 years versus 10 years of tamoxifen with respect to recurrence (A) and breast cancer mortality (B). RR, relative risk. (Reproduced with permission from Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet*. 2013 Mar 9;381(9869):805-816.)**

The 1996 meta-analysis by the EBCTCG demonstrated that for women younger than age 50 years, there was a distinct advantage in OS and DFS when they were treated with ovarian ablation versus no adjuvant therapy. In addition, the outcomes for these patients were similar to those who received the CMF regimen. The Zoladex Early Breast Cancer Research Association (ZEBRA) trial displayed similar results in hormone receptor–positive patients when comparing a luteinizing hormone–releasing hormone analog, goserelin, with CMF.[85]

The Supression of Ovarian Function Trial (SOFT) and Tamoxifen adn Exemestane Trial (TEXT) trials were designed to determine the value of the addition of adjuvant ovarian suppression to tamoxifen or exemestane in premenopausal patients with hormone receptor–positive breast cancer. The patients were randomized to receive tamoxifen, tamoxifen plus ovarian suppression, or exemestane plus ovarian suppression for 5 years (Table 35–5). In the total population, the addition of ovarian suppression to tamoxifen did not produce a significant benefit. However, in the high-risk cohort who received chemotherapy (most of whom had lymph node involvement), ovarian suppression plus tamoxifen improved 5-year DFS when compared with tamoxifen alone (HR, 0.78; 95% CI, 0.60–1.02). The combined analysis also showed that 5-year DFS with adjuvant endocrine therapy with exemestane was significantly more effective than tamoxifen when ovarian suppression was added (HR, 0.65; 95% CI, 0.49–0.87). The benefit of ovarian suppression was also more pronounced in patients who were younger than age 35 years. Longer follow-up is needed to evaluate survival data.[86,87] Given the results of the TEXT and SOFT trials, we recommend discussing ovarian suppression therapy with premenopausal patients, particularly high-risk patients. It is important to mention that ovarian suppression does come at significant costs because the adverse effects are not trivial. In these trials, women receiving ovarian suppression developed significant hot flashes, vaginal dryness, depression, sexual dysfunction, and possible long-term health implications such as hypertension, diabetes, and osteoporosis.

SYSTEMIC THERAPY FOR TRIPLE-NEGATIVE BREAST CANCER

Principles of Treatment

Cytotoxic chemotherapy remains the most effective systemic therapy for TNBC. Third-generation regimens including anthracyclines and taxanes are considered to be preferred and are associated with improved outcomes compared with anthracycline or taxane-only regimens. Current National Comprehensive Cancer Network (NCCN) guidelines recommend chemotherapy for all patients with TNBC with tumors larger than 1 cm.[88]

Neoadjuvant Therapy

As noted earlier in this chapter, neoadjuvant chemotherapy can improve surgical outcomes while also allowing clinicians to assess treatment response. The cornerstone of treatment of TNBC is chemotherapy, specifically, anthracycline- and taxane-based regimens. Two major studies sought to determine the efficacy of a platinum-containing neoadjuvant chemotherapy regimens in TNBC. The GeparSixto trial randomly assigned untreated patients with stage II and III TNBC to receive paclitaxel and liposomal doxorubicin with or without carboplatin. The pCR rate with carboplatin was 53.2% vs 36.9% without carboplatin.[89] The CALBG 40603 study compared outcomes in patients in with stage II and III untreated TNBC who received paclitaxel with or without carboplatin followed by dose-dense AC with or without bevacizumab. The addition of carboplatin increased the rate of pCR; however, the addition of carboplatin or bevacizumab did not improve long-term outcomes.[90] Although the routine use of platinum is not generally recommended by current guidelines, its use can be useful in high-risk patients in whom optimal local control is paramount. When making the individualized decision of using carboplatin in addition to an anthracycline and taxane-based regimen, consideration to side effects is crucial given the

TABLE 35–5 Five-Year Rates of Recurrence of Patients in Supression of Ovarian Function Trial (SOFT) and Tamoxifen adn Exemestane Trial (TEXT) Stratified by Chemotherapy Use

	No Chemotherapy			Previous Chemotherapy		
	E + OS	T + OS	T	E + OS	T + OS	T
5-Year Rate	(*n* = 470)	(*n* = 473)	(*n* = 476)	(*n* = 544)	(*n* = 542)	(*n* = 542)
FBC (%)	97.1	95.1	95.8	85.7	82.5	78
FDR (%)	99.3	98.7	98.6	87.8	84.8	83.6

E, exemestane; FBC, freedom from breast cancer; FDR, free from distant recurrence; OS, ovarian suppression; T, tamoxifen.
Data from Francis PA, Regan MM, Fleming G, et al. Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med*. 2015;372(5):436-446.

increased side effects associated with the addition of carboplatin.

Although immunotherapy has not shown much activity across all breast cancer subtypes, trials of immunotherapy in TNBC have shown promise. The KEYNOTE-522 trial investigated the efficacy of the anti–PD-1 (programmed cell death protein 1) monoclonal antibody pembrolizumab in women with early-stage TNBC. Investigators randomized patients with untreated stage II and III TNBC to receive neoadjuvant therapy with either four cycles paclitaxel and carboplatin plus either pembrolizumab or placebo followed by an additional four cycles of pembrolizumab or placebo. Patients in both groups received either AC or Epirubicin and cyclophosphamide (EC). A total of 64.8% of patients who received pembrolizumab with chemotherapy achieved pCR compared with 51.2% of patients in the placebo–chemotherapy group. With a median follow-up period of 15.5 months, 7.4% of patients in the pembrolizumab–chemotherapy group and 11.8% of patients in the placebo–chemotherapy group had disease progression, local or distant recurrence, or second primary tumor or died from any cause.[91] Although immunotherapy is not currently approved by the Food and Drug Administration (FDA) for treatment of patients with early-stage TNBC, there is growing evidence of its potential to improve outcomes.

Adjuvant Therapy

The use of anthracycline and taxane-based regimens in the adjuvant setting has been well established. However, until recently, it was not known if any systemic therapy should be given to patients who received neoadjuvant therapy but did not achieve pCR by time of surgery. The Capecitabine for Residual Cancer as Adjuvant Therapy (CREATE-X) trial randomized patients with HER2-negative residual invasive breast cancer after neoadjuvant chemotherapy with an anthracycline and/or a taxane to receive standard postsurgical therapy with or without capecitabine (Fig. 35–3). DFS at 5 years was 74.1% versus 67.6% for capecitabine vs control group, respectively. In a subgroup analysis among patients with TNBC, DFS for the capecitabine group was 69.8% compared with 56.1% for the control group. OS was also improved in the capecitabine group (78.8% vs 70.3%)[92](Fig. 35–4). Additionally, a 2019 meta-analysis showed improved DFS and OS among patients with early-stage TNBC treated with

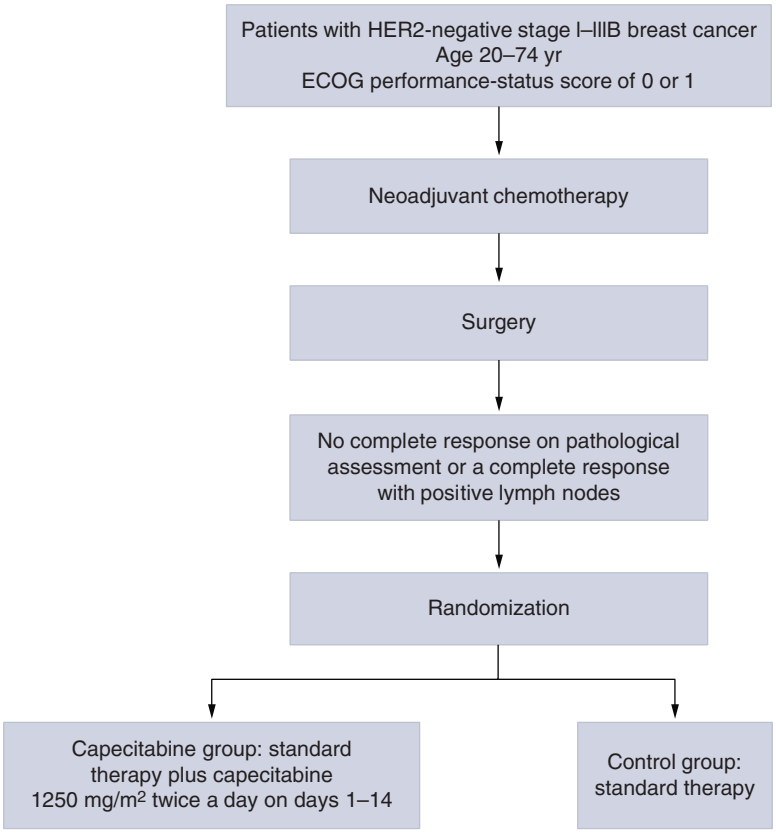


FIGURE 35-3 **Capecitabine for Residual Cancer as Adjuvant Therapy trial design. ECOG, Eastern Cooperative Oncology Group. (Reproduced with permission from Masuda N, Lee SJ, Ohtani S, et al: Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy, *N Engl J Med* 2017 Jun 1;376(22):2147-2159.)**

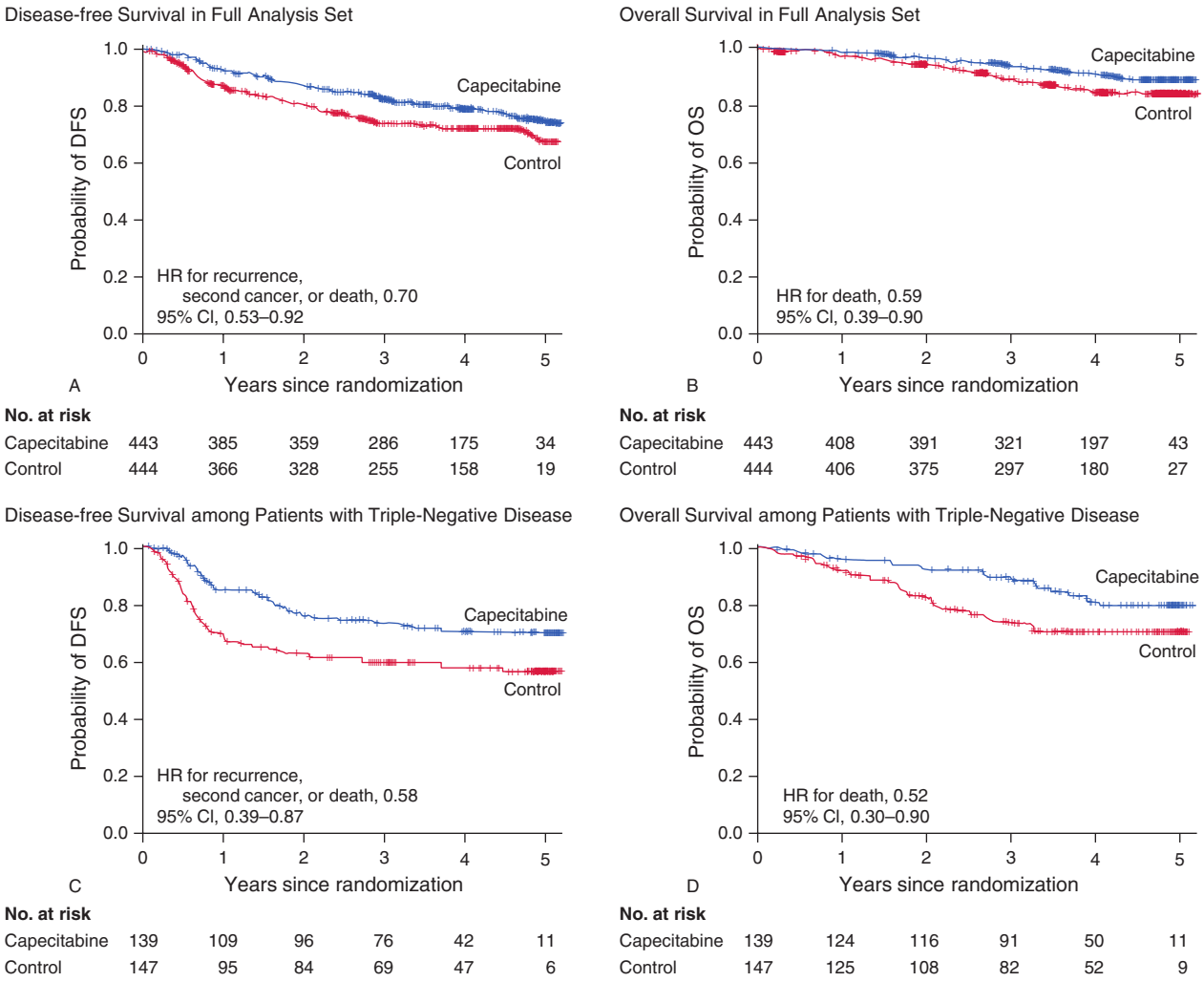


FIGURE 35-4 **Capecitabine for Residual Cancer as Adjuvant Therapy disease-free survival (DFS) and overall survival (OS) results. A. DFS in the full analysis set. B. OS in the full analysis set. C. DFS among patients with triple-negative breast cancer (TNBC). D. OS among patients with TNBC. CI, confidence interval; HR, hazard ratio. (Reproduced with permission from Masuda N, Lee SJ, Ohtani S, et al: Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy, *N Engl J Med* 2017 Jun 1;376(22):2147-2159.)**

anthracyclines and taxanes who received adjuvant capecitabine.[93] The NCCN and ASCO guidelines recommend considering six to eight cycles of adjuvant capecitabine for patients with TNBC and residual disease after neoadjuvant chemotherapy.

SYSTEMIC THERAPY FOR HORMONE RECEPTOR–NEGATIVE AND HER2-POSITIVE BREAST CANCER

Principles of Treatment

The advent of anti-HER2 targeted therapy has significantly improved outcomes in patients with HER2-positive breast cancer and is now a backbone of treatment. Numerous trials have demonstrated that trastuzumab improves DFS and OS. The Herceptin Adjuvant (HERA) trial study team was designed to answer the question regarding the optimal duration of trastuzumab. Patients were assigned to observation or 1 or 2 years of trastuzumab. Patients were allowed a variety of standard neoadjuvant or adjuvant chemotherapies and had node-positive or high-risk node-negative disease. A recent update includes mature data from patients receiving trastuzumab for 2 years. Comparing 1 year of trastuzumab versus observation revealed an HR of 0.76 (95% CI, 0.67–0.86; P <.0001) for DFS and 0.76 (95% CI, 0.65–0.88; P =.0005) for OS despite significant (52%) crossover. No significant differences in DFS or OS were noted between the 1- and 2-year groups.[32]

The Protocol for Herceptin as Adjuvant therapy with Reduced Exposure (PHARE) trial and PERSEPHONE trials also attempted to answer the appropriate duration for trastuzumab by comparing 6 versus 12

months of adjuvant therapy. After a median follow-up period of 42.5 months in the PHARE trial, the 2-year DFS rate was 93.8% for the 12-month group versus 91.1% for the 6-month group, with an HR of 1.28 (95% CI, 1.05–1.56).[94] In the PERSEPHONE trial, DFS for 6 months of adjuvant trastuzumab was noninferior to 12 months (HR, 1.07; 95% CI, 0.93–1.24).[95] Currently, 1 year of trastuzumab remains standard of care.

Patients who have hormone receptor–positive and HER2-positive breast cancer should also receive adjuvant endocrine therapy as outlined earlier in this chapter.

Node-Positive Disease

Adjuvant Therapy

Trastuzumab is a high-affinity humanized monoclonal antibody that recognizes the *HER2/neu* receptor and is a targeted therapeutic for tumors that overexpress this growth factor receptor. Trastuzumab has been evaluated extensively in the *HER2/neu*-overexpressing metastatic setting and has been shown to be effective as a single agent both before[96] and after chemotherapy[97] and in combination with multiple agents.[98] One notable side effect has been a high rate of cardiotoxicity, particularly when trastuzumab is combined with anthracycline-based chemotherapy. This is partly because of overlapping toxicities and the long half-life of trastuzumab (up to 32 days). The toxicity rarely occurs in patients without a history of cardiac disease and not previously or simultaneously exposed to chemotherapy, especially anthracyclines.[99]

The NSABP B-31 and North Central Cancer Treatment Group (NCCTG) N9831 trials randomized patients to receive AC plus paclitaxel with the addition of trastuzumab versus placebo. The joint analysis of these trials showed an absolute difference in DFS of 12% at 3 years and a 33% reduction in the risk of death (P =.015).[100] An updated analysis with a mean time of 8.4 years in the study showed a 37% relative improvement in OS (95% CI, 0.54–0.73; P <.001) and an increase in 10-year OS from 75.2% to 84%.[101]

The Breast Cancer International Research Group (BCIRG) 006 trial was designed to evaluate the efficacy and safety of docetaxel and carboplatin plus 52 weeks of trastuzumab (TCH).[33] Patients were randomly assigned to standard doses of AC followed by docetaxel (100 mg/m^2) every 3 weeks (AC-T), the same regimen plus 52 weeks of trastuzumab (AC-TH), or docetaxel (75 mg/m^2) and carboplatin (area under the curve [AUC], 6 mg/mL/min) plus 52 weeks of trastuzumab (TCH). At a median follow-up period of 65 months, the 5-year estimated DFSs were 75% for patients receiving AC-T, 84% with AC-T, and 81% with TCH. Estimated rates of OS were 87%, 92%, and 91%, respectively. All trastuzumab regimens were statistically superior for DFS and OS to the nontrastuzumab regimen. The trial was not designed to evaluate differences in both DFS and OS between AC-TH and TCH. Rates of cardiac dysfunction were significantly higher with AC-TH compared with TCH (P =.001).

Neoadjuvant Therapy

The addition of trastuzumab to standard chemotherapy when given preoperatively has been shown to have improved pCR.[102] Additionally, neoadjuvant therapy has helped accelerate approval of promising drugs because clinical and pathologic responses can be quickly obtained. At MDACC, when we treat patients with TNBC and HER2-positive tumors, we favor the use of neoadjuvant chemotherapy.

Dual Therapy

A number of trials have investigated dual blockade of HER2 signaling. Pertuzumab is a monoclonal antibody that inhibits dimerization with other HER receptors, notably HER3, and binds to an independent domain from trastuzumab. With impressive results in the metastatic setting,[103] pertuzumab was studied in the neoadjuvant setting. The NeoSphere trial was designed to evaluate the safety and efficacy of pertuzumab along with trastuzumab in locally advanced, inflammatory, and early HER2-positive breast cancer.[104] The phase II study randomly assigned patients to four treatment groups: trastuzumab plus docetaxel (75 mg/m,^{2} escalating if tolerated to 100 mg/m,^{2} every 3 weeks), pertuzumab (loading dose of 840 mg followed by 420 mg every 3 weeks) and trastuzumab plus docetaxel, pertuzumab plus trastuzumab, or pertuzumab plus docetaxel. After completing this regimen, all patients underwent surgery and then received 5-fluorouracil (600 mg/m^2), epirubicin (90 mg/m^2), and cyclophosphamide 600 mg/m^2) (FEC) every 3 weeks. Patients receiving dual HER2-targeted therapy with docetaxel achieved a pCR of 45.8% compared with 29.0% among patients receiving trastuzumab and docetaxel alone (see Fig. 35–2).

The TRYPHAENA trial was a phase II study that explored the tolerability and efficiency of pertuzumab and trastuzumab given with three different chemotherapy regimens.[105] A total of 225 patients were randomized to receive one of the following regimens FEC (doses of 500 mg/m,^{2}100 mg/m,^{2}600 mg/m^2 respectively) with trastuzumab and pertuzumab followed by docetaxel (FEC + H + P × 3 → T + H + P × 3; arm A), FEC followed by docetaxel plus pertuzumab and trastuzumab all at same dose and schedule as (FEC → T+H+P × 3; arm B), or carboplatin (AUC, 6) and docetaxel plus pertuzumab and trastuzumab (TCHP × 6; arm C). Upon completion of chemotherapy, all

patients underwent surgery and then received adjuvant trastuzumab to complete 1 full year. pCR rates were 50.7%, 45.3%, and 51.9% in arms A, B, and C, respectively. Eleven patients experienced a decline in left ventricular ejection fraction to less than 50%, and diarrhea was the most common adverse event.

Given the results of these phase II trials, the FDA granted accelerated approval of pertuzumab in combination with docetaxel for neoadjuvant therapy for patients with tumors of at least 2 cm or node-positive, HER2-positive breast cancer.

The Adjuvant Pertuzumab and Herceptin in Initial Therapy in Breast Cancer (APHINITY) evaluated the impact of pertuzumab in the adjuvant setting, randomizing women with early HER2-positive breast cancer to receive trastuzumab-based chemotherapy in addition to either pertuzumab or placebo. Women who received pertuzumab showed improved 3-year DFS compared with women who received trastuzumab alone (94.1% vs 93.2%). This benefit was more evident among patients with nodal involvement in subgroup analysis (87.9% vs 83.4%).[105,106] Current ASCO guidelines state that adjuvant pertuzumab is preferred in patients with nodal disease and discouraged in patients with node-negative disease, with the exception of high-risk node-negative disease, such as T4N0.

Lapatinib, a dual tyrosine kinase inhibitor, improved progression-free survival when given with capecitabine in the metastatic setting.[108] In the Neoadjuvant Lapatiib and/or Trastuzumab Treatment Optimization Study (NeoALTTO) trial, trastuzumab and lapatinib (1000 mg orally daily) were investigated in the neoadjuvant setting. The pCR was significantly higher with both medications (51.3%) versus trastuzumab alone (29.5%; difference 21.1%, 9.1–34.2%; P =.0001).[109] The interest in lapatinib was blunted by the first results from the ALTTO trial.[110] The four-arm trial compared 1 year of lapatinib alone, trastuzumab alone, or both agents in sequence or in combination. After 4.5 years of follow-up, DFS was not significantly different between the patients receiving trastuzumab alone versus the patients receiving the combination. This was surprising given the doubling of the pCR rate seen in NeoALTTO. Lapatinib is not approved by the FDA to be use in the early-stage setting.

After Neoadjuvant Therapy

The KATHERINE trial sought to improve outcomes in patients with early HER2-positive breast cancer and residual disease after neoadjuvant therapy. Patients were randomly assigned to receive adjuvant trastuzumab emtansine (T-DM1) or trastuzumab for 14 cycles (Fig. 35–5). Invasive DFS was better among patients who received T-DM1 compared with those with trastuzumab (88.3% vs 77%), with an HR of 0.5 (95% CI, 0.39–0.64)110 (Fig. 35–6). T-DM1 is now FDA approved and has a category 1 recommendation for adjuvant treatment for residual disease in patients with HER2-positive breast cancer.

Extended Therapy

The Extended Adjuvant Treatment of Breast Cancer with Neratinib (ExteNET) trial demonstrated that treatment with 1 year of neratinib, a potent tyrosine kinase inhibitor, after completion of trastuzumab-based adjuvant therapy improved 2-year invasive DFS.

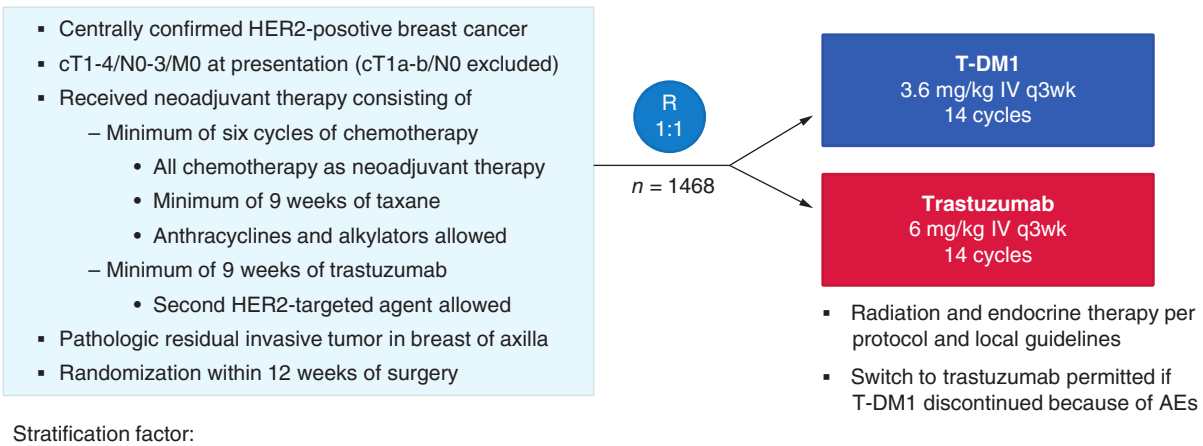


FIGURE 35-5 **KATHERINE trial design. AE, adverse event; ER, estrogen receptor; q, every; PR, progesterone receptor; T-DM1, trastuzumab emtansine.**

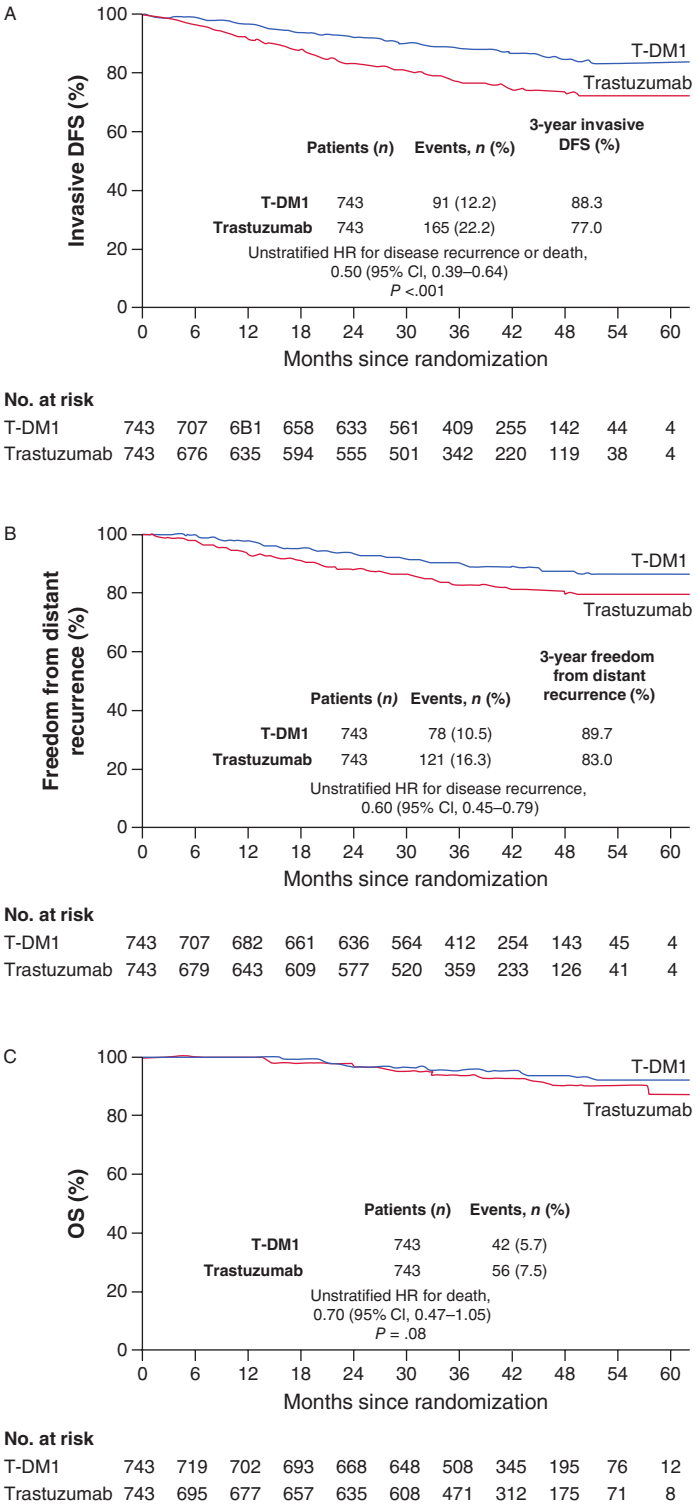


FIGURE 35-6 **KATHERINE results.CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; T-DM1, trastuzumab emtansine. (Reproduced with permission from von Minckwitz G, Huang CS, Mano MS, et al: Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer, *N Engl J Med* 2019 Feb 14;380(7):617-628.)**

An updated analysis at 5 years showed DFSs were 90.2% in the neratinib group and 87.7% in the control group. Of note, 40% patients who received neratinib experienced grade 3 diarrhea compared with 2% of patients who received placebo. Clinicians should take this significantly increased risk of an adverse event into account when considering extended therapy with neratinib.[112] Neratinib is approved by the FDA to be used after trastuzumab-based therapy has been completed; however, clinicians must be cognizant of the

toxicities associated with this regimen. ASCO guidelines preferentially recommend considering using it among patients with hormone receptor–positive disease based on the results of subgroup analysis. It important to mention that the impact in outcomes associated with neratinib among patients previously treated with pertuzumab or T-DM1 is unknown.

Node-Negative and Small Tumors

Patients with HER2-positive tumors smaller than 1 cm and no lymph node involvement can be treated with surgery alone without adjuvant systemic therapy. Particularly in T1a and T1b tumors, the benefit of anti-HER2 targeted therapy is uncertain. Clinicians should weigh risks associated with treatment, such as cardiac toxicity, with the potential benefits. The Adjuvant Paclitaxel and Trastuzumab trial was a phase II study of adjuvant paclitaxel and trastuzumab for 12 weeks followed by trastuzumab alone for 9 months in 410 patients with HER2-postitive breast cancer with tumors 3 cm or smaller and no nodal involvement. The 7-year DFS was 93%, and the 7-year OS was 97.5%.[113] At MDACC, most patients with node-negative disease, particularly those with tumors that are 1 cm or smaller in size, receive this regimen.

FOLLOW-UP

Although all treatment strategies are aimed at reducing the risk of recurrence, we still cannot predict which individual patients will experience a recurrence. Long-term follow-up in cancer survivors is essential to minimize the long-term side effects associated with systemic therapy. Among patients with hormone receptor–positive disease, long-term follow-up helps to ensure adherence to and management of side effects associated with endocrine therapy. Per NCCN guidelines, most patients at MDACC are evaluated every 3 to 4 months for the first 2 years, then every 6 months during years 3 to 5, and then yearly. Breast imaging is performed yearly in most patients but can be performed at shorter intervals if clinically indicated. Bone mineral density scans are performed before patients start endocrine therapy and periodically thereafter. The routine use of computed tomography, positron emission tomography, or tumor markers is not recommended, and any test should be driven by symptoms or clinical examination findings. Patients should be encouraged to maintain close communication with providers to evaluate any symptoms that could be associated with a recurrence in a timely manner.

CONCLUSION

Treatment of patients with breast cancer has evolved from single-agent therapies to more contemporary combinations. Combined-modality approaches with refinement in local therapies (surgery, irradiation) have resulted in progressive improvement in survival in this disease. This is reflected in the national trends in 5-year breast cancer survival as reported by the SEER Program (Fig. 35–7). A summary of approach to treatment can be seen in Table 35–6, and a list of common

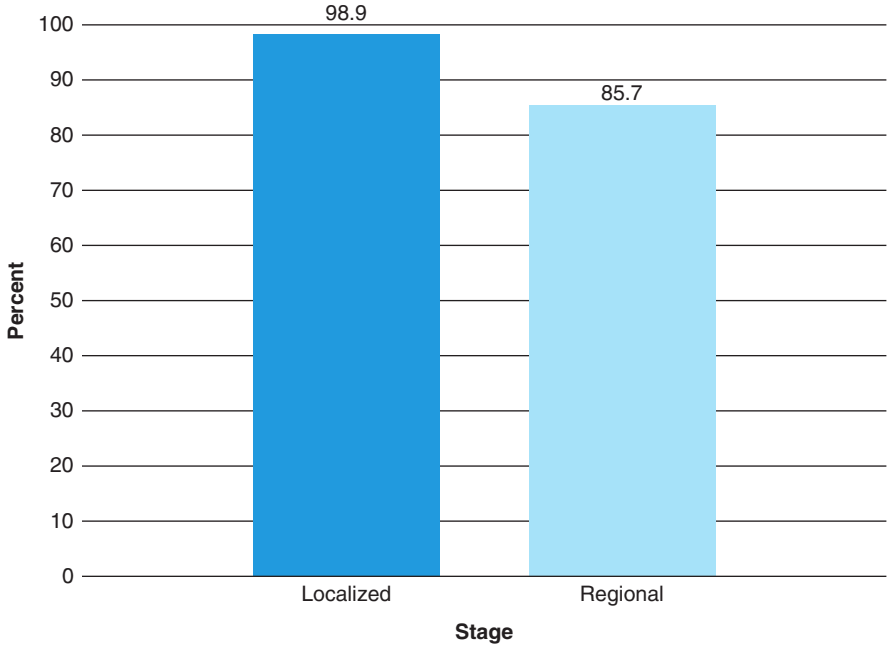


FIGURE 35-7 Five-year relative survival percent from 2010 to 2016 by stage. (Data from National Cancer Institute. SEER Cancer Stat Facts: Female Breast Cancer. Bethesda, MD: National Cancer Institute; 2020 https://seer.cancer.gov/statfacts/html/breast.html)

and serious side effects of various breast cancer therapies can be seen in Figure 35–8.

Over the past six decades, there have been significant advances in the care of patients with early-stage, locally advanced breast cancer. The use of optimal stage- and hormone receptor–specific therapy is of utmost importance and can significantly affect the risk of recurrence and death from breast cancer. Outcomes have improved with the addition of neoadjuvant therapy, taxanes, new hormonal therapy strategies, and HER2-targeted therapy. Coordinated and timely multidisciplinary therapy is of foremost importance to achieve optimal outcomes. At all times, treatment must be individualized, and clinical trial participation should be encouraged. Clinicians must take into account tumor and patients comorbidities as well as their preferences. There is strong interest among clinicians across all three cancer treatment modalities to deescalate therapy without compromising outcomes. For surgical oncology, this interest has resulted in a shift from radical mastectomy to BCS and from axillary dissection to SLNB even in some patients with nodal disease. For radiation oncology, this has led to more selective administration of radiation therapy,

TABLE 35–6 Summary of Approach to the Systemic Treatment of Patients with Breast Cancer

		HR+/HER2-		TNBC		HR-/HER2+		HR+/HER2+	
		Node Negative	Node Positive	Node Negative	Node Positive	Node Negative	Node Positive	Node Negative	Node Positive
Chemotherapy (neoadjuvant or adjuvant)	T ≤ 0.5 cm	No	Yes	No	Yes	Consider	Yes	No	Yes
	T 0.6–1 cm	Depending on OncotypeDX score	Could consider OncotypeDX (1-3LN)	Consider				Consider	
	T > 1 cm			Yes		Yes		Yes	
Endocrine therapy	T ≤ 0.5 cm	Consider	Yes	No		No		Consider	Yes
	T > 0.5 cm	Yes						Yes	
HER2-targeted therapy	T ≤ 0.5 cm	No		No		Consider	Yes	Consider	Yes
	T 0.6–1 cm								
	T > 1 cm					Yes		Yes	
Adjuvant therapy for residual disease		No		Yes		Yes		Yes	

HR, hormone receptor; TNBC, triple-negative breast cancer.
Data from NCCN Guidelines Version 4.2020.

Chemotherapy (anthracyclines, taxanes, platinums, capecitabine)	General: nausea, diarrhea, myelosuppression, alopecia, amenorrhea
	Anthracyclines: cardiotoxicity, secondary leukemia
	Taxanes: neuropathy, hypersensitivity reaction
	Platinums: neuropathy, hypersensitivity reaction, ototoxicity, nephrotoxicity
	Capecitabine: hand–foot syndrome, stomatitis
HER2-Targeted Therapy (trastuzumab, pertuzumab, T-DM1, neratinib)	General: diarrhea, cardiotoxicity
	T-DM1: thrombocytopenia, peripheral neuropathy, hyperbilirubinemia, transaminitis
Endocrine Therapy (SERMs, SERDs, aromatase inhibitors, ovarian suppression)	General: hot flashes, arthralgia, myalgia, nausea, headache, vaginal dryness, mood swings, weight gain, hair thinning
	Tamoxifen: endometrial cancer, venous thromboembolism, cataracts
	Aromatase inhibitors: decreased bone mineral density

FIGURE 35-8 Common and serious side effects of breast cancer therapies. SERD, selective estrogen receptor downregulator; SERM, selective estrogen receptor modulator; T-DM1, trastuzumab emtansine.

with some patients receiving APBI or hypofractionated therapy without affecting outcomes. Within medical oncology, we are now able to avoid chemotherapy in approximately half of HR-positive, HER2-negative patients using genomic prognostic assays, and we are reconsidering the need for 10 years of adjuvant endocrine therapy. Efforts to better identify patients that benefit from escalation and de-escalation strategies are ongoing and will in the future allow us to personalize treatment and avoid unnecessary toxicities.

MD ANDERSON PRACTICE TIPS

- Integrate clinical information with imaging, pathologic staging, and molecular characteristics to optimize treatment efficacy and, whenever possible, perform BCS.
- Involve surgical oncology and radiation oncology early in the treatment planning process to optimize a multidisciplinary approach. Other important team members include fertility specialists, nutritionist, plastic surgeons, and genetic counselors, among others.
- Prognostic staging is preferred for patient care when biomarker analysis is available.
- Neoadjuvant chemotherapy is preferred in patients with TNBC and HER2-positive breast cancer as well as patients with large primary tumors.
- We recommend treatment with trastuzumab and paclitaxel in most patients with node-negative disease, particularly those with tumors that are 1 cm or smaller in size.

REFERENCES

1. National Cancer Institute. SEER Cancer Statistics Factsheets: Breast Cancer. National Cancer Institute; 2020. http://seer.cancer.gov/statfacts/html/breast.html
2. Chu KC, Tarone RE, Kessler LG, et al. Recent trends in U.S. breast cancer incidence, survival, and mortality rates. *J Natl Cancer Inst*. 1996;88(21):1571-1679.
3. Li CI, Daling JR, Malone KE. Incidence of invasive breast cancer by hormone receptor status from 1992 to 1998. *J Clin Oncol*. 2003;21(1):28-34.
4. Ravdin PM, Cronin KA, Howlader N, et al. The decrease in breast-cancer incidence in 2003 in the United States. *N Engl J Med*. 2007;356(16):1670-1674.
5. Willett WC RB, Hankinson SE, Hunter DJ, Colditz GA. *Epidemiology and Nongenetic Causes of Breast Cancer. Diseases of the Breast*. 2nd ed. Lippincott Williams & Wilkins; 2000:175-220.
6. Fedewa SA, Ward EM, Stewart AK, Edge SB. Delays in adjuvant chemotherapy treatment among patients with breast cancer are more likely in African American and Hispanic populations: a national cohort study 2004-2006. *J Clin Oncol*. 2010;28(27):4135-4141.
7. American Cancer Society. Breast Cancer Risk and Prevention. 2020. https://www.cancer.org/cancer/breast-cancer/risk-and-prevention.html
8. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst*. 1989;81(24):1879-1886.
9. Claus EB, Risch N, Thompson WD. Genetic analysis of breast cancer in the cancer and steroid hormone study. *Am J Hum Genet*. 1991;48(2):232-242.
10. Collaborative Group on Hormonal Factors in Breast Cancer. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. *Lancet*. 2001;358(9291):1389-1399.
11. Antoniou AC, Casadei S, Heikkinen T, et al. Breast-cancer risk in families with mutations in PALB2. *N Engl J Med*. 2014;371:497-506.
12. Frank TS, Deffenbaugh AM, Reid JE, et al. Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals. *J Clin Oncol*. 2002;20(6):1480-1490.
13. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. *Lancet*. 1999;353(9169):1993-2000.
14. Hsieh CC, Trichopoulos D, Katsouyanni K, Yuasa S. Age at menarche, age at menopause, height and obesity as risk factors for breast cancer: associations and interactions in an international case-control study. *Int J Cancer*. 1990;46(5):796-800.
15. Layde PM, Webster LA, Baughman AL, et al. The independent associations of parity, age at first full term pregnancy, and duration of breastfeeding with the risk of breast cancer. Cancer and Steroid Hormone Study Group. *J Clin Epidemiol*. 1989;42(10):963-973.
16. Brinton LA, Schairer C, Hoover RN, Fraumeni JF Jr. Menstrual factors and risk of breast cancer. *Cancer Invest*. 1988;6(3):245-254.
17. Bruzzi P, Negri E, La Vecchia C, et al. Short term increase in risk of breast cancer after full term pregnancy. *BMJ*. 1988;297(6656):1096-1098.
18. Hankinson SE, Colditz GA, Manson JE, et al. A prospective study of oral contraceptive use and risk of breast cancer (Nurses' Health Study, United States). *Cancer Causes Control*. 1997;8(1):65-72.
19. Marchbanks PA, McDonald JA, Wilson HG, et al. Oral contraceptives and the risk of breast cancer. *N Engl J Med*. 2002;346(26):2025-2032.
20. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. *Lancet*. 1996;347(9017):1713-1727.
21. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women:

principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288(3):321-333.
22. Hortobagyi G, Connolly JL, D'Orsi CJ, et al. Breast. In: Edge SB, Byrd DR, Compton CC, et al, eds. *AJCC Cancer Staging Manual.* 8th edition. Springer; 2017:587-628.
23. Gasparini G, Pozza F, Harris AL. Evaluating the potential usefulness of new prognostic and predictive indicators in node-negative breast cancer patients. *J Natl Cancer Inst*. 1993;85(15):1206-1219.
24. Weiss RB, Woolf SH, Demakos E, et al. Natural history of more than 20 years of node-positive primary breast carcinoma treated with cyclophosphamide, methotrexate, and fluorouracil-based adjuvant chemotherapy: a study by the Cancer and Leukemia Group B. *J Clin Oncol*. 2003;21(9):1825-1835.
25. Nemoto T, Vana J, Bedwani RN, et al. Management and survival of female breast cancer: results of a national survey by the American College of Surgeons. *Cancer*. 1980;45(12):2917-2924.
26. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. *Histopathology*. 1991;19(5):403-410.
27. Allison KH, Hammond MEH, Dowsett M, et al. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP Guideline Update [published online ahead of print, 2020 Jan 13]. *J Clin Oncol*. 2020;38(12):1346-1366.
28. Kontzoglou K, Palla V, Karaolanis G, et al. Correlation between Ki67 and breast cancer prognosis. *Oncology*. 2013;84(4):219-225.
29. Wolff AC, Hammond MEH, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update. *J Clin Oncol*. 2018;36(20):2105-2122.
30. Tandon AK, Clark GM, Chamness GC, et al. HER-2/neu oncogene protein and prognosis in breast cancer. *J Clin Oncol*. 1989;7(8):1120-1128.
31. Gonzalez-Angulo AM, Litton JK, Broglio KR, et al. High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller. *J Clin Oncol*. 2009;27(34):5700-5706.
32. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, et al. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. *Lancet*. 2013;382(9897):1021-1028.
33. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med*. 2011;365(14):1273-1283.
34. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*. 2002;347(16):1233-1241.
35. Olson JA Jr, McCall LM, Beitsch P, et al. Impact of immediate versus delayed axillary node dissection on surgical outcomes in breast cancer patients with positive sentinel nodes: results from American College of Surgeons Oncology Group trials Z0010 and Z0011. *J Clin Oncol*. 2008;26(21):3530-3535.
36. Veronesi U, Bonadonna G, Zurrida S, et al. Conservation surgery after primary chemotherapy in large carcinomas of the breast. *Ann Surg*. 1995;222(5):612-618.
37. 102. Rouzier R, Extra JM, Carton M, et al. Primary chemotherapy for operable breast cancer: incidence and prognostic significance of ipsilateral breast tumor recurrence after breast-conserving surgery. *J Clin Oncol*. 2001;19(18):3828-3835.
38. Correa C, Harris E, Leonardi M, et al. Accelerated partial breast irradiation: executive summary for the update of an ASTRO evidence-based consensus statement. *Pract Radiat Oncol.* 2017;7(2):73-79.
39. Recht A, Edge SB. Evidence-based indications for postmastectomy irradiation. *Surg Clin North Am*. 2003;83(4):995-1013.
40. Blumenschein GR, Montague ED, Eckles NE, et al. Sequential combined modality therapy for inflammatory breast cancer. *Breast*. 1976;2:16-20.
41. De Lena M, Zucali R, Viganotti G, et al. Combined chemotherapy-radiotherapy approach in locally advanced (T3b-T4) breast cancer. *Cancer Chemother Pharmacol*. 1978;1(1):53-59.
42. Fisher B, Brown A, Mamounas E, et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. *J Clin Oncol*. 1997;15(7):2483-2493.
43. Rouzier R, Extra JM, Klijanienko J, et al. Incidence and prognostic significance of complete axillary downstaging after primary chemotherapy in breast cancer patients with T1 to T3 tumors and cytologically proven axillary metastatic lymph nodes. *J Clin Oncol*. 2002;20(5):1304-1310.
44. Green MC, Buzdar AU, Smith T, et al. Weekly paclitaxel improves pathologic complete remission in operable breast cancer when compared with paclitaxel once every 3 weeks. *J Clin Oncol*. 2005;23(25):5983-5992.
45. McCready DR, Hortobagyi GN, Kau SW, et al. The prognostic significance of lymph node metastases after preoperative chemotherapy for locally advanced breast cancer. *Arch Surg*. 1989;124(1):21-25.
46. Huang E, McNeese MD, Strom EA, et al. Locoregional treatment outcomes for inoperable anthracycline-resistant breast cancer. *Int J Radiat Oncol Biol Phys*. 2002;53(5):1225-1233.
47. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet.* 2014;384:164-172.
48. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med*. 2004;351(27):2817-2826.
49. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol*. 2006;24(23):3726-3734.
50. Sparano JA. TAILORx: trial assigning individualized options for treatment (Rx). *Clin Breast Cancer*. 2006;7(4):347-350.
51. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med. 2018;*379:111-121.
52. Sparano JA, Gray RJ, Ravdin PM, et al. Clinical and genomic risk to guide the use of adjuvant therapy for breast cancer. *N Engl J Med*. 2019;380:2395-2405.
53. Mamounas EP, Russell CA, Lau A, et al. Clinical relevance of the 21-gene Recurrence Score® assay in treatment decisions for patients with node-positive breast cancer in the genomic era. *NPJ Breast Cancer.* 2018;4:27.
54. Cardoso F, van't Veer LJ, Bohaerts J, et al. 70-gene signature as an aid to treatment decisions in early-stage breast cancer. *N Engl J Med.* 2016;375:717-729.
55. Fisher B, Ravdin RG, Ausman RK, et al. Surgical adjuvant chemotherapy in cancer of the breast: results of a decade of cooperative investigation. *Ann Surg*. 1968;168(3):337-356.
56. Nissen-Meyer R, Kjellgren K, Mansson B. Preliminary report from the Scandinavian adjuvant chemotherapy study group. *Cancer Chemother Rep*. 1971;55(5):561-566.
57. Polychemotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet*. 1998;352(9132):930-942.
58. Sparano JA, Wang M, Martino S, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. *N Engl J Med*. 2008;358(16):1663-1671.
59. Jones S, Holmes FA, O'Shaughnessy J, et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year

follow-up of US Oncology Research Trial 9735. *J Clin Oncol*. 2009;27(8):1177-1183.
60. Blum JL, Flynn PJ, et al. Anthracyclines in early breast cancer: the ABC trials—USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 (NRG Oncology). *J Clin Oncol*. 2017;35(23):2647-2655.
61. Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol*. 2003;21(8):1431-1439.
62. Swain SM, Tang G, Geyer CE Jr, et al. Definitive results of a phase III adjuvant trial comparing three chemotherapy regimens in women with operable, node-positive breast cancer: the NSABP B-38 trial. *J Clin Oncol*. 2013;31(26):3197-3204.
63. Budd GT, Barlow WE, Moore HC, et al. SWOG S0221: a phase III trial comparing chemotherapy schedules in high-risk early-stage breast cancer. *J Clin Oncol*. 2015;33(1):58-64.
64. Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment with illustrative cases. *Lancet*. 1896;2(3803):104-107.
65. Elwood V. Jensen EV, and Jordan VC. The estrogen receptor. *Clin Cancer Res.* 2003;9(6):1980-1989.
66. Controlled trial of tamoxifen as adjuvant agent in management of early breast cancer. Interim analysis at four years by Nolvadex Adjuvant Trial Organisation. *Lancet*. 1983;1(8319):257-261.
67. Fisher B, Costantino J, Redmond C, et al. A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. *N Engl J Med*. 1989;320(8):479-484.
68. Rutqvist LE, Cedermark B, Glas U, et al. Randomized trial of adjuvant tamoxifen in node negative postmenopausal breast cancer. Stockholm Breast Cancer Study Group. *Acta Oncologica*. 1992;31(2):265-270.
69. Stewart HJ. The Scottish trial of adjuvant tamoxifen in node-negative breast cancer. Scottish Cancer Trials Breast Group. *J Natl Cancer Inst Monogr*. 1992;11:117-120.
70. Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet*. 1998;351(9114):1451-1467.
71. Brodie AM, Njar VC. Aromatase inhibitors and their application in breast cancer treatment. *Steroids*. 2000;65(4):171-179.
72. Baum M, Buzdar A, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses. *Cancer*. 2003;98(9):1802-1810.
73. Buzdar AU, ATAC Trialists' Group. Arimidex (anastrozole) versus tamoxifen as adjuvant therapy in postmenopausal women with early breast cancer—efficacy overview. *J Steroid Biochem Mol Biol*. 2003;86(3-5):399-403.
74. Sainsbury R. Beneficial side-effect profile of anastrozole compared with tamoxifen confirmed by additional 7 months of exposure data: a safety update from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial. *Breast Cancer Res Treat*. 2002;76(suppl):S156.
75. Dowsett M, Cuzick J, Ingle J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J Clin Oncol*. 2010;28(3):509-518.
76. Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med*. 2003;349(19):1793-1802.
77. Breast International Group 1-98 Collaborative Group, Thurlimann B, Keshaviah A, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med*. 2005;353(26):2747-2757.
78. Breast International Group 1-98 Collaborative Group, Mouridsen H, Giobbie-Hurder A, et al. Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. *N Engl J Med*. 2009;361(8):766-776.
79. Coombes RC, Hall E, Gibson LJ, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med*. 2004;350(11):1081-1092.
80. Chan A, Speers C, O'Reilly S, et al. Adherence of adjuvant hormonal therapies in post-menopausal hormone receptor positive (HR+) early stage breast cancer: a population based study from British Columbia [abstract]. *Cancer Res*. 2009;69:36.
81. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet*. 2013;381(9869):805-816.
82. Gray RG, Rea D, Handley SJB, et al. aTTom: long term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 6 years in 6,953 women with early breast cancer [abstract]. *J Clin Oncol*. 2013;31:5.
83. Goss PE, Ingle JN, Pritchard KI, et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. *N Engl J Med.* 2016;375:209-219.
84. Burstein HJ, Lacchetti C, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor–positive breast cancer: ASCO clinical practice guideline focused update. *J Clin Oncol*. 2019;37(5):423-438.
85. Jonat W, Kaufmann M, Sauerbrei W, et al. Goserelin versus cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy in premenopausal patients with node-positive breast cancer: the Zoladex Early Breast Cancer Research Association Study. *J Clin Oncol*. 2002;20(24):4628-4635.
86. Chlebowski RT, Pan K. Exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med*. 2014;371(14):1358.
87. Francis PA, Regan MM, Fleming GF, et al. Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med*. 2015;372(5):436-446.
88. National Comprehensive Cancer Network Guidelines Version 2.2020 Invasive Breast Cancer.
89. von Minckwitz G, Schneeweiss A, Loibl S, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. *Lancet Oncol*. 2014;15(7):747-756.
90. Sikov WM, Polley M-Y, Twohy E, et al. CALGB (Alliance) 40603: long-term outcomes (LTOs) after neoadjuvant chemotherapy (NACT) +/- carboplatin (Cb) and bevacizumab (Bev) in triple-negative breast cancer (TNBC) [abstract]. *J Clin Oncol* 37(15 suppl):591.
91. Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for early triple negative breast cancer. *N Engl J Med*. 2020;382:810-821.
92. Masuda N, Lee S-J, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *N Engl. J Med.* 2017;376:2147-2159.
93. Li Y, Zhou Y, Mao F, et al. Adjuvant addition of capecitabine to early-stage triple-negative breast cancer patients receiving standard chemotherapy: a meta-analysis. *Breast Cancer Res Treat*. 2020;179(3):533-542.
94. Pivot X, Romieu G, Debled M, et al. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. *Lancet Oncol*. 2013;14(8):741-748.
95. Earl HE, Hiller L, Vallier A-L, et al. 6 versus 12 months of adjuvant trastuzumab for HER2-positive early breast cancer (PERSEPHONE): 4-year disease free survival results

of a randomized phase 2 non-inferiority trial. *Lancet.* 2019;393(10191):2599-2612.
96. Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *J Clin Oncol*. 2002;20(3):719-726.
97. Cobleigh MA, Vogel CL, Tripathy D, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. *J Clin Oncol*. 1999;17(9):2639-2648.
98. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001;344(11):783-792.
99. Perez EA. Cardiac toxicity of ErbB2-targeted therapies: what do we know? *Clin Breast Cancer*. 2008;8(suppl 3):S114-S120.
100. Perez EA, Romond EH, Suman VJ, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. *J Clin Oncol*. 2014;32(33):3744-3752.
101. Perez EA, Romond EH, Suman VJ, et al. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. *J Clin Oncol*. 2011;29(25):3366-3373.
102. Buzdar AU, Ibrahim NK, Francis D, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. *J Clin Oncol*. 2005;23(16):3676-3685.
103. Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med*. 2012;366(2):109-119.
104. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2012;13(1):25-32.
105. Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann Oncol*. 2013;24(9):2278-2284.
106. Piccart M, Procter M, Fumagalli D, et al. Interim overall survival analysis of APHINITY (BIG 4-11): a randomized, multicenter, double-blind, placebo-controlled trial comparing chemotherapy plus trastuzumab plus pertuzumab vs chemotherapy plus trastuzumab plus placebo as adjuvant therapy in patients with operable HER2-positive early breast cancer. Presented at: 2019 San Antonio Breast Cancer Symposium; San Antonio, TX; 2019.
107. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med.* 2017;377:122-131.
108. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med*. 2006;355(26):2733-2743.
109. Baselga J, Bradbury I, Eidtmann H, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. *Lancet*. 2012;379(9816):633-640.
110. Piccart MJ, Holmes AP, Baselga J, et al. First results from the phase III ALTTO trial (BIG 2-06; NCCTG [Alliance] N063D) comparing one year of anti-HER2 therapy with lapatinib alone (L), trastuzumab alone (T), their sequence (T→L), or their combination (T+L) in the adjuvant treatment of HER2-positive early breast cancer (EBC) [abstract]. *J Clin Oncol*. 2014;32:LBA4.
111. von Minckwitz G, Huang C-S, Mano M, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med. 2019;380:617-628.*
112. Martin PM, Holmes FA, Ejlertsen B, et al. Neratinib after trastuzumab-based adjuvant therapy in HER-2-positive breast cancer (ExteNET): 5-year analysis of a randomized, double-blind, placebo controlled, phase 3 trial. *Lancet.* 2017;18(12):1688-1700.
113. Tolaney SM, Guo H, Pernas S, et al. Seven-year follow-up analysis of adjuvant paclitaxel and trastuzumab trial for node-negative, human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol.* 2019;37(22):1868-1875.

36 Metastatic Breast Cancer

Haven R. Garber
Meghan S. Karuturi
Gabriel N. Hortobagyi

KEY CONCEPTS

- Metastatic breast cancer (MBC) most commonly arises from prior early-stage breast cancer and is incurable, with prognosis influenced by disease subtype (hormone receptor [HR] and HER2 receptor status).
- Treatment of MBC is increasingly guided by disease biology, and the armamentarium of treatments includes several targeted agents, antibodies and antibody-drug conjugates, and checkpoint inhibitors.
- Patients can live many years with MBC and preserving quality of life, minimizing toxicity, and shared patient-physician decision making are paramount in planning the best treatment strategy.
- Endocrine therapy remains the backbone of treatment for HR-positive MBC and now includes CDK4/6 inhibitors as standard frontline treatment.
- The clinical outcomes of patients with HER2-positive MBC continue to improve because of the efficacy of therapies that target the HER2 kinase pathway including pertuzumab, ado-trastuzumab emtansine, and tucatinib.
- Metastatic triple-negative breast cancer remains the breast cancer subtype with the worst prognosis. However, multiple clinical trials are underway that incorporate immunotherapy, antibody-drug conjugates, and targeted therapies in an effort to improve outcomes over those achieved with standard chemotherapy.

Breast cancer is the most common malignancy diagnosed in women in the United States and is a significant cause of morbidity and mortality. Approximately 268,600 new cases of invasive breast cancer occurred in the United States in 2019. Although lung cancer has surpassed breast cancer as the leading cause of cancer death among women, an estimated 41,760 deaths occurred from breast cancer in 2019.[1]

Since the 1970s, advances in combined-modality therapies have improved the outcomes of patients with early-stage breast cancer. Still, a significant proportion of patients with early-stage, localized breast cancer will have relapse with distant metastatic disease. The risk and timing of relapse varies widely among patients with breast cancer and is dependent on hormone receptor (HR) (estrogen receptor [ER] and progesterone receptor [PR]) and HER2/neu receptor (HER2) status as well as initial tumor (T) and nodal (N) staging. For example, among patients with ER-positive, stage T1 disease, the risk of distant recurrence at 20 years is 13% for patients without nodal involvement, 20% for 1 to 3 involved nodes, and 34% for 4 to 9 involved nodes, and the recurrence risk remains steady up to 20 years after diagnosis.[2] For patients with HER2-positive or triple-negative breast cancer (TNBC), the risk of recurrence after treatment of a primary breast tumor is highest within the first 5 years of diagnosis and depends not only on the initial TN staging, but also on the degree of sensitivity to HER2-targeted treatment and/or chemotherapy. For example, in the HER2-positive, neoadjuvant TRYPHAENA trial, 3-year disease-free survival was 87% to 90% regardless of regimen; however, patients achieving a pathologic complete response (pCR) were far more likely to be disease-free at 3 years (hazard ratio 0.27; 95% CI 0.11–0.64). Patients with TNBC with a pCR or minimal residual disease after neoadjuvant chemotherapy have an 80% to 90% chance of cure, whereas patients with significant residual disease have a more than 50% risk of relapse.[3,4]

Metastatic breast cancer (MBC) is diagnosed at the time of presentation, ie, de novo metastatic disease, in 6% to 10% of patients, depending on the series.[1,5] Bone is the most common site of distant metastasis in breast cancer; other common sites include lymph nodes, lung, liver, and, less frequently, brain. MBC is considered incurable, though there are reports of long-term durable remissions in around 2% of patients with MBC treated with anthracycline therapy and in a small subset of oligometastatic patients. The median overall survival (OS) of patients with MBC continues to improve owing to multiple new agents. For patients with HR-positive, HER2-negative MBC, the median OS in the pre-CDK4/6 inhibitor era was estimated at 57 months.[6] Analysis of more recent data that incorporate the widespread use of CDK4/6 inhibitors is ongoing. With respect to metastatic HER2-positive breast cancer, the CLEOPATRA trial reported a median OS of 56.5 months for patients in the experimental arm (vs 40.8 months in the control arm).[7] Metastatic TNBC remains the subtype with the poorest survival. The IMpassion130 trial for patients with metastatic TNBC reported an OS of 21 months in the experimental arm (vs 17.6 months in the control arm).[8] In general, patients with oligometastatic disease and/or bone-only disease live longer than patients with significant visceral involvement. Survival and response to therapy are affected by several factors, including performance status, number and sites of disease, and the disease-free interval (DFI) since prior treatment.

The therapeutic objectives for patients with MBC are distinct from those with early-stage disease. Improving survival, achieving disease control, and preventing/delaying serious complications remain important in MBC. However, because MBC is incurable and some patients can live for many years, preserving quality of life, minimizing toxicity, controlling symptoms, and shared patient-physician decision making are also paramount. Regular discussions regarding the goals of care are a key part of the treatment plan. Treatment for MBC includes endocrine therapy, chemotherapy, targeted therapy, and immunotherapy and is increasingly guided by disease biology. In select cases, there is a role for local therapy, including radiation and surgery. Patient performance status, comorbidities, organ function, prior therapies and response duration, and site(s)/extent of disease are important in each treatment decision.

Breast cancer is classified into three molecularly and clinically different subtypes: HR-positive/HER2-negative disease, HER2-positive/any HR breast cancer, and TNBC. Significant heterogeneity exists within each subtype and is the focus of many ongoing clinical trials. The breast cancer subtypes have different clinical courses, prognoses, metastatic patterns, and responses to available therapies. Although systemic treatment is not curative, it has been shown to prolong survival, palliate symptoms, and enhance or preserve quality of life. The OS of patients with MBC continues to improve because of increasingly effective therapies and supportive care. This chapter reviews standard care for patients with MBC and the current practice at MDACC.

DIAGNOSTIC WORKUP

Once metastatic disease is suspected, careful evaluation of the primary tumor disease history, current symptoms, and existing comorbid diseases is essential. A review of the initial presentation should include disease stage, histology, HR and HER2 status, and treatment modalities used. Knowledge of the initial tumor histology may yield clues about the sites of disease as well as its biology. For instance, infiltrating ductal carcinoma most commonly involves the bone, lungs, pleura, liver, and brain.[9] Infiltrating lobular carcinoma frequently recurs in unusual sites such as the bone marrow, meninges, peritoneum, and retroperitoneal structures, such as the ureters.[10]

A biopsy of the metastatic site is required to confirm histology and receptor status. Discordance in the receptor status from diagnosis to recurrence is common, and treatment is tailored to the receptor status of the relapsed disease.[11] Pathologic confirmation is also essential in patients with atypical presentations, including single-lesion metastasis, unusual metastatic sites, and long DFI. Solitary lesions should always be biopsied and may represent a benign process or a distinct tumor type. In rare cases, when biopsy of metastatic disease is infeasible or the results are uninterpretable, treatment is guided by the primary tumor histology/receptor subtype, though biopsy should be reattempted at the time of progression.

In addition to a comprehensive physical examination, basic laboratory evaluation should include a complete blood count with differential, renal and liver function tests including alkaline phosphatase, and serum calcium. Alkaline phosphatase is correlated with bone metastasis in patients with breast cancer but is neither sensitive nor specific.[12] In addition, the serum tumor markers CA 15-3, CA 27-29, and CEA are elevated in approximately 70% of patients with MBC and can be helpful in monitoring response to therapy; however, they are rarely used in isolation to determine disease response. Our baseline imaging consists of a computed tomography (CT) scan of the chest, abdomen, and pelvis, and a bone scan. In cases where baseline imaging is equivocal, positron emission tomography-CT scan or magnetic resonance imaging of the abdomen (eg for liver metastasis) can be informative. We reserve brain imaging for patients who report neurologic symptoms.

Several therapeutic agents have been approved in the past 3 years that require additional biomarker testing in blood or tumor tissue. These assays should be performed on tissue obtained from a metastatic site at the time of progression and not on the archived primary tumor sample. This is because molecular tumor evolution can occur over time, particularly in the context of adjuvant therapies. Patients with TNBC should have their tumors tested for programmed cell death–ligand 1 (PD-L1) expression on tumor-infiltrating immune cells to guide the appropriateness of therapy with checkpoint inhibitors.[8,13] Patients with HR-positive, HER2-negative MBC who have previously been treated with endocrine therapy are candidates for therapy with fulvestrant in combination with the PI3K inhibitor, alpelisib, which is effective only in patients with activating *PIK3CA* mutations and requires plasma or tumor polymerase chain reaction testing.[14] Germline testing for *BRCA1/2* mutations is also important for patients with MBC given the efficacy of talazoparib and olaparib for patients with HER2-negative MBC. Additional biomarker testing is relevant only for clinical trials or in rare MBC cases. For example, mismatch repair deficiency is rare in breast cancer (~1% of patients) and may be rational only for patients with Lynch syndrome, particularly given the number of other effective therapies in MBC.[15–17] Furthermore, clinical data regarding the activity of pembrolizumab in patients with mismatch repair–deficient MBC is limited. Similarly, tropomyosin receptor kinase fusions are uncommon in breast cancer (<1%) except in the very rare secretory subtype where fusions are highly prevalent. Moreover, secretory breast carcinomas rarely metastasize.[18] Finally, a priority at MDACC is to enroll patients with MBC into clinical trials and we use an institutional next-generation sequencing assay on tumor tissue to help guide selection of clinical trials for patients. We do not perform this assay in patients with MBC who are unable to participate in clinical trials.

TREATMENT

General Considerations

The decision to use endocrine therapy, targeted therapy, immunotherapy, and/or chemotherapy in the treatment of MBC is guided by several factors including hormone and HER2 receptor status and the presence or absence of visceral crisis. Regardless of receptor status, patients with visceral crisis but good performance status are often treated initially with chemotherapy, and sometimes combination chemotherapy, to try to achieve a significant and rapid tumor response. Patients with HR-positive, HER2-negative MBC, including those with symptomatic visceral disease, are treated with endocrine therapy paired with a CDK4/6 inhibitor, given the comparable response rates (RRs) to that of chemotherapy. For patients with HER2-positive MBC, novel therapies have transformed the treatment paradigm and have improved the prognosis for a disease that historically ranked among the most aggressive and lethal cancers. Patients with HER2-positive MBC are initially treated with anti-HER2 therapy in combination with chemotherapy, because this provides a significant survival advantage. The majority of patients with HER2-positive disease have breast cancer that also expresses hormone receptors. Because the HER2-positive component is more aggressive, anti-HER2 therapy is typically prioritized over endocrine therapy, which can be incorporated during periods when cytotoxic chemotherapy is omitted and patients are on anti-HER2 antibodies alone. Patients with TNBC are treated with chemotherapy, with or without immunotherapy.

Multiple agents are active against hormone-responsive tumors. Endocrine therapy is at least as effective as chemotherapy and is the initial preferred treatment option. Endocrine therapy is associated with fewer side effects and helps patients maintain a superior quality of life compared with cytotoxic chemotherapy. Many patients with HR-positive disease can be treated with multiple lines of sequential endocrine therapy. However, in the case of very rapid progression within the first few weeks of initial endocrine therapy or refractory disease after multiple lines of endocrine therapy, systemic chemotherapy is the best option.

A minority of patients with MBC (<5%) have a solitary metastasis or oligometastases, a unique subset of patients that have been a focus of research at MDACC. For patients with recurrent breast cancer and limited sites of metastasis (ie, not de novo metastatic disease), there are no phase 3 randomized data that support aggressive, multimodal local management of oligometastatic disease over systemic therapy, though multiple trials of stereotactic body radiation therapy/ablation and surgical resection are ongoing. Data from phase 1/2 trials suggest that combined-modality treatment with curative intent for patients with limited metastatic sites may improve survival and even yield MBC cures.[19,20] MDACC is participating in NRG-BR002, a phase 2R/3 trial of systemic therapy with or without local therapy for newly diagnosed oligometastatic breast cancer to help clarify this important clinical question.

Regarding patients with de novo metastatic disease and management of the primary breast tumor, the phase 3 E2108 study randomly assigned 256 patients with de novo MBC and no disease progression after 4 to 8 months of systemic therapy to either locoregional treatment for the intact primary breast tumor plus

systemic treatment or systemic treatment alone. The primary end point was OS and there was no significant difference in the 3-year OS (68.4% in the locoregional group vs 67.9% in the control group; hazard ratio 1.09; 95% CI 0.8–1.49), though the rate of locoregional recurrence/progression was expectedly higher in the control group (25.6% vs 10.2% at 3 years).[21]

At MDACC, we do offer combination systemic therapy and aggressive local therapy to a select group of patients with MBC who have few (≤4) small tumors in sites amenable to radiation or safe complete resection and to patients who have demonstrated a long DFI after prior treatments. Unfortunately, patients with TNBC are often excluded from this approach because of the aggressive nature of their disease.

Bone-Directed Agents

Bone is the most common site of distant metastasis in breast cancer and is the only site of disease in a subset of patients with HR-positive MBC. Bone metastases can cause significant debility and pain and are a treatment priority across MBC subtypes. The primary bone-targeting agents used at MDACC in patients with MBC are zoledronic acid, a bisphosphonate, and denosumab, an antibody against RANK ligand. Bone-targeting agents are palliative and no trials have shown an impact on survival. Bisphosphonates and denosumab are given in combination with other cancer-directed therapies. In addition, all patients should take the recommended daily amount of calcium (1200–1500 mg) and vitamin D (800 IU).

Bisphosphonates are pyrophosphate analogs that bind hydroxyapatite crystals and inhibit bone resorption by osteoclasts. They are used to prevent skeletal complications including pathologic fracture, pain requiring radiation and/or surgery, cord compression, and hypercalcemia.[22] Importantly, routine monitoring of renal function is required during bisphosphonate treatment because zoledronic acid can cause renal toxicity, requires dose reductions for chronic kidney disease, and is contraindicated in acute kidney injury. Physicians should also be aware of the risk of osteonecrosis of the jaw, a rare but serious complication of bisphosphonate therapy. Patients should have a dental exam before initiating a bone-targeting agent, and invasive dental procedures should be completed before starting or resuming bisphosphonates. Trials support the use of bisphosphonates for at least 2 years—benefit beyond 2 years is unproven. The OPTIMIZE-2 trial evaluated the frequency of zoledronic acid administration in 403 women with bone metastasis who had previously received at least nine doses of an intravenous (IV) bisphosphonate. The study demonstrated that administering zoledronic acid 4 mg IV every 3 months was as effective as giving it monthly. The rate of skeletal-related events was 22% in the monthly group versus 23.2% in the every-three-month group. The less frequent dosing also corresponded with lower rates of renal failure and osteonecrosis of the jaw.[23]

Denosumab is a monoclonal antibody that targets RANK ligand, a protein that activates osteoclasts via the RANK receptor. Denosumab is indicated for treatment of osteoporosis, therapy-induced bone loss, and bone metastases. A randomized controlled trial evaluated denosumab versus zoledronic acid in 2033 patients with MBC and bone metastases. Denosumab proved superior to zoledronic acid in delaying or preventing the first skeletal-related event (hazard ratio 0.82; 95% CI 0.71–0.95), supporting the use of monthly denosumab in the management of bone metastases.[24] Denosumab is administered subcutaneously, an advantage over zoledronic acid, which requires an IV line. A disadvantage is that administration is monthly and continuous. The optimal duration of denosumab therapy is unknown. The risk of osteonecrosis of the jaw with denosumab is similar to that of bisphosphonates, and patients with a creatinine clearance less than 30 mL/min are at an increased risk of development of hypocalcemia. At MDACC, all patients with MBC and bone metastases who do not have a contraindication to receive bone-targeting agents are treated with zoledronic acid or denosumab.

HORMONE RECEPTOR–POSITIVE, HER2-NEGATIVE BREAST CANCER

Patients with HR-positive, HER2-negative disease compose two-thirds of patients with MBC.[25] Breast cancers with 1% to 100% ER and/or PR positivity by immunohistochemistry are considered HR-positive and eligible for endocrine therapy. However, in practice, patients harboring tumors with 1% to 10% ER/PR expression are deemed HR low-positive and often have more aggressive disease. Depending on individual clinical features (presence/absence of visceral disease, number and volume of metastatic sites, biopsy site, initial primary tumor receptor status), a subset of patients with HR low-positive disease are treated initially with endocrine therapy, but with a low threshold to switch to cytotoxic chemotherapy in the event of rapid progression. Most other patients with adverse clinical features and HR low-positive disease are treated similarly to patients with TNBC with initial chemotherapy. A switch to endocrine therapy can then be tried later in the disease course for patients with excellent chemotherapy responses. Likewise, patients with ER-negative/PR-positive disease are a distinct group with unpredictable responses to endocrine therapy, and oncologists should have a low threshold to repeat a biopsy or switch to chemotherapy in the event of rapid progression.

Endocrine therapy, with or without a CDK4/6 inhibitor, is the standard frontline treatment for most patients with HR-positive, HER2-negative MBC, including for patients with de novo metastatic disease (Fig. 36–1). The optimal endocrine therapy varies for patients with recurrent disease and depends on whether the recurrence occurred while on endocrine therapy or within one year of stopping adjuvant endocrine therapy. For patients who have recurrrence while on or within one year of stopping an aromatase inhibitor (AI), a change in endocrine therapy is recommended, and the optimal regimen is fulvestrant in combination with a CDK4/6 inhibitor. Of note, CDK4/6 inhibitors are approved in women who are postmenopausal or in pre/perimenopausal women treated concurrently with a luteinizing hormone–releasing hormone (LHRH) agonist (eg, goserelin). The first CDK4/6 inhibitor received FDA approval in 2015 in combination with endocrine therapy, heralding a new class of drugs integral to the treatment of MBC. Because the CDK4/6 inhibitors are a new update to this edition, we will discuss the important clinical trials that led to their approval and will then review the principles of endocrine and chemotherapy in patients with HR-positive MBC.

CDK4/6 Inhibitors

In HR-positive breast cancer, estrogen drives accumulation of cyclin D1, which complexes with and activates the cyclin-dependent 4 and 6 kinases to hyperphosphorylate the retinoblastoma (Rb) tumor suppressor, leading to Rb inactivation. The end result is bypass of the G1/S cell-cycle checkpoint and unrestricted breast cancer cell proliferation. The CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) inhibit CDK4 and CDK6, thus preventing Rb hyperphosphorylation and reinstating the G1/S checkpoint in breast cancer cells.[26]

Palbociclib, in combination with an AI, received FDA approval in 2015 for the treatment of postmenopausal women with HR-positive/HER2-negative MBC. Approval was based on PALOMA-1, a randomized phase 2 study of palbociclib plus letrozole versus letrozole alone in the first-line treatment of patients with HR-positive, HER2-negative MBC (Table 36–1). A clear progression-free survival (PFS) advantage for the combination was seen in the initial cohort of 165 patients (20.2 months for the combination vs 10.2 months for letrozole alone).[27] The confirmatory study was PALOMA-2, a randomized, double-blind phase 3

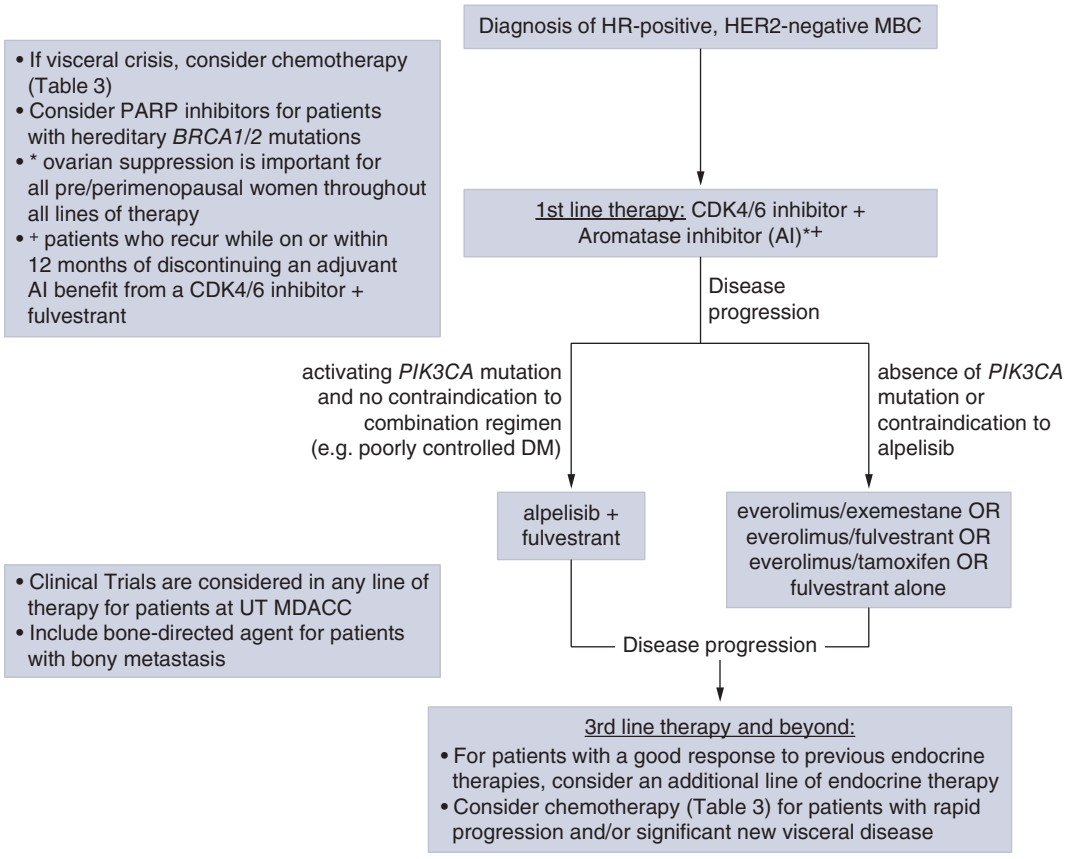


FIGURE 36–1 Concise algorithm for the treatment of patients with HR-positive, HER2-negative MBC at MDACC.

Table 36–1 CDK4/6 Inhibitors in HR-Positive, HER2-Negative MBC

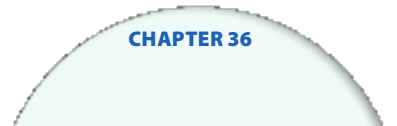
Agent and Trial	n	Patients	Treatment	Outcomes	Notes
Palbociclib					
PALOMA-1[27]	165 (1:1)	Frontline treatment for MBC (~40% w/prior chemotx, 33% w/prior endocrine tx)	Palbociclib + letrozole vs letrozole	PFS (20.2 vs 10.2 mo, HR 0.49; 95% CI 0.32–0.75); ORR (55% vs 39%); CBR (81% vs 58%)	Accelerated FDA approval in 2015 for frontline treatment
PALOMA-2[28]	666 (2:1)	Frontline treatment for MBC (~50% w/prior chemotx, 56% w/prior endocrine tx)	Palbociclib + letrozole vs letrozole	PFS (24.8 vs 14.5 mo, HR 0.58; 95% CI 0.46–0.72); ORR (55% vs 44%); CBR (85% vs 70%)	Regular FDA approval in 2017 for frontline treatment; grade 3/4 neutropenia in 66.4% on combo arm
PALOMA-3[29]	521 (2:1)	Second-line treatment for MBC after progression on prior endocrine therapy	Palbociclib + fulvestrant vs fulvestrant	PFS (9.5 vs 4.6 mo, HR 0.46; 95% CI 0.36–0.59); ORR (25% vs 11%); CBR (67% vs 40%)	FDA approval in 2016 for treatment of patients with progression on previous endocrine therapy; OS benefit seen in patients with endocrine-sensitive disease
Ribociclib					
MONALEESA-2[31,32]	668 (1:1)	Frontline treatment for MBC (~43% w/prior chemotx, 52% w/prior endocrine tx)	Ribociclib + letrozole vs letrozole	PFS (25.3 vs 16 mo, HR 0.57; 95% CI 0.46–0.7); ORR (55% vs 39%); CBR (80% vs 73%)	FDA approval in 2017 for frontline treatment; grade 3/4 neutropenia in 59.3% on combo arm; QTc prolongation in ~3% of patients on combo arm
MONALEESA-3[33,34]	726 (2:1)	Second-line treatment for MBC after progression on prior endocrine tx (and first-line for ~20% of patients with de novo metastatic disease)	Ribociclib + fulvestrant vs fulvestrant	PFS (20.5 vs 12.8 mo, HR 0.59; 95% CI 0.48–0.83); ORR (40.9% vs 28.7%); CBR (70.2% vs 62.8%); OS at 42 mo (57.8% vs 45.9%, HR 0.72; 95% CI 0.57–0.92)	Led to an additional FDA indication for the frontline or subsequent line treatment of patients with MBC with progression on prior endocrine therapy
MONALEESA-7[35,36]	672 (1:1)	Frontline endocrine treatment for pre/perimenopausal women with MBC (~40% w/ prior endocrine tx; 55% w/ prior chemotx [14% for MBC])	Ribociclib + either tamoxifen or AI vs tamoxifen or AI (all w/ goserelin)	PFS (23.8 vs 13 mo, HR 0.55; 95% CI 0.44–0.69); ORR (41% vs 30%); CBR (79% vs 70%); OS at 42 mo (70.2% vs 46%, HR 0.71; 95% CI 0.54–0.95)	Median age 44 y (vs ~60 in most other CDK4/6 inhibitor trials); QTc prolongation was more pronounced in the ribociclib + tamoxifen group, which is not an FDA-approved regimen

(*Continued*)

Table 36–1 CDK4/6 Inhibitors in HR-Positive, HER2-Negative MBC (*Cont.*)

Agent and Trial	n	Patients	Treatment	Outcomes	Notes
Abemaciclib					
MONARCH 1[39]	132 (single arm)	Patients with pretreated MBC (median 3 prior lines), all had received prior chemotx for MBC	Abemaciclib monotherapy	ORR 19.7%, median PFS 6 mo; CBR 42.4%, OS 17.7 mo	FDA approval in 2017 as monotherapy after endocrine therapy and chemotherapy in the metastatic setting
MONARCH 2[38]	669 (2:1)	Second-line treatment for MBC after progression on prior endocrine therapy	Abemaciclib + fulvestrant vs fulvestrant	PFS (16.4 vs 9.3 mo, HR 0.55; 95% CI 0.45–0.68); ORR (48.1% vs 21.3%); CBR (72.2% vs 56.1%); OS (46.7 vs 37.3 mo, HR 0.76; 95% CI.61–.95)	Regular FDA approval in 2017; grade 3/4 diarrhea in 13.4% on combo arm (more than other CDK4/6i), grade 3/4 neutropenia in 26.5% on combo arm (less than other CDK4/6i)
MONARCH 3[37]	493 (2:1)	Frontline treatment for MBC (~40% w/prior chemotx, ~47% w/prior endocrine tx)	Abemaciclib + NSAI (physician's choice) vs NSAI	PFS (28.2 vs 14.8 mo, HR 0.54; 95% CI 0.42–0.7); ORR (61% vs 45.5%); CBR (78% vs 71.5%)	FDA approval in 2018 as frontline treatment;, grade 3/4 diarrhea in 9.5%, grade 3/4 neutropenia in 21.1%

AI, aromatase inhibitor; CBR, clinical benefit rate; HR, hazard ratio; MBC, metastatic breast cancer; NSAI, nonsteroidal aromatase inhibitor; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; tx, therapy.



trial. Patients (n = 666) with HR-positive, HER2-negative MBC and postmenopausal ovarian status, were randomly assigned 2:1 to frontline treatment with palbociclib and letrozole versus letrozole alone. The primary end point was PFS. Median PFS was 24.8 months in the palbociclib-letrozole group versus 14.5 months in the placebo-letrozole group (hazard ratio 0.58; 95% CI 0.46–0.72). The most common grade 3/4 adverse events (AEs) were neutropenia in 66% of patients, other cytopenias, and fatigue.[28] Of note, neutropenia and a rare risk of interstitial lung disease (ILD) are class effects of the CDK4/6 inhibitors.

Palbociclib received expanded approval in 2016 for use in combination with fulvestrant based on results from the PALOMA-3 trial. PALOMA-3 was a double-blind, placebo-controlled, randomized phase 3 study conducted in 521 patients with HR-positive, HER2-negative MBC whose disease had progressed on prior endocrine therapy. In the adjuvant setting, patients had to have relapsed while on or within 12 months of adjuvant therapy completion. Patients were randomly assigned 2:1 to fulvestrant and palbociclib versus fulvestrant and placebo. PFS was 9.5 months in the fulvestrant-palbociclib group versus 4.6 months in the fulvestrant-placebo group (hazard ratio 0.46; 95% CI 0.36–0.59).[29] There was an OS benefit for patients with sensitivity to previous endocrine therapy only, defined as clinical benefit from at least one prior endocrine therapy in the context of metastatic disease or the receipt of at least 24 months of endocrine therapy in the adjuvant setting before recurrence. In this group, OS was 39.7 months in the fulvestrant-palbociclib group compared with 29.7 months in the fulvestrant-placebo group (hazard ratio 0.58; 95% CI 0.47–0.73). Again, neutropenia was the most common grade 3/4 AE.[30] Importantly, palbociclib is also approved for the treatment of male breast cancer patients based on postmarketing data.

Ribociclib gained FDA approval in 2017 and has two indications for treatment of patients with HR-positive, HER2-negative MBC. First, as use in combination with an AI or fulvestrant for initial endocrine therapy and, second, as use in combination with fulvestrant for subsequent-line treatment of patients whose disease progressed on prior endocrine therapy. These approvals are based on the trials MONALEESA-2, 3, and 7. MONALEESA-2 trialed ribociclib with letrozole in 668 postmenopausal women with HR-positive, HER2-negative MBC as first-line therapy versus letrozole-placebo. PFS for ribociclib-letrozole was 25.3 months versus 16 months for placebo-letrozole (hazard ratio 0.57; 95% CI 0.46–0.70), with a RR of 54.5% versus 38.8%.[31,32] MONALEESA-3 evaluated the combination of ribociclib and fulvestrant versus placebo-fulvestrant in treatment-naïve patients and in patients treated with one prior endocrine therapy for metastatic disease. Approximately 20% of patients had untreated, de novo metastatic disease, representing a group of patients that were not included in PALOMA-3. The addition of ribociclib improved both median PFS (20.5 vs 12.8 months; hazard ratio 0.59; 95% CI 0.48–0.83) and survival, with an estimated OS at 42 months of 57.8% in the ribociclib group versus 45.9% in the placebo group (hazard ratio 0.72; 95% CI 0.57–0.92). Patients with de novo metastatic disease experienced a PFS of 33.6 months with ribociclib-fulvestrant compared with 19.2 months in the placebo-fulvestrant group.[33,34]

MONALEESA-7 tested ribociclib versus placebo in combination with goserelin and either tamoxifen or a nonsteroidal AI in 672 pre/perimenopausal women with HR-positive, HER2-negative MBC. This was the first and only CDK4/6 trial to include solely pre/perimenopausal women. Patients had not received prior endocrine therapy for metastatic disease, though approximately 40% had received adjuvant endocrine therapy and 14% had received chemotherapy for metastatic disease. Significant improvements in PFS and OS were observed with the addition of ribociclib.[35,36] Side effects of ribociclib are similar to palbociclib (neutropenia, other cytopenias, fatigue, nausea); however, ribociclib carries a warning for QT prolongation and requires routine electrocardiographic monitoring. Because tamoxifen was found to further prolong the QT interval, ribociclib is not approved in combination with tamoxifen.

Finally, for the CDK4/6 inhibitors, abemaciclib is the third approved agent with indications similar to palbociclib, with one important exception: abemaciclib is also approved as monotherapy for patients with HR-positive, HER2-negative MBC after disease progression on prior endocrine or chemotherapy. Approval was based on the MONARCH-1, 2, and 3 clinical trials. MONARCH 3 evaluated the combination of abemaciclib and a nonsteroidal AI (physician's choice) versus a nonsteroidal AI alone as frontline therapy for postmenopausal women with HR-positive, HER2-negative MBC. PFS was 28.2 months for the combination arm versus 14.8 months for AI monotherapy (hazard ratio 0.54; 95% CI 0.42–0.7).[37] Of note, the hazard ratios in PALOMA-2, MONALEESA-2, and MONARCH-3 are remarkably similar, suggesting comparable efficacy among the kinase inhibitors and a consistent benefit from the class. MONARCH-2 evaluated abemaciclib in combination with fulvestrant versus fulvestrant alone (2:1) in patients with disease that had progressed on one prior endocrine therapy. In the 669 women enrolled, PFS was 16.4 months versus 9.3 months (hazard ratio 0.55; 95% CI 0.45–0.68) and OS was improved by about 9.5 months.[38] Importantly, neutropenia occurred at one-third the rate seen with either palbociclib or ribociclib despite continuous dosing of abemaciclib. However, grade 3/4 diarrhea was

far more common with abemaciclib (9.5%) than with the other kinase inhibitors.

MONARCH-1 was a phase 2 trial with a unique design, focused on patients who had received multiple lines of prior therapy in the metastatic setting (median = 3). All patients had received previous endocrine and chemotherapy, including at least one line of chemotherapy for metastatic disease. Patients with prior CDK4/6 treatment were excluded. Patients (n = 132) were treated with abemaciclib monotherapy and the RR was 19.7% with a median PFS of 6 months, supporting its activity as a single agent.[39]

In practice, all three CDK4/6 inhibitors are used, and the agent is selected based on patient/physician preference, frequency of monitoring, ease of dose adjustment, patient comorbidities, and side effects. As of this writing, there are insufficient data to support continuing a CDK4/6 inhibitor after progression on a CDK4/6 inhibitor-containing regimen, either alone or in combination therapy, although this remains an active area of investigation.

Endocrine Therapy

Endocrine therapy has dramatically improved outcomes for patients with HR-positive breast cancer. Not only does endocrine therapy prolong survival, but the medicines can also palliate symptoms and improve quality of life. Manipulation of the endocrine system as a treatment for MBC was introduced in 1896, when Beatson demonstrated objective regression of breast cancer after oophorectomy. Today, a number of endocrine therapies are used in patients with hormone-sensitive MBC that reduce the synthesis of estrogen or block or downregulate ERs in hormone-dependent tumors.

Patients whose tumors express both estrogen and progesterone receptors have a 50% to 70% chance of clinical benefit from endocrine therapy, whereas patients with either ER- or PR-positive disease have around a 30% chance of benefit from endocrine therapy.[40] Importantly, patients with MBC who responded to prior endocrine therapy have a 30% to 50% chance of clinical benefit from a second hormonal regimen. Higher RRs to endocrine therapy are generally seen in patients with MBC with low-volume disease, bone-only disease, and good performance status. Importantly, though, patients with visceral metastases comprised more than half of patients accrued to the CDK4/6 trials and received substantial clinical benefit from combination endocrine therapy and kinase inhibition. The duration of first response with endocrine therapy alone is about 9 to 12 months, similar to that with chemotherapy. The selection of endocrine therapy depends on the menopausal status of the patient. Tamoxifen can be used regardless of menopausal status, whereas AIs and fulvestrant require ovarian suppression/ablation in pre/perimenopausal women. The side effect profile also guides use because the agents are similarly effective.[41] A substantial minority of patients with HR-positive MBC benefit from sequential, single-agent endocrine monotherapy, though this clinical situation is becoming rarer owing to CDK4/6 inhibitor use. Some patients benefit from 3 to 4 lines of endocrine therapy, and a subset will respond for many years. In addition, for patients whose tumors are unusually sensitive to endocrine therapy, repeat treatment with a previously effective agent may offer benefit if a long interval has elapsed since discontinuation.

Several types of endocrine therapy are used in MBC. These include ovarian ablation (oophorectomy, ovarian radiation) or functional suppression (LHRH agonists), tamoxifen, nonsteroidal and steroidal AIs, fulvestrant, progestins, androgens, and estrogens. For premenopausal women with HR-positive MBC, ovarian ablation/suppression is a critical and longitudinal part of endocrine therapy. Medical ovarian suppression is achieved with LHRH agonists, though many patients elect for laparoscopic surgical oophorectomy to eliminate the need for frequent injections. In postmenopausal women, the ovaries are naturally suppressed. There is no indication for adrenalectomy or hypophysectomy in MBC.

Tamoxifen, a selective estrogen receptor modulator (SERM) that competitively binds to estrogen receptors, was first approved to treat advanced breast cancer in postmenopausal women in 1977 and is still widely used, particularly in the adjuvant setting. Toremifene is another SERM that was approved in 1997 for the treatment of HR-positive MBC. In MBC, both AIs and fulvestrant have proven slightly more effective than tamoxifen, and because tamoxifen is not approved with CDK4/6 inhibition, it is often reserved for later lines of treatment or for patients with intolerable side effects on other endocrine treatments. An early publication of tamoxifen use in 46 postmenopausal women with advanced breast cancer showed near equivalence with androgens and estrogens, which were the standard treatments at the time.[42] In a meta-analysis of four randomized trials of LHRH agonists versus LHRH agonists plus tamoxifen in premenopausal patients with MBC, there was a significant PFS (hazard ratio 0.7) and OS (hazard ratio 0.78) benefit in favor of the combination treatment.[43]

The third-generation AIs that are currently in practice were approved in the mid-1990s. AIs inhibit the aromatase enzyme system, which is responsible for catalyzing the final step in the conversion of androgens to estrogens in ovarian and peripheral tissues and in breast tumors. AIs do not completely block ovarian estrogen production in premenopausal women, and the use of an AI in young patients can cause a reflexive

increase in gonadotropin levels and resultant ovarian hyperstimulation. For this reason, AIs are used in pre/perimenopausal women only in combination with ovarian ablation/suppression.

Anastrozole was compared with tamoxifen as first-line therapy in 353 postmenopausal patients with MBC in a 1:1 randomized, double-blind study. RRs for anastrozole and tamoxifen were 21% and 17%, respectively. Time to progression (TTP) was 11.1 months for anastrozole compared with 5.6 months for tamoxifen.[44,45] Letrozole, the other commonly used nonsteroidal AI, was also compared with tamoxifen as first-line treatment in 916 postmenopausal patients with MBC and showed improved RR (32% vs 21%) and improved PFS (9.4 vs 6 months).[46] Finally, exemestane is the only approved steroidal AI and is indicated for treatment of MBC after progression on tamoxifen. A randomized, phase 3 clinical trial compared exemestane with tamoxifen in the first-line treatment of 371 postmenopausal women with MBC. Patients treated with exemestane had improved RR (46% vs 31%) and early PFS (9.9 vs 5.8 months), though there was no long-term PFS or survival benefit.[47] In practice, the AIs demonstrate similar efficacy, and large meta-analyses have supported their near equivalence. Letrozole and anastrozole are used interchangeably in combination with CDK4/6 inhibitors. Exemestane was previously felt to offer significant benefit after progression on a nonsteroidal AI; however, a large, randomized trial showed little benefit from exemestane monotherapy post–nonsteroidal AI, though it did demonstrate a benefit in combination with everolimus (discussed below).[48]

Fulvestrant is a selective estrogen receptor downregulator (SERD) that binds and downregulates estrogen receptors on tumor and other cells and has no agonist effects. Fulvestrant gained initial FDA approval in 2002 and is approved as monotherapy in first- or subsequent-line treatment (after prior endocrine therapy) of patients with HR-positive MBC. It is also approved in combination with CDK4/6 inhibitors and the PIK3CA inhibitor, alpelisib (discussed below). The CONFIRM trial tested fulvestrant at doses of 500 mg versus 250 mg in 736 postmenopausal women with ER-positive MBC who had progressed after prior endocrine therapy. Both PFS (6.5 vs 5.5 months) and OS (26.4 vs 22.3 months) were longer with the 500-mg dose.[49] The FALCON trial compared fulvestrant (500 mg) with anastrozole in a phase 3, 1:1 randomized trial of 462 postmenopausal women with HR-positive MBC who had not received prior endocrine therapy. The clinical benefit rate was similar between the two arms; however, PFS was significantly longer in the fulvestrant arm compared with the anastrozole arm (16.6 vs 13.8 months; hazard ratio 0.80 ;95% CI 0.64–0.999). Survival data remain immature. Combination fulvestrant and anastrozole is also an acceptable first-line treatment for patients with de novo MBC who are naïve to endocrine therapy based on the phase 3 SWOG S0226 trial.[50] Fulvestrant is also effective in combination with several targeted agents in subsequent-line therapy, which is discussed below. In practice, fulvestrant is usually reserved for second or later lines of therapy because of the inconvenience and discomfort associated with monthly injections in both gluteal muscles.

Endocrine therapy causes fewer side effects than cytotoxic chemotherapy and remains the standard backbone in clinical trials of new agents for HR-positive MBC. However, there are several unique complications and side effects of endocrine therapy. SERMs and estrogens (but not AIs or fulvestrant) can cause flare, which is defined clinically by an abrupt, diffuse onset of musculoskeletal pain and/or increased size or erythema of skin lesions within the first month of endocrine therapy. Flare can also worsen the appearance of bone lesions on bone scan, which can complicate the assessment of response to endocrine therapy. The most serious manifestation of flare is hypercalcemia, which can occur in patients with bone metastases, and manifests within the first two weeks of starting therapy. The underlying mechanism is the predominating early agonist effect of SERMs and estrogens. Low-dose prednisone (10–30 mg/day) can abrogate the initial flare-related bone pain.

Other side effects of endocrine therapy include hot flashes and mood disturbances, which are related to estrogen deprivation and are common with tamoxifen, AIs, and fulvestrant. These side effects are most pronounced in young women who begin ovarian suppression, an abrupt and early menopause. Tamoxifen has estrogenic effects that are beneficial in some tissues—it lowers serum cholesterol and protects against bone loss and cardiovascular disease, but tamoxifen is also associated with an increased risk of endometrial cancer and thromboembolic events. Randomized trials of tamoxifen do not support an association with weight gain. Common side effects of the AIs include arthralgia, myalgia, and bone density loss.

Older endocrine therapies that are not commonly used in current practice include progestins, androgens, and estrogens. These agents are typically reserved for patients who have progressed on all other endocrine therapies and who are not candidates for either targeted therapy or chemotherapy. Progestins are synthetic derivatives of progesterone that have a progesterone-agonist effect. Progestins such as megestrol acetate and medroxyprogesterone acetate are active in treating MBC. These drugs have anti-estrogenic properties through their disruption of the pituitary-ovarian axis. Androgens (fluoxymesterone, danazol, etc) also have efficacy in MBC, including in patients treated with multiple endocrine therapies. Before the identification of hormone receptors and the development of SERMs, high-dose estrogens were commonly used to treat MBC. Their efficacy is similar to that of

tamoxifen, although high-dose estrogens (DES, ethinyl estradiol, etc) are associated with more severe side effects including nausea/vomiting, fluid retention, congestive heart failure, and thromboembolic disease.

At MDACC, our preferred first-line endocrine therapy for patients with HR-positive MBC is a CDK4/6 inhibitor combined with an AI (and a bone-targeting agent in the case of bone metastasis). For patients whose disease recurs while on an adjuvant AI or within 12 months of discontinuing an AI, we typically use a CDK4/6 inhibitor in combination with fulvestrant. The choice of treatment after progression on initial endocrine therapy and a CDK4/6 inhibitor is more nuanced and depends on several factors, including the duration of response to initial endocrine therapy, disease burden, performance status, comorbidities, and *PIK3CA* mutation status (see below). In general, for patients with a reasonable response to initial endocrine therapy in the metastatic setting, we continue endocrine therapy and change the endocrine therapy agent (eg, AI to fulvestrant). Patients who respond to initial endocrine therapy have a higher probability of response to second-line endocrine therapies. In cases where endocrine therapy agents (with or without targeted agents, see below) have been exhausted or there is rapid progression, we initiate single-agent chemotherapy. At MDACC, we also consider available clinical trials. The treatment algorithm used for treating patients with HR-positive MBC at MDACC is illustrated Fig. 36–1.

Intrinsic (de novo) resistance to endocrine therapy is an unfortunate reality for a subset of patients with HR-positive MBC and eventual acquired resistance to endocrine therapies is universal. There are multiple genetic and epigenetic mechanisms that underlie endocrine resistance, a subject that remains an intense area of investigation in breast cancer.[51–53] Fortunately, some of these mechanisms are targetable in the clinic, and we will discuss these approaches below.

Targeted Therapy

mTOR inhibition

Activation of the PI3K-Akt-mTOR pathway in breast cancer has been implicated as one mechanism of resistance to endocrine therapy. Everolimus is an inhibitor of mammalian target of rapamycin (mTOR) and was approved in 2012 in combination with exemestane for the treatment of HR-positive MBC after progression on nonsteroidal AI monotherapy. Everolimus in combination with either fulvestrant or tamoxifen has also proven effective, and these regimens are reasonable considerations after progression on an AI (Table 36–2).

Table 36–2 Summary of Targeted Therapies for MBC

Class and Agent	Disease Subtype	References from Text	Class and Agent	Disease Subtype	References from Text
CDK4/6 Inhibitors (see Table 36–1)			**Tyrosine Kinase Knhibitors**		
Palbociclib	HR+/HER2- negative MBC	See Table 36–1	Lapatinib	HER2-positive MBC	121–125, 129, 130
Ribociclib			Neratinib		
Abemaciclib			Tucatinib		
PARP Inhibitors			**Antibodies**		
Olaparib	Hereditary *BRCA1* or *BRCA2* mutations	56, 57	Trastuzumab	HER2-positive MBC	111–117
Talazoparib			Pertuzumab		
mTOR Inhibitor			**Antibody-Drug Conjugates**		
Everolimus	HR+/HER2- MBC	48, 54, 55	T-DM1	HER2-positive MBC	118, 119
PI3K Inhibitor			Trastuzumab Derutxtecan		122, 183
Alpelisib	HR+/HER2 MBC; w/an activating *PIK3CA* mutation	14	Sacituzumab govitecan-hziy	TNBC	159
			Checkpoint Inhibitor		
			Atezolizumab	TNBC	8, 157

Approval of combination everolimus and exemestane was based on the BOLERO-2 study, a randomized, phase 3 trial that assigned 724 patients with HR-positive MBC with recurrence or progression on a prior nonsteroidal AI, to receive exemestane alone or exemestane plus everolimus.[48] The combination resulted in improved PFS (10.6 vs 4.1 months; hazard ratio 0.36; 95% CI 0.27–0.47) but not improved OS. Common AEs of everolimus included stomatitis, infections, rash, fatigue, diarrhea, reduced appetite, and a 3% risk of pneumonitis.

The combination of everolimus and fulvestrant was trialed in a similar context, MBC patients with progression on prior AI therapy, in the phase 2 PrE0102 study. Patients (n = 131) were randomly assigned to receive fulvestrant (500 mg) versus everolimus and fulvestrant. Again, the combination demonstrated superior PFS (10.3 vs 5.1 months; hazard ratio 0.61; 95% CI 0.4–0.92).[54] Finally, the combination of tamoxifen and everolimus versus tamoxifen alone also showed benefit in patients with MBC with AI resistance. In a phase 2, open-label trial of 111 postmenopausal women, TTP was 8.6 months with tamoxifen-everolimus versus 4.5 months with tamoxifen alone (hazard ratio 0.54; 95% CI 0.36–0.81).[55]

Importantly, these trials were all conducted before the widespread use of CDK4/6 inhibitors and so their efficacy in breast cancer patients exposed to these agents is less certain. There are no data to support the use of everolimus after progression on an everolimus-containing regimen.

PI3K Inhibition

Approximately 40% of patients with HR-positive breast cancer have mutations in the gene *PIK3CA*, which encodes the alpha isoform (p110α) of phosphatidylinositol 3-kinase (PI3K). PI3K plays a critical role in breast tumor cell growth, and endocrine therapy is thought to select for *PIK3CA* activating mutations, conferring endocrine resistance. To test this hypothesis, the SOLAR-1 study evaluated the combination of fulvestrant and the PI3Kα inhibitor alpelisib versus fulvestrant alone in patients with HR-positive MBC who had received prior AI therapy. Two cohorts were enrolled and were stratified by the presence or absence of *PIK3CA* mutations in tumor tissue. In 2019, the FDA approved alpelisib based on a demonstrated PFS benefit for the 341 patients with *PIK3CA* mutations (11 months in the fulvestrant-alpelisib arm vs 5.7 months for fulvestrant alone; hazard ratio 0.65; 95% CI 0.5–0.85).[14] Of note, alpelisib did not significantly affect PFS in patients without *PIK3CA* activating mutations. A companion diagnostic was also approved to test for activating *PIK3CA* mutations in the plasma or tumor tissue, preferably obtained at the time of progression. Unfortunately, grade 3/4 hyperglycemia and rash were common, occurring in 36.6% and 9.9% of patients, respectively, and accounted for a 25% rate of discontinuation of the combination therapy. Importantly, only about 6% (n = 20 with a mutation) of patients in SOLAR-1 had received prior CDK4/6 inhibition and so the efficacy of alpelisib in patients with disease progressing on CDK4/6 agents is uncertain. The adoption of this regimen at our center and in the community will depend on the ease of managing its frequent toxicity.

Poly (ADP-Ribose) Polymerase Inhibition

Germline mutations in *BRCA1* and *BRCA2* (*gBRCA*) are present in 5% of breast cancer patients and account for 40% of hereditary breast cancer diagnoses. Poly (ADP-ribose) polymerase (PARP) inhibitors are particularly effective in patients with *gBRCA* because of the concept of synthetic lethality. PARP inhibitors prevent the repair of DNA single-strand breaks and, in BRCA1/2-deficient tumors that harbor an endogenous impairment in DNA double-strand break repair, this results in tumor cell death.

In 2018, the FDA approved the PARP inhibitors olaparib and talazoparib for the treatment of HER2-negative, *gBRCA*-associated MBC. The olaparib indication requires exposure to previous chemo- and endocrine therapy, whereas talazoparib does not. Talazoparib was approved based on the phase 3 EMBRACA trial, which randomly assigned (2:1) 431 patients with HER2-negative MBC to talazoparib monotherapy versus physician's choice chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine). PFS was superior in the talazoparib arm (8.6 vs 5.6 months; hazard ratio 0.54; 95% CI 0.41–0.71). Impressively, the RR was also higher for talazoparib (62.6% vs 27.2%) as were patient-reported outcomes.[56] OLYMPIAD trialed (2:1) olaparib versus physician's choice chemotherapy (capecitabine, eribulin, or vinorelbine) in 302 *gBRCA* patients with HER2-negative MBC. Despite the majority of patients having received previous chemotherapy for metastatic disease, the PARP inhibitor again proved superior in terms of PFS (7 vs 4.2 months; hazard ratio 0.58; 95% CI 0.43–0.8) and RR (59.9% vs 28.8%).[57] The common side effects of PARP inhibitors include hematologic toxicity—primarily macrocytic anemia but also thrombocytopenia and neutropenia/leukopenia—as well as nausea and fatigue. Multiple clinical trials are underway that combine PARP inhibitors with other agents, including immunotherapies, in an effort to improve response duration.

Chemotherapy

In HR-positive MBC, chemotherapy is reserved for patients with endocrine resistance or for patients in

visceral crisis.[58] In TNBC and HER2-positive MBC, chemotherapy is used in the first line (discussed below).

There is no standard sequence for chemotherapy in HR-positive MBC. Consideration is given to previous therapies and response, comorbidities, organ function, dosing and monitoring frequency, and patient preference regarding side effects (eg, alopecia, neuropathy). In general, choosing successive agents from different mechanistic classes is preferable (Table 36–3). Many patients have received anthracyclines and taxanes in the early breast cancer setting, in which case they are reserved for later therapy lines, particularly if recurrence was within a few years of treatment.

The choice between sequential single-agent chemotherapy and combination chemotherapy is controversial. The principle of nonoverlapping mechanisms of action and resistance provides a rationale for combination chemotherapy. However, numerous randomized trials have evaluated single- versus multiagent regimens in MBC and have generally shown that combination chemotherapy achieves higher RRs and longer PFS, but OS is unchanged.[59] Combination chemotherapy is usually associated with increased toxicity, including neutropenia and nausea/vomiting. In two randomized trials of combination versus single-agent therapy in MBC, formal quality-of-life analyses favored the single-agent arms, even though RRs were slightly lower.[60,61]

At MDACC, we generally reserve combination chemotherapy for patients with visceral crisis and for fit patients with rapid progression or symptomatic, large-volume disease. MBC is unfortunately incurable, and single-agent chemotherapy is best suited to the goal of prolonging survival without compromising quality of life. This is in agreement with consensus recommendations from several oncologic societies.[62] Ultimately, the choice of sequential versus combination chemotherapy depends on a careful evaluation of the risks and benefits for each patient. One additional potential indication for combination therapy is oligometastatic disease before consolidation with surgery or radiation.

Several studies have compared continuous chemotherapy with intermittent therapy in MBC. One systematic review and meta-analysis of these data showed a statistically significant improvement in OS for patients receiving first-line chemotherapy for a preplanned longer versus shorter duration.[63] A European trial randomly assigned patients with MBC to intermittent (two sets of four cycles) versus continuous first- or second-line chemotherapy and found that the continuous schedule was better in terms of efficacy and quality of life.[64,65] Some chemotherapies, including anthracyclines, have inherent dose-limiting toxicities that prohibit prolonged use. Other agents, such as capecitabine, lend themselves to extended therapy. Most clinical trials are designed to treat patients until there is progression of disease or limiting toxicities. The practice at MDACC is to treat patients with MBC with continuous chemotherapy unless unacceptable toxicity arises and/or Eastern Cooperative Oncology Group performance status declines to 3 or higher. Within this framework, though, we are mindful of the importance of treatment breaks, including for significant life events.

Table 36–3 Chemotherapy Options for MBC

Class and Agent	References From Text			References From Text
Anthracyclines		**Platinum Salts**		
Doxorubicin	66–69	Carboplatin		101–103, 135, 174
Liposomal doxorubicin	71	Cisplatin		167, 168, 175
Taxanes		**Alkylating agent**		
Paclitaxel	72,73	Cyclophosphamide		80, 95
Docetaxel	74–76	**Combination Chemotherapy regimens**		
Nab-paclitaxel	77,78	Doxorubicin/cyclophosphamide (AC)		95, 96
Antimetabolites		Doxcetaxel/capecitabine		99
Capecitabine	79–82	Gemcitabine/paclitaxel		100
Gemcitabine	83–85	Carboplatin/paclitaxel		101–103
Non-taxane micotubule inhibitors		Gemcitabine/carboplatin		164
Eribulin	86–88	Capecitabine/methotrexate/fluorouracil (CMF)		80
Vinorelbine	89–91	Capecitabine/ixabepilone		106, 107
Ixabepilone	92–94	gemcitabine/capecitabine		109

Single-Agent Chemotherapy

Anthracyclines

The introduction of anthracyclines (doxorubicin and epirubicin) in the 1970s was a significant advance in treating MBC. Anthracyclines work by intercalating DNA and inhibiting topoisomerase II, inhibiting DNA repair. RRs to single-agent doxorubicin (25–75 mg/m^2 every 3 weeks) range from 25% to 50% for MBC and are heavily influenced by patient characteristics such as prior chemotherapy exposure, performance status, and extent and sites of disease.[66–69] At MDACC, doxorubicin-containing regimens are the initial chemotherapy of choice for patients with MBC with good cardiac function who have not received a prior anthracycline. Patients treated with a prior anthracycline occasionally benefit from repeat administration of doxorubicin (or liposomal doxorubicin) in later lines of therapy. However, given the increasing number of active agents in MBC, repeat anthracycline therapy should be reserved for patients in whom other treatments have failed, given the potential risk of heart failure.

Epirubicin is a doxorubicin analog that was shown to have similar efficacy and slightly less toxicity than doxorubicin at equimolar doses. A formal comparison of two different anthracyclines in combination regimens (FAC versus FEC) at equimolar doses found both regimens to be equally effective in terms of RR, TTP, and survival. The FEC regimen was associated with fewer gastrointestinal, hematologic, and cardiac toxicities.[70]

Efforts to improve the safety profile of doxorubicin led to the development of liposomal doxorubicin. In a phase 3 clinical trial, the efficacy and safety of pegylated liposomal doxorubicin was compared with that of conventional doxorubicin as first-line cytotoxic therapy in patients with MBC.[71] A total of 509 patients received pegylated liposomal doxorubicin (50 mg/m^2 once every 4 weeks) or conventional doxorubicin (60 mg/m^2 once every 3 weeks). The median PFS and OS were similar in both groups (6.9 vs 7.8 months and 20.1 vs 22.0 months, respectively). The incidence of alopecia, myelosuppression, and nausea/vomiting were lower with pegylated liposomal doxorubicin compared with conventional doxorubicin. Importantly, pegylated liposomal doxorubicin was associated with a significantly lower incidence of cardiotoxicity, even at higher cumulative doses (hazard ratio 3.16; 95% CI 1.58–6.31, $P < .001$).[71] One important dose-limiting toxicity of pegylated liposomal doxorubicin is palmar-plantar erythrodysesthesia (hand-foot syndrome), which is both dose- and duration-related. As with all liposomal drug delivery systems, there is a low incidence of hypersensitivity reactions.

Taxanes

Taxanes (paclitaxel, docetaxel, and nanoparticle albumin–bound paclitaxel [nab-paclitaxel]) are among the most active classes of cytotoxic drugs in breast cancer treatment. Taxanes stabilize microtubules during the mitotic phase, preventing cell division. They rival the anthracyclines in terms of RR and response duration. Taxanes are frequently used as first-line cytotoxic therapy in chemotherapy-naïve patients with MBC or as second-line chemotherapy after anthracyclines.

In the Intergroup E1193 study, similar RRs (36% for doxorubicin vs 34% for paclitaxel) and TTP (5.8 vs 6 months) were observed using either doxorubicin (60 mg/m^2 every 3 weeks) or paclitaxel (175 mg/m^2 every 3 weeks).[72] A meta-analysis compared paclitaxel 80 mg/m^2 given weekly with paclitaxel 175 mg/m^2 given every 3 weeks and found that weekly dosing resulted in better OS and a lower incidence of AEs, though the RR was slightly better for the every 3-week dosing schedule.[73] At MDACC, the most popular taxane regimen for MBC is weekly paclitaxel 80 mg/m,^{2} very commonly in a 3-weeks-on/1-week off or 2-weeks-on/1-week-off schedule.

Docetaxel is a semisynthetic taxane with several pharmacologic differences from paclitaxel. It is associated with a 37% to 57% RR in patients with anthracycline-resistant breast tumors and was initially FDA-approved for this indication at a dose of 60–100 mg/m^2 every 3 weeks. At these doses, hematologic toxicity is common, and the rates of neutropenia are similar to those observed with paclitaxel given every 3 weeks. In one clinical trial that aimed to establish the optimal docetaxel dose, 527 patients were randomly assigned to receive docetaxel 60, 75, or 100 mg/m^2 every 3 weeks. A positive relationship between increasing dose of docetaxel and RR was observed, but at the expense of greater toxicity.[74] One phase 3 trial of 449 patients with MBC directly compared docetaxel 100 mg/m2 every 3 weeks with paclitaxel 175 mg/m2 every 3 weeks. All patients had progressed after prior anthracycline-based chemotherapy. Docetaxel 100 mg/m^2 was associated with longer TTP (hazard ratio 1.64; 95% CI 1.33–2.02) and improved OS (hazard ratio 1.64; 95% CI 1.33–2.02) versus every-3-week paclitaxel, but also resulted in a greater incidence of treatment-related toxicity.[75] The most commonly used single-agent taxane regimens, paclitaxel 80 mg/m^2 weekly and docetaxel 75 mg/m^2 every 3 weeks, have not been directly compared. In patients who have received prior paclitaxel chemotherapy, subsequent treatment with docetaxel achieved RRs of 18% to 21%, demonstrating a partial lack of cross-resistance between the two agents.[76] Docetaxel administered every 3 weeks at doses between 75 and 100 mg/m^2 is an appropriate choice as first-line therapy for MBC; in most cases at MDACC, we use 75 mg/m.^{2} Moderate nail changes, cumulative neuropathy, and fatigue are commonly seen with paclitaxel and docetaxel treatment. Diarrhea, stomatitis, and

neutropenia are more common with docetaxel compared with weekly paclitaxel. There is the potential for fluid retention in patients who receive docetaxel at a cumulative dose greater than 300 mg/m^2, though premedication with steroids can mitigate this side effect. At MDACC, we routinely prescribe dexamethasone 4 mg orally twice daily for 3 days, beginning the day before starting docetaxel.

The last commonly used taxane is nab-paclitaxel, a nanoparticle albumin–bound formulation of paclitaxel. In several comparisons, nab-paclitaxel has proven as effective, and, in some cases, more effective than the other taxanes.[77,78] One distinct advantage of nab-paclitaxel over paclitaxel is that it does not require cremophor for solubility, and accordingly, nab-paclitaxel is associated with a much lower risk of hypersensitivity reactions. In a phase 3 study, 454 patients with MBC were randomly assigned to 3-week cycles of nab-paclitaxel 260 mg/m^2 or paclitaxel 175 mg/m.^{2} Nab-paclitaxel demonstrated significantly higher RRs compared with paclitaxel (33% vs 19%) and longer TTP (23.0 vs 16.9 weeks). Grade 3 sensory neuropathy was more common with nab-paclitaxel, the incidence of grade 4 neutropenia was significantly lower with nab-paclitaxel, and the rate of febrile neutropenia was similar in both groups.[78] A phase 2, four-arm study compared nab-paclitaxel (300 mg/m^2 every 3 weeks, 150 mg/m^2 weekly, or 100 mg/m^2 weekly) and docetaxel (100 mg/m^2 every 3 weeks). Weekly nab-paclitaxel at 150 mg/m^2 demonstrated longer PFS than docetaxel (12.9 vs 7.5 months). Grade 3/4 fatigue, neutropenia, and febrile neutropenia were less frequent in the nab-paclitaxel arms, but the rate and severity of peripheral neuropathy were similar across all groups.[77] At MDACC, nab-paclitaxel is frequently used as first- or second-line therapy administered in a weekly schedule (100 mg/m^2, typically 3 weeks on/1 week off), and it is the taxane of choice for patients with contraindications to steroid use. Nab-paclitaxel can be trialed in patients with hypersensitivity to either paclitaxel or docetaxel.

Antimetabolites

Capecitabine. Capecitabine is an oral fluoropyrimidine approved by the FDA in 1998 as single-agent therapy for the treatment of MBC resistant to anthracyclines and taxanes. In September 2001, capecitabine received an additional indication for use in combination with docetaxel in patients with MBC previously treated with an anthracycline. The first phase 2 study of capecitabine in MBC included 162 patients who had received prior treatment with paclitaxel for metastatic disease. Most patients had also received a prior anthracycline. Capecitabine was administered at 2510 mg/m^2 per day in two divided doses for 2 weeks on/1 week off. The RR was 20%, the median TTP was 93 days, the median duration of response was 8.1 months, and the median OS was 12.8 months.[79] In a separate phase 2 trial, O'Shaughnessy and colleagues randomly assigned (2:1) patients with MBC who had not received any prior cytotoxic therapy for metastatic disease to receive capecitabine or IV cyclophosphamide, methotrexate, and 5-fluorouracil (CMF). The trial was designed to accrue older patients in an effort to avoid anthracycline-related toxicity and the median age was 69 years. Capecitabine achieved an overall RR of 30% versus 16% for CMF; no differences in TTP (4.1 vs 3 months) or OS (19.6 vs 17.2 months) were seen. Similar levels of nausea, vomiting, and stomatitis were observed in both groups. More cases of grade 3/4 diarrhea (8%), fatigue (5%), and hand-foot syndrome (15%) were noted with capecitabine. In the capecitabine group, 34% of patients required treatment interruption and/or dose modification and 10 (16%) patients discontinued the medicine as a result of AEs.[80]

The FDA-approved dose and schedule for capecitabine are 2500 mg/m^2 per day given orally in two divided doses for 14 days, followed by one week of rest. Retrospective studies suggest that a lower starting dose (2000 mg/day) or a week on/week off schedule are better tolerated, with fewer dose reductions and preserved efficacy.[81,82] At MDACC, capecitabine is often used as first-line cytotoxic therapy for patients previously treated with anthracyclines and/or taxanes in the adjuvant or neoadjuvant setting, though there are several additional options. We prefer to start at 1800–2000 mg/m^2 per day (divided twice daily) for 2 weeks on/1 week off, but tolerance, patient age, and comorbidities (such as concomitant renal disease) factor importantly in each patient's dosing schedule.

Gemcitabine. Gemcitabine, a nucleoside analog, was approved in combination with paclitaxel by the FDA in April 2004 for the treatment of MBC. Gemcitabine is phosphorylated intracellularly to gemcitabine diphosphate and gemcitabine triphosphate, which are both active cytotoxins. The taxane combination regimen is discussed below; however, several small phase 2 trials of gemcitabine monotherapy were also conducted in patients with MBC. Single-agent RRs range from 14% to 37%.[83–85] The differing RRs are attributable to differences in dosing (800–1200 mg/m^2 in the referenced trials) and the extent of prior treatment. In general, chemotherapy-naïve patients tolerate doses of 800–1200 mg/m^2 per week on days 1, 8, and 15 every 28 days. Dose reductions and/or omission of the day 15 dose are frequently necessary to prevent cycle delays. Pretreated patients may require further dose reductions to limit thrombocytopenia and neutropenia. There is also a small risk of hemolytic uremic syndrome and pulmonary toxicity. As alluded to above, gemcitabine has been investigated in many doublet and triplet combinations. At MDACC, gemcitabine

is rarely used as monotherapy for first-line cytotoxic therapy in patients with HR-positive MBC because of its modest activity; however, it is a useful drug in patients with renal or hepatic impairment or in later lines of treatment.

Non-Taxane Microtubule Inhibitors

Eribulin. Eribulin mesylate is a non-taxane inhibitor of microtubule dynamics that works by inhibiting microtubule growth. Eribulin was approved for patients with MBC in 2011 based on the registration trial, EMBRACE. In this phase 3, open-label, randomized study, 762 patients who had received a median of four previous chemotherapy regimens were randomly assigned (2:1) to either eribulin 1.4 mg/m^2 on days 1 and 8 every 21 days versus physician's choice chemotherapy (primarily vinorelbine, gemcitabine, or capecitabine). Patients treated with eribulin had improved OS (13.1 vs 10.6 months; hazard ratio 0.81; 95% CI 0.66–0.99). Median PFS was 3.7 months with eribulin and the RR was 12% by independent review. Asthenia, fatigue, and neutropenia were the most common side effects associated with eribulin, and peripheral neuropathy led to discontinuation of treatment in 5% of patients in the eribulin arm.[86]

A phase 2 study then evaluated the efficacy of eribulin in the treatment of HER2-negative MBC in the first-line setting.[87] Fifty-six patients were treated, the majority having received anthracycline and/or taxane-containing chemotherapy in the adjuvant setting. The RR was 29%, the clinical benefit rate was 52%, and the median PFS was 6.8 months.

Finally, a second phase 3 randomized trial directly compared eribulin with capecitabine in patients with MBC who had previously received a taxane and an anthracycline. A total of 1102 patients were randomly assigned (1:1) to eribulin or capecitabine as first-, second-, or third-line cytotoxic therapy for MBC. Median OS was 15.9 months for eribulin versus 14.5 months for capecitabine (hazard ratio 0.88; 95% CI 0.77–1.00; P = .056), and PFS was similar at 4.1 vs 4.2 months; RR was 11% for eribulin and 11.5% for capecitabine.[88] Based on the evidence, MDACC oncologists use either eribulin or capecitabine for patients with HR-positive MBC who have received prior taxane and/or anthracycline treatment. Capecitabine is convenient as an oral regimen, though eribulin is also well tolerated and is infused over only 5 minutes. Capecitabine causes less alopecia.

Vinorelbine. Vinorelbine is a semisynthetic vinca alkaloid that interferes with microtubule assembly and is active in the treatment of MBC. Vinblastine and vincristine are other agents in the vinca alkaloid class that are widely used in other tumor types. Vinorelbine was FDA-approved in 1994 for the treatment of lung cancer. In an early phase 2 trial, 183 patients with MBC and prior anthracycline exposure were randomly assigned (2:1) to weekly vinorelbine 30 mg/m^2 versus melphalan. Vinorelbine demonstrated a 16% RR and time to treatment failure was significantly longer with vinorelbine than melphalan (12 vs 8 weeks).[89] A separate phase 2 trial evaluated vinorelbine 35 mg/m^2 weekly (with growth factor support) in patients with MBC treated with a prior anthracycline and taxane and reported a RR of 25% and TTP of 13 weeks. The dose-limiting toxicity was neutropenia despite growth factor support.

Vinorelbine has also been evaluated as first-line cytotoxic therapy in the metastatic setting. One-hundred fifty-seven patients with MBC, many with visceral disease, were treated with weekly vinorelbine 30 mg/m^2. The trial reported a RR of 41% and time to treatment failure of 6 months. Grade 3/4 neutropenia occurred in 72% of patients.[90] Finally, vinorelbine has been evaluated in multiple combinations. A phase 3 trial randomized 252 patients with MBC to either vinorelbine monotherapy 30 mg/m^2 on days 1 and 8 every 21 days versus combination vinorelbine and gemcitabine. All patients had received prior anthracycline and taxane chemotherapy and 75% of patients had visceral disease. RR (36% vs 26%) and PFS (6 vs 4 months; hazard ratio 0.66; 95% CI 0.5–0.88) were significantly improved with the combination; however, OS was similar between arms (15.9 vs 16.4 months). Hematologic toxicity was more significant in patients treated with the combination regimen.[91] Vinorelbine carries a black box warning for myelosuppression. Other adverse effects include neuropathy, flu-like symptoms, and gastrointestinal symptoms such as nausea and constipation. At MDACC, vinorelbine is used as third-line (or later) cytotoxic therapy for patients with MBC. We typically start vinorelbine at a dose of 25 mg/m^2 weekly on days 1, 8, and 15 of a 28-day cycle.

Ixabepilone. Ixabepilone is an epothilone B analog that stabilizes microtubules causing mitotic arrest. It was approved by the FDA in October 2007 and is approved in combination with capecitabine for patients with MBC whose disease has progressed after anthracycline and taxane treatment. Ixabepilone is also approved as monotherapy for patients with MBC who have received a prior anthracycline, taxane, and capecitabine.

Ixabepilone monotherapy was evaluated in a single-arm, phase 2 trial of 126 patients with MBC who had received a prior anthracycline, taxane, and capecitabine. Most patients (88%) had received at least two prior lines of therapy in the metastatic setting. The RR was 11.5%, the median response duration was 5.7 months, and the PFS was 3.1 months. Grade 3/4 neutropenia occurred in 54% of patients and grade 3/4 peripheral neuropathy in 14%.[92] When used as first-line cytotoxic therapy in 65 patients with MBC who had received previous adjuvant anthracycline treatment, the RR was 41.5% with a median duration of response of 8.2 months.[93] Finally, in a separate phase

2 trial, ixabepilone monotherapy was evaluated in 49 patients with MBC who had received prior anthracycline chemotherapy and who had experienced recent disease progression on taxane therapy. The trial mandated that taxanes had to be the most recent chemotherapy. In these patients, the RR was 12% with a median duration of response of 10.4 months. TTP was 2.2 months.[94] At MDACC, we sometimes use ixabepilone in patients who have received anthracyclines, taxanes, capecitabine, and, often, eribulin. Its use is more common in TNBC (see below). We typically start ixabepilone at 40 mg/m,^{2} but dose reductions to 32 mg/m^2 are common. Neuropathy is predominantly sensory-type and is largely reversible.

Combination Chemotherapy

As discussed above, sequential single-agent chemotherapy is preferred over combination chemotherapy for most patients with ER-positive MBC. Patients in visceral crisis or fit patients with rapidly progressing, endocrine-resistant disease are potential candidates for combination chemotherapy. There have been numerous trials of combination chemotherapy in MBC and an exhaustive list of these results is outside the scope of this chapter. However, we will outline the evidence for several combination therapies that we use at MDACC. We reserve anthracycline- or taxane-based combinations for patients who are naïve to these agents.

Anthracycline-Based Combination Regimens

The combination of doxorubicin and cyclophosphamide (AC) is a standard neoadjuvant/adjuvant regimen in early-stage breast cancer that remains effective in the metastatic setting for AC-naïve patients. Doxorubicin/paclitaxel was compared with standard AC as first-line chemotherapy in 275 patients with MBC in a randomized, phase 2 trial. The regimens were doxorubicin 60 mg/m^2 and paclitaxel 175 mg/m^2 every 3 weeks versus doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks for a maximum of six cycles. Median PFS was 6 months in both arms and RR was 58% for doxorubicin/paclitaxel versus 54% for AC. Neutropenic fever was more common in the doxorubicin/paclitaxel arm (32%) compared with AC (9%) and compromised doxorubicin dose delivery in that group.[95]

Standard AC chemotherapy was also compared with another taxane-based regimen, doxorubicin and docetaxel (AT) as first-line chemotherapy in 429 patients with MBC. AT (doxorubicin 50 mg/m^2 and docetaxel 75 mg/m^2 every 3 weeks) modestly improved TTP (37.3 vs 31.9 weeks; P = .014) and overall RR (59% vs 47%; P = .008) compared with AC, but there was no difference in OS. The lack of survival benefit was partially attributable to patients in the AC arm crossing over to taxane chemotherapy during subsequent lines of therapy. Neutropenic fever and other infections were more frequent for AT (33%) than AC (10%). Grade 3/4 cardiac events were similar (3% for AT vs 4% for AC).[96] Based on this evidence, we prefer AC to either doxorubicin/paclitaxel or doxorubicin/docetaxel in patients with MBC.

The use of triple-combination therapy is far rarer than doublet chemotherapy in our current practice for MBC. However, for many years at MDACC, FAC (500/50/500 mg/m^2) was the standard regimen for patients with MBC. Nabholtz et al[97,98] compared the use of docetaxel/doxorubicin/cyclophosphamide (TAC 75/50/500 mg/m^2) with FAC as first-line therapy for MBC (n = 484). The RR was 55% for TAC versus 44% for FAC (hazard ratio 1.5; 95% CI 1.1–2.2; P = .02). There was no significant difference in TTP or OS between treatment arms. Febrile neutropenia occurred more frequently with TAC (29% vs 5%) but similar rates of infection were seen.

Taxane-Based Combination Regimens

The combination of docetaxel and capecitabine was approved by the FDA in 2001 for patients with MBC previously treated with an anthracycline. The registration trial was a phase 3, randomized study of docetaxel/capecitabine (75 mg/m^2 every 3 weeks, 1250 mg/m^2 twice daily on days 1–14 every 21 days) versus docetaxel alone (100 mg/m^2 every 3 weeks) in 511 anthracycline-refractory patients with MBC. The RRs for the single-agent and combination regimens were 30% and 42%, respectively. The TTP was 4.2 versus 6.1 months for the combination (hazard ratio 0.65; 95% CI 0.55–0.78). The OS was also superior for the combination, with a median OS of 11.5 months for docetaxel alone versus 14.5 months for docetaxel/capecitabine (hazard ratio 0.775; 95% CI 0.63–0.95). Approximately two-thirds of patients (65%) in the combination arm required dose reductions versus 36% in the docetaxel group. Grade 3 AEs were more common in the combination arm (71% vs 49% for docetaxel alone).[99]

Gemcitabine/paclitaxel (GT) was approved as combination therapy for MBC by the FDA in 2004. Approval was based on a randomized phase 3 trial of GT versus paclitaxel alone as frontline chemotherapy for patients who had received a prior adjuvant anthracycline. A total of 266 patients were randomly assigned to receive gemcitabine (1250 mg/m^2 on days 1 and 8) plus paclitaxel (175 mg/m^2 on day 1) every 21 days versus paclitaxel alone (175 mg/m^2 every 21 days). Median survival was 18.6 months for GT versus 15.8 months for paclitaxel monotherapy (hazard ratio 0.78; 95% CI 0.64–0.96) and RR was 41.4% for the combination versus 26.2% for paclitaxel alone. The TTP was longer for the combination (6.14 vs 3.98 months). Hematologic toxicity, primarily neutropenia, was more common in the GT arm.[100]

Briefly, there are also data for combination carboplatin/paclitaxel or carboplatin/docetaxel[101–103] and combination paclitaxel/bevacizumab[104,105] in ER-positive MBC. At our institution, platinum chemotherapy is used more commonly in TNBC and *gBRCA*-associated breast cancers. Bevacizumab was approved for use in combination with paclitaxel for MBC in 2008; however, the breast cancer indication was later removed in 2011 based on the absence of an OS benefit. At MDACC, bevacizumab is rarely used in treating MBC outside of clinical trials or metaplastic histology.

Capecitabine Combination Regimens

Capecitabine in combination with ixabepilone was approved to treat patients with MBC in 2007, supported by two similarly designed randomized, phase 3 trials. The first trial randomly assigned 752 patients with MBC to either ixabepilone 40 mg/m^2 plus capecitabine 2000 mg/m^2 on days 1 to 14 every 21 days or capecitabine 2500 mg/m^2 on the same schedule. All patients had received prior anthracycline and taxane therapy. The combination demonstrated improved PFS (5.8 vs 4.2 months; hazard ratio 0.75; 95% CI 0.64–0.88) and overall RR (35% vs 14%). Grade 3/4 toxicity was more pronounced in the combination arm, including peripheral neuropathy (21% vs 0%) and neutropenia (68% vs 11%). The rate of death was also increased with combination therapy (3% vs 1%). Patients with liver dysfunction are at higher risk of complications and should not be treated with this regimen.[106] The second trial included the same patient population and randomly assigned 1221 patients to the identical two regimens but evaluated OS rather than PFS as the primary end point. No difference in OS was detected (16.4 months for the combo vs 15.6 months for capecitabine alone; hazard ratio 0.9; 95% CI .08–1.03; P = .12), though improvements in PFS and RR again favored the combination.[107] Despite its toxicity, this combination represents a reasonable alternative for fit patients with resistant disease in whom a tumor response is critical.

The combination of gemcitabine and capecitabine has been evaluated in small, phase 2 trials. A total of 76 patients with MBC and prior anthracycline treatment were treated with gemcitabine 1000 mg/m^2 on days 1 and 8 plus capecitabine 830 mg/m^2 twice daily on days 1 to 14 every 21 days. Slightly more than half of the patients received this regimen as frontline cytotoxic therapy. The ORR was 55.2% with a TTP of 11.1 months. Grade 3/4 neutropenia occurred in 60% of patients, asymptomatic hepatotoxicity in 13.5%, and hand-foot syndrome in 16%.[108] The gemcitabine/capecitabine combination was tested against gemcitabine/cisplatin and gemcitabine/vinorelbine in a randomized trial in Germany and again demonstrated reasonable safety and efficacy. A total of 49 patients with MBC and prior anthracycline therapy were treated in the gemcitabine/capecitabine arm (identical gemcitabine dosing as the above study, but with a lower dose of capecitabine at 650 mg/m^2 twice daily on the same schedule). RR was 34.7% in the gemcitabine/capecitabine arm, with a PFS of 8.3 months and the regimen was well tolerated.[109]

Finally, at MDACC we infrequently utilize the CMF regimen (also discussed in the capecitabine section) in older patients who have received multiple previous treatments and who are unable to tolerate capecitabine.[80]

HER2-POSITIVE BREAST CANCER

HER-2 positive disease accounts for around 15% of all diagnosed breast cancers. Before the development of anti-HER2 monoclonal antibodies, HER2-positive breast cancer was among the most aggressive subtypes with a poor prognosis.[110,111] Multiple novel therapies have entered the clinic over the past two decades that improve the survival and quality of life of patients with HER2-positive MBC (Table 36–4). In this section, we will review the most relevant data associated with anti-HER2 treatment regimens, including the sequence we use at MDACC (Fig. 36–2).

Docetaxel/Trastuzumab/Pertuzumab—First-Line Therapy

The HER2/neu protein, a transmembrane receptor tyrosine kinase, plays a critical role in tumor development and progression when overexpressed in breast cancer. Trastuzumab is a murine-human chimeric monoclonal antibody that binds the extracellular domain of the HER2 protein and mediates antibody-dependent cellular toxicity. Trastuzumab was approved by the FDA in 1998 for the treatment of HER2-positive MBC after clinical trials demonstrated its efficacy as a single agent and in combination with chemotherapy.[111–113] Early trials reported an approximate 2.5% risk of cardiotoxicity related to trastuzumab that was usually reversible with discontinuation, with the potential for safe rechallenge.[114] Trastuzumab cardiotoxicity was exacerbated by concurrent anthracycline treatment and the combination is contraindicated. Combination taxane and trastuzumab therapy remained a standard of care regimen for many years until the development of a second anti-HER2 monoclonal antibody, pertuzumab.

Pertuzumab is a humanized anti-HER2 monoclonal antibody approved by the FDA in 2012 for the treatment of HER2-positive MBC. Pertuzumab binds to a different epitope of the HER2 extracellular domain than trastuzumab and prevents its heterodimerization with other HER family members, particularly HER3. The combination of pertuzumab, trastuzumab, and docetaxel (THP) was tested against trastuzumab and

Table 36–4 Recent Trials Relevant to the Management of HER2-Positive MBC and Metastatic TNBC

Trial	n	Patients	Treatment	Outcomes	Notes
HER2-positive MBC					
CLEOPATRA[7,115]	808 (1:1)	Frontline treatment for MBC (~46% had received prior chemotherapy and 10% had received previous trastuzumab)	THP (docetaxel, trastuzumab, pertuzumab) vs trastuzumab + docetaxel	PFS (18.5 vs 12.4 mo, HR 0.62; 95% CI 0.51–0.75); ORR (80.2% vs 69.3%); OS (57.1 vs 40.8 mo, HR 0.69; 95% CI 0.58–0.82)	Remains standard frontline tx; the median number of docetaxel cycles delivered in each arm was 8; 3.8% of patients in the THP arm (vs 6.6% in control arm) had LVEF decline of ≥10%; grade 3/4 diarrhea in ~8% in THP arm
EMILIA[118,119]	991 (1:1)	MBC patients with previous trastuzumab and taxane treatment (40% had received >1 chemotx for MBC, 84% had received trastuzumab for MBC)	T-DM1 vs lapatinib + capecitabine	PFS (9.6 vs 6.4 mo, HR 0.65; 95% CI 0.55–0.77); ORR (43.6% vs 30.8%); OS (29.9 vs 25.9 mo, HR 0.75; 95% CI 0.64–0.88)	Led to FDA approval in 2013 of T-DM1 as second-line tx for MBC; grade 3/4 thrombocytopenia in 12.9% on T-DM1 arm; grade 3/4 AST/ALT elevation in 7.2%
MARIANNE[120]	1095 (1:1:1)	Frontline treatment for MBC (~55% had received prior neoadjuvant/adjuvant therapy)	Trastuzumab + taxane vs T-DM1 vs T-DM1 + pertuzumab	PFS (13.7 vs 14.1 vs 15.2 mo); ORR (67.9% vs 59.7% vs 64.2%)	T-DM1 and T-DM1 + pertuzumab are noninferior but not superior to trastuzumab + taxane in terms of PFS, which further cements THP as the frontline regimen for HER2-positive MBC
HER2CLIMB[121]	612 (2:1)	Subsequent-line treatment for MBC (all patients had received previous pertuzumab, trastuzumab, and T-DM1)	Tucatinib + trastuzumab + capecitabine vs trastuzumab + capecitabine	PFS (7.8 vs 5.6 mo, HR 0.54; 95% CI 0.42–0.71); ORR (40.6% vs 22.8%); OS (21.9 vs 17.4 mo, HR 0.66; 95% CI 0.5–0.88)	FDA approval in 2020 after 1 or more prior anti-HER2 lines for MBC; among 219 patients with brain metastases, PFS at 1 year was 24.9% in the tucatinib arm vs 0% in the control arm; 81% of patients in the tucatinib arm experienced diarrhea and there was grade 3/4 AST/ALT elevation in 5%
DESTINY-Breast01[122]	184 (single arm)	Subsequent-line treatment for MBC (median 6 prior lines, all patients had received prior trastuzumab and T-DM1)	Trastuzumab deruxtecan	ORR 60.9% (median duration of response 14.8 mo); PFS 16.4 mo	FDA accelerated approval in 2019 after at least 2 prior anti-HER2 regimens for MBC; 13.6% of patients with ILD/pneumonitis (2.2% fatal); agent also had activity in low HER2-expression MBC
NALA[123]	662 (1:1)	Subsequent line treatment for MBC (patients had received at least 2 prior anti-HER2 therapies for metastatic disease)	Neratinib + capecitabine vs lapatinib + capecitabine	PFS (8.8 vs 6.6 mo, HR 0.76; 95% CI 0.63–0.93); ORR (32.8% vs 26.7%); OS at 1 year (72.5% vs 66.7%, HR 0.88; 95% CI 0.72–1.07)	FDA approval in 2020 after at least 2 prior anti-HER2 regimens for MBC; grade 3 diarrhea in 24%; neratinib combo also delayed the time to intervention for symptomatic CNS disease

(*Continued*)

Table 36–4 Recent Trials Relevant to the Management of HER2-Positive MBC and Metastatic TNBC (*Cont.*)

Trial	n	Patients	Treatment	Outcomes	Notes
Metastatic TNBC					
IMpassion130[8,157]	902 (1:1)	Frontline treatment for mTNBC (~50% had received prior taxane and/or anthracycline chemotx)	Atezolizumab + nab-paclitaxel vs nab-paclitaxel	For any PD-L1, PFS (7.2 vs 5.5 mo, HR 0.8; 95% CI 0.69–0.92); in the 40% of patients with PD-L1+ disease, PFS (7.5 vs 5 mo, HR 0.62; 95% CI 0.49–0.78); ORR (any PD-L1, 56% vs 45.9%)	FDA accelerated approval in 2019 for PD-L1+ mTNBC; no OS was demonstrated in the ITT population; however, in the PD-L1+ group OS (25 vs 18 mo, HR 0.71; 95% CI 0.54–0.93); hypothyroidism in 17.3% in the atezolizumab arm
IMMU-132-01[159]	108 (single arm)	Subsequent-line treatment for mTNBC (median 3 previous therapies)	Sacituzumab govitecan-hziy	RR 33.3% (3 CRs and 33 PRs); median duration of response 7.7 mo; CBR 45.4%; median PFS 5.5 mo	FDA accelerated approval in 2020 for patients with mTNBC after 2 lines of therapy for metastatic disease

CBR, clinical benefit rate; HR, hazard ratio; ITT, intention to treat; LVEF, left ventricular ejection fraction; MBC, metastatic breast cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; tx, therapy.

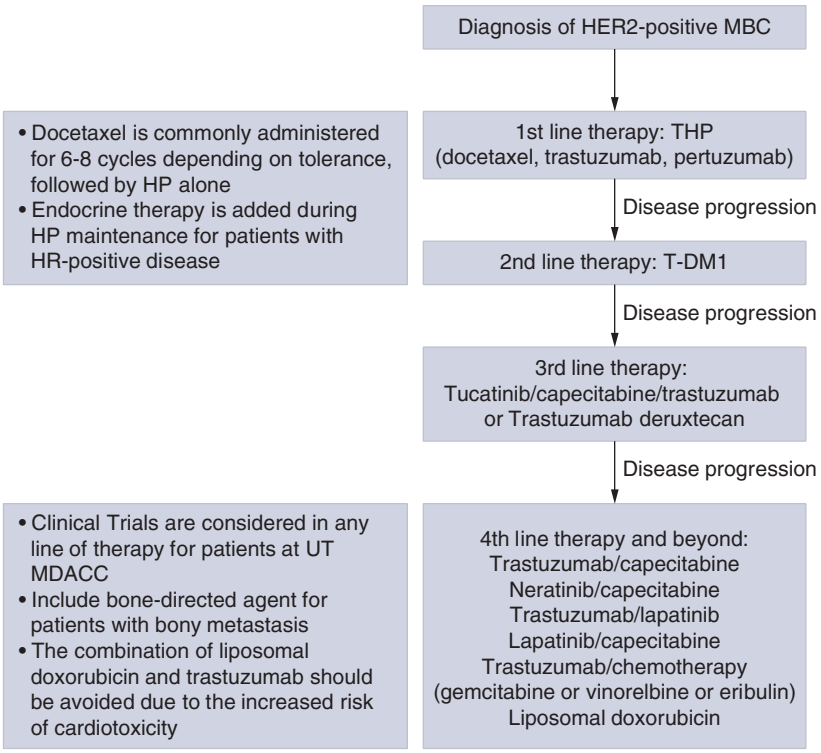


FIGURE 36–2 Concise algorithm for the treatment of patients with HER2-positive MBC at MDACC.

docetaxel in a landmark clinical trial, CLEOPATRA. About 10% of patients had received trastuzumab in either the neoadjuvant or adjuvant setting. A total of 808 patients with HER2-positive MBC were randomized and THP demonstrated remarkable efficacy versus docetaxel/trastuzumab. PFS was 18.5 months in the THP arm versus 12.4 months in the control group (hazard ratio 0.62; 95% CI 0.51–0.75). The rate of grade 3/4 neutropenic fever and diarrhea were higher in the THP arm, but cardiotoxicity was similar between groups.[115] The end-of-study results were recently published for CLEOPATRA. Median OS was 57.1 months for the THP arm versus 40.8 months for docetaxel/trastuzumab (hazard ratio 0.69; 95% CI 0.58–0.82). At 8 years, the OS in the THP group was 37% compared with 23% in the docetaxel/trastuzumab arm.[7] At MDACC, THP (or paclitaxel/trastuzumab/pertuzumab[116,117]) remains the standard first-line regimen for most patients with HER2-positive MBC. T-DM1 is a more appropriate first-line therapy for patients who experience distant metastatic recurrence within 6 months of receiving neoadjuvant or adjuvant chemotherapy and trastuzumab/pertuzumab.

T-DM1—Second-Line Therapy

Ado-trastuzumab emtansine (T-DM1) is a HER2-antibody drug conjugate, linking trastuzumab with the microtubule inhibitor, DM1 (a maytansine derivative). T-DM1 was approved by the FDA in 2013 for the treatment of patients with HER2-positive MBC, previously treated with trastuzumab and a taxane. The registration trial, EMILIA, was an open-label, randomized phase 3 study comparing T-DM1 versus capecitabine/lapatinib in 991 patients with HER2-positive MBC who had previously received trastuzumab and a taxane. A significant improvement in PFS was observed with T-DM1 (9.6 vs 6.4 months; hazard ratio 0.65; 95% CI 0.55–0.77).[118] Median OS was also improved with T-DM1 (29.9 vs 25.9 months; hazard ratio 0.75; 95% CI 0.64–0.88).[119] Rates of grade 3/4 toxicity were higher with capecitabine/lapatinib, though thrombocytopenia and elevated aspartate aminotransferase/alanine aminotransferase (AST/ALT) were more common with T-DM1. T-DM1 carries a warning label for risk of liver failure and requires routine liver function test monitoring. In addition, routine echocardiograms are recommended for patients on T-DM1 as with trastuzumab and pertuzumab. All HER2-specific therapies, including T-DM1, are contraindicated in pregnancy because of the risk of oligohydramnios.

The MARIANNE trial was a large, randomized, phase 3 trial of candidate frontline therapies for HER2-positive MBC. A total of 1095 patients were randomly assigned (1:1:1) to trastuzumab plus taxane versus T-DM1 versus T-DM1 plus pertuzumab. The T-DM1 regimens were noninferior to trastuzumab/taxane in terms of the primary PFS end point but did

not demonstrate superiority. PFS was 13.7 months for trastuzumab/taxane versus 14.1 months T-DM1 versus 15.2 months for T-DM1 plus pertuzumab. Peripheral neuropathy of any grade occurred in 28% of patients in the control arm, 13.3% on T-DM1, and 17.8% on T-DM1 plus pertuzumab.[120]

At MDACC, T-DM1 3.6 mg/kg every 21 days is standard second-line therapy for HER2-positive MBC. Dose reductions are common for thrombocytopenia. T-DM1 was recently approved for early-stage HER2-positive breast cancer in the setting of residual disease, and this will change the treatment paradigm for patients who experience distant recurrence within 6 to 12 months of completing adjuvant therapy. In that situation, we would consider one of the third-line therapies.

Tucatinib/Trastuzumab/Capecitabine or Trastuzumab Deruxtecan—Third-Line Therapies

Two different regimens received recent FDA approval for HER2-positive MBC. In the HER2CLIMB trial, 612 patients with HER2-positive MBC who had previously received trastuzumab, pertuzumab, and T-DM1 were randomly assigned (2:1) to either tucatinib plus trastuzumab plus capecitabine versus placebo/trastuzumab/capecitabine. Tucatinib is an oral tyrosine kinase inhibitor that is highly selective for the HER2 kinase domain. At 1 year, PFS was 33.1% in the tucatinib combination arm versus 12.3% in the control arm (hazard ratio 0.54; 95% CI 0.42–0.71), with a median PFS of 7.8 months compared with 5.6 months. OS at 2 years was 44.9% in the tucatinib group versus 26.6% in the control group (hazard ratio 0.66; 95% CI 0.5–0.88), with a median OS of 21.9 versus 17.4 months. Importantly, patients with treated or untreated brain metastases were eligible provided they did not require urgent local intervention. Among the 219 patients with brain metastases in the initial PFS analysis, PFS at 1 year was 24.9% in the tucatinib arm versus 0% in the control arm, and the median PFS was 7.6 months compared with 5.4 months (hazard ratio 0.48; 95% CI 0.34–0.69). The most common AEs in patients assigned to the tucatinib regimen were diarrhea (81% of patients) and hand-foot syndrome (63% of patients). Diarrhea was reportedly manageable in most patients with preventive medicines. Approximately 5% of patients in the tucatinib arm had grade 3/4 elevations in AST/ALT and the FDA has provided guidance on dose reductions for hepatic impairment.[121] The tucatinib/capecitabine/trastuzumab regimen was approved by the FDA in 2020 for treatment of patients with HER2-positive MBC after one or more prior anti-HER2–based regimens in the metastatic setting. MDACC participated in the HER2CLIMB trial, and we expect this regimen to be widely adopted, particularly in patients with brain metastasis.

The other novel agent that garnered recent accelerated FDA approval in 2019 is trastuzumab deruxtecan, an antibody-drug conjugate that links a humanized monoclonal antibody analogous to trastuzumab with the topoisomerase I inhibitor, DXd. The conjugate is internalized by tumor cells and DXd is released intracellularly, causing DNA damage and tumor cell death. Approval was based on an open-label, single-arm, phase 2 trial known as DESTINY-Breast01. A total of 184 patients with HER2-positive MBC and a median of six prior lines of therapy were treated with trastuzumab deruxtecan 5.4 mg/kg every 21 days. All patients had received prior T-DM1. The RR was 60.9% (6% CR, 55% PR) and the median PFS was 16.4 months (95% CI, 12.7–not reached). For context, the RR for the tucatinib arm in HER2 CLIMB was 40.6%. With trastuzumab deruxtecan, nausea/vomiting, neutropenia (~20% grade 3/4), and anemia were common AEs. By independent review, ILD developed from trastuzumab deruxtecan in 25 patients (13.6%), including four patients (2.2%) who ultimately died from ILD. Pneumonitis was treated with drug discontinuation and glucocorticoids in many patients.[122] The potency of trastuzumab deruxtecan will have to be carefully weighed against its risk of ILD. Two randomized trials are currently underway (vs T-DM1 and vs physician's choice treatment) that will help further clarify the toxicity and the role of trastuzumab deruxtecan in HER-2 positive MBC.

Other Regimens for HER2-Positive MBC

Previous second- and third-line therapies have now been relegated to later use in patients with HER2-positive MBC owing to the efficacy of the aforementioned novel agents. For example, neratinib was approved in 2020 in combination with capecitabine for the third-line treatment of patients with HER2-positive MBC, but most oncologists at MDACC prefer either the tucatinib combination or trastuzumab deruxtecan because of their apparent superior efficacy and side-effect profile, understanding that cross-trial comparisons are problematic. Neratinib was approved for MBC based on the NALA trial, a randomized, phase 3 trial of neratinib plus capecitabine versus lapatinib plus capecitabine in 662 patients with MBC who had received at least two prior HER2-directed regimens. Both neratinib and lapatinib are small-molecule, tyrosine kinase inhibitors that inhibit HER1 and HER2; however, neratinib inhibits HER4 and possesses other pharmacologic differences. The combination of neratinib/capecitabine proved superior in terms of PFS (8.8 months in the neratinib arm vs 6.6 months in the lapatinib arm), with 1-year PFS rates of 29% versus 15% (hazard ratio 0.76; P = .006). Grade 3 diarrhea was

more significant with neratinib (24% vs 13% for the lapatinib group).[123] Trials of neratinib in the early-stage and metastatic settings have consistently reported significant diarrhea, and daily antidiarrheal prophylaxis is recommended for all patients starting on neratinib. Notably, both neratinib and lapatinib have been shown to have modest activity against HER2-positive central nervous system disease.[124,125]

In general, HER2 pathway blockade is continued despite tumor progression on initial therapies. Typically, this is achieved with trastuzumab or a tyrosine kinase inhibitor once trastuzumab and pertuzumab have been used concurrently in any treatment line, because the benefit of their combined use beyond progression has not been proven. The optimal sequence of agents beyond the third line is unknown and the clinical trials that tested the regimens were conducted before the use of T-DM1, tucatinib, and trastuzumab deruxtecan. Combination regimens with activity in refractory, HER2-positive MBC include capecitabine/trastuzumab,[126–128] capecitabine/lapatinib,[129] trastuzumab/lapatinib,[130] and trastuzumab with chemotherapies, including eribulin,[131] vinorelbine[132,133] and gemcitabine.[134] Carboplatin also has activity in HER2-positive MBC; however, the data are in combination with taxanes, which are now used in early-stage or frontline metastatic treatment.[135] Anthracyclines are active in HER2-positive disease, but as discussed, the risk of cardiotoxicity precludes their use in combination with trastuzumab. The use of single-agent anthracycline treatment (eg, liposomal doxorubicin) is reasonable in later treatment lines for patients with refractory disease who are anthracycline-naïve.[111]

HER2-Positive, HR-Positive Breast Cancer

Nearly 70% of HER2-amplified breast tumors also express the ERs and/or PRs and are known as "triple-positive" tumors. HER2-positive/HR-positive breast cancers exhibit different biology than HER2-positive/HR-negative breast cancers. For example, HER2-positive/HR-negative early breast cancers have higher rates of pCR to neoadjuvant therapy than triple-positive tumors.[136,137] There is some evidence that in HR-positive tumors, the responsiveness to anti-HER2 therapies is positively correlated with the degree of HER2 amplification.[138,139] In addition, HER2-positive/HR-negative tumors are usually more aggressive, with a higher risk of relapse in the first 5 years since diagnosis; however, HER2-positive/HR-positive tumors are more likely to recur after 5 years, particularly in patients with node-positive disease.[140–142] Accordingly, the treatment of HER2-positive breast cancer varies based on HR expression. In both groups, anti-HER2 therapies are prioritized because the HER2-positive component harbors more aggressive biology; however, endocrine therapies can be added in HR-positive patients during treatment periods that do not contain chemotherapy. Chemotherapy targets both HR-positive and HER2-positive tumor cells but is generally not combined with endocrine therapy because of theoretical concerns that endocrine therapy, which is cytostatic, will limit the tumor cell division that chemotherapy exploits for its potency.

Trials in HER2-positive, HR-positive breast cancer have shown a PFS advantage for adding trastuzumab (with or without pertuzumab) to AI endocrine therapy.[143,144] A benefit in PFS was also demonstrated for adding lapatinib (with or without trastuzumab) to AI endocrine therapy for patients with triple-positive breast cancer.[145,146] There are limited data for tamoxifen or fulvestrant in combination with trastuzumab (or pertuzumab) in metastatic disease, though data from the adjuvant setting suggest the combinations are safe and possibly beneficial.[147,148] There is also rationale for integrating CDK4/6 inhibitors with endocrine therapy and anti-HER2 therapy in patients with triple-positive breast cancer and these clinical trials are ongoing.[149] At MDACC, we commonly begin AI endocrine therapy (with ovarian suppression in pre/perimenopausal women) when patients transition to maintenance trastuzumab and pertuzumab from frontline, induction THP after the docetaxel has been discontinued. Endocrine therapy is discontinued when patients proceed to second- and third-line therapies with T-DM1, trastuzumab deruxtecan, or tucatinib/capecitabine/trastuzumab. There is also a role for combined anti-HER2 and endocrine regimens for patients with triple-positive MBC who cannot tolerate cytotoxic therapies.

TRIPLE-NEGATIVE BREAST CANCER

TNBC accounts for about 15% of breast cancer cases diagnosed in the US and disproportionately affects young and non-White patients. The 5-year OS for patients who have metastatic TNBC (mTNBC) is 11.2%.[150] There is considerable intertumoral heterogeneity among HR-positive and HER2-positive breast tumors and the same is true for TNBC; however, the disease is uniformly characterized by aggressive biology and a lack of targetable hormone and HER2 receptors.[151] Until recently, cytotoxic chemotherapy was the only treatment option for patients with TNBC (Fig. 36–3). When checkpoint inhibitor immunotherapies arrived in the clinic, TNBC was a rational target because tumor-infiltrating lymphocytes were known to be prognostic.[152,153] Unfortunately, the RRs to single-agent checkpoint blockade were disappointing, with an ORR of about 5% in unselected patients and, at best, around 20% in the half of patients variably defined as having a favorable tumor microenvironment.[154–156]

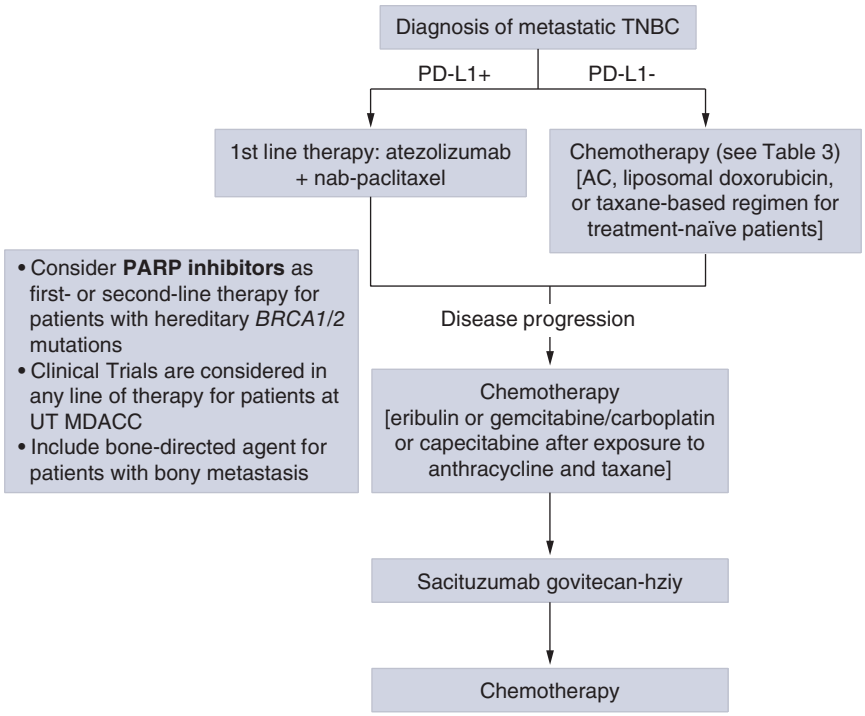


FIGURE 36–3 **Concise algorithm for the treatment of patients with metastatic TNBC at MDACC.**

New Agents—Atezolizumab and Sacituzumab Govitecan-Hziy

The trial that led to the accelerated approval of the first immunotherapy for breast cancer, atezolizumab, was IMpassion130. This was a phase 3, randomized, double-blind study that compared atezolizumab plus nab-paclitaxel versus nab-paclitaxel alone as frontline therapy for mTNBC. Approximately half of patients had received prior taxane and/or anthracycline chemotherapy. Each group included 451 patients, and PFS was 7.2 months for the combination versus 5.5 months for nab-paclitaxel alone (hazard ratio 0.8; 95% CI 0.69–0.92). There was no survival benefit for the overall population (21 vs 18.7 months). About 40% of patients had PD-L1–positive disease, defined as PD-L1 expression on tumor-infiltrating immune cells greater than or equal to 1%. In this subgroup, PFS was 7.5 months for atezolizumab/nab-paclitaxel versus 5 months for nab-paclitaxel alone and, in an exploratory analysis, improved OS was observed for the immunotherapy arm (25 vs 18 months). The most common grade 3/4 AEs were neutropenia and neuropathy.[8,157] There is now great interest in biomarkers apart from PD-L1 that might predict response to immunotherapy in breast cancer, including tumor mutational burden and specific molecular alterations.[158]

The second recently approved agent (under FDA accelerated approval) for mTNBC is sacituzumab govitecan-hziy, an antibody-drug conjugate composed of a humanized monoclonal antibody targeting trophoblast cell-surface antigen 2 (Trop 2) linked to the topoisomerase I inhibitor SN-38. Trop 2 is a transmembrane calcium signal transducer that is overexpressed in many epithelial cancers. The design was as a phase 1/2, single-group basket study in patients with pretreated, advanced epithelial cancers. A total of 108 patients with mTNBC who had received at least two prior chemotherapy lines for metastatic disease were treated with sacituzumab govitecan-hziy at 10 mg/kg on days 1 and 8 every 21 days. The median number of prior treatment lines was three and most patients had received a previous taxane and anthracycline. The RR was 33.3% with a duration of response of 7.7 months and a PFS of 5.5 months. The clinical benefit rate (which includes stable disease for at least 6 months) was 45.4%. Nausea and diarrhea were common AEs, and the most common grade 3/4 AEs were anemia and neutropenia.[159] We are hopeful that the ongoing randomized trials will confirm the remarkable efficacy of this drug and expect early adoption at MDACC given the modest activity of standard chemotherapy in pretreated disease. As of this writing, sacituzumab govitecan-hziy is approved after two prior lines of treatment for metastatic disease.

Cytotoxic Chemotherapy

For patients with mTNBC whose disease progresses on frontline atezolizumab and nab-paclitaxel or who

have PD-L1–negative disease, further treatment is with cytotoxic chemotherapy or in a clinical trial (Fig. 36–3). mTNBC patients with *gBRCA* are a special population that are discussed below. There is no standard sequence of chemotherapies for mTNBC and, similar to HR-positive disease, disease-specific and patient-specific factors should be considered. The chemotherapies used in mTNBC are nearly identical to those used for HR-positive MBC (see Chemotherapy section above), with several nuances that we will briefly review here. The strategy is also similar where successive chemotherapies are used until disease progression or limiting toxicities. Sequential single-agent chemotherapy is preferred, though there is a role for combination chemotherapy in mTNBC. Importantly, the majority of clinical trials that evaluated various chemotherapies included all breast cancer subtypes, though there have been recent trials focused exclusively on mTNBC.

The majority of patients with mTNBC received treatment with anthracycline and taxane chemotherapy in the neoadjuvant or adjuvant setting. For patients with de novo metastatic disease or who are anthracycline- and/or taxane–naïve, these agents are commonly used in the initial lines of treatment for metastatic disease.[160] Much of the efficacy data is extrapolated from the neoadjuvant and adjuvant settings where AC chemotherapy preceded or followed by taxane chemotherapy remains the standard of care with the highest rate of pCR (~40%–60%).[161–163] Either liposomal doxorubicin or conventional doxorubicin can be used. At MDACC, we commonly administer liposomal doxorubicin or AC chemotherapy for fit patients with de novo metastatic TNBC who are PD-L1–negative. We typically opt for combination chemotherapy in mTNBC patients with bulky disease, visceral crisis, or rapid progression provided they have a good performance status and organ function.

Taxanes can be used in mTNBC regimens as monotherapy or in combination with several different partners (eg, atezolizumab as discussed above, gemcitabine, or platinum chemotherapy). The tnAcity trial studied three different frontline chemotherapy combinations for mTNBC. A total of 191 patients were randomly assigned (1:1:1) to nab-paclitaxel plus carboplatin versus nab-paclitaxel plus gemcitabine versus gemcitabine plus carboplatin. A significantly longer PFS was demonstrated for nab-paclitaxel plus carboplatin than the other combinations (8.3 vs 6 months for gemcitabine/carboplatin vs 5.5 months for nab-paclitaxel/gemcitabine). RRs were 73%, 44%, and 39%, respectively.[164]

Platinum chemotherapy has been a particular focus in TNBC because of data suggesting a higher prevalence of homologous recombination deficiency in TNBC than in other breast cancer subtypes.[165] Platinum salts induce double-strand DNA breaks and are potent in patients with *BRCA* mutations with inherent homologous recombination deficiency. There have been numerous trials of platinum monotherapy and combinations in early and metastatic TNBC.[166–168] One study of particular interest was a phase 3 study that evaluated the combination of gemcitabine and carboplatin (GC) versus gemcitabine, carboplatin and iniparib (GCI). Iniparib was later shown not to be a true PARP inhibitor, and so the trial serves as a good measure of the efficacy of GC in patients with refractory mTNBC. A total of 519 patients were randomly assigned and PFS was 4.1 months for GC (5.1 months for GCI) with a RR of 33.7% for GC (33.7% for GCI). Approximately 90% of the patients had received a prior anthracycline and taxane.[169]

The other chemotherapies with activity in mTNBC include eribulin, capecitabine, ixabepilone, and vinorelbine. In general, each subsequent line of chemotherapy is effective for a shorter duration than the most recent therapy. In a subset analysis of a phase 3 trial comparing capecitabine with eribulin in 1102 previously treated patients with MBC, PFS was similar between treatment arms for the TNBC subset, though there was a trend toward improved survival for patients randomly assigned to receive eribulin (14.4 vs 9.4 months for capecitabine).[170] Both agents are used commonly at MDACC in patients with mTNBC who have received previous anthracycline and taxane chemotherapy.

The activity of ixabepilone as a single agent or in combination with capecitabine in refractory mTNBC has also been carefully reviewed.[171,172] A pooled analysis showed the PFS for ixabepilone/capecitabine versus capecitabine alone in mTNBC patients was 4.2 months versus 1.7 months (hazard ratio 0.64; 95% CI 0.52–0.78). The combination also doubled the RR (31% vs 15%). Median OS was not different between the two arms within the TNBC subset (10.4 vs 9 months).

Patients with *gBRCA* are a special patient population with unique responses to treatment. TNBC is far more common among patients with *gBRCA1*, with rates as high as 60%.[173] In the "Targeted Therapy" section, the efficacy of the PARP inhibitors in patients with *gBRCA* was reviewed. *gBRCA* breast tumors also show pronounced sensitivity to platinum chemotherapies because of an underlying deficit in DNA repair. As an example, the TNT trial randomly assigned 376 patients with mTNBC or *gBRCA* (with any breast cancer subtype) to receive either carboplatin or docetaxel. In the total population (338 with TNBC, 43 with *gBRCA*), the RR was similar (31.4% vs 34%) as was PFS (3.1 vs 4.4 months). However, the 43 patients with *gBRCA* demonstrated a RR of 68% with carboplatin compared with 33% for docetaxel as well as a longer PFS (6.8 vs 4.4 months).[174] Platinum sensitivity in patients with *gBRCA1*-associated breast cancer is also supported by data from the neoadjuvant setting.[175]

Platinum chemotherapies and PARP inhibitors have not been compared head-to-head and both are effective options in patients with *gBRCA* MBC.

mTNBC remains an active area of preclinical and clinical investigation because of its aggressive behavior and the attendant poor prognosis with available therapies. At MDACC, clinical trials are always a consideration for patients with mTNBC for any line of therapy. In addition, there are several rare variants of mTNBC that are outside the scope of this chapter including metaplastic breast cancer[176] and the luminal androgen receptor subtype[151] that have been expertly reviewed by others.

MANAGEMENT OF THE PRIMARY TUMOR

Most patients with MBC were originally treated for early-stage breast cancer before distant recurrence, including surgical resection of the primary breast tumor and axillary lymph nodes. For patients with de novo metastatic disease, the management of the primary breast tumor in the context of distant metastatic disease is controversial, though recent data from a phase 3 randomized trial, E2108, support the nonsurgical approach (discussed below). Standard practice is to treat with systemic therapy alone because the mortality from MBC results from distant metastasis rather than the primary tumor itself. Breast and axillary surgery are considered for palliation, including for skin ulceration, bleeding, and pain.

Conversely, several retrospective studies suggested a survival benefit for primary tumor resection in selected patients with MBC.[177,178] It is unclear whether these reports merely represent selection bias where heathier patients with more indolent disease (and who would be expected to live longer) were those who underwent primary breast surgery. There have been three prospective randomized trials that addressed this question. Investigators in the phase 3 ECOG-ACRIN E2108 trial (NCT01242800) recruited 390 women between February 2011 and July 2015 to determine whether the addition of locoregional treatment improved OS for patients with de novo MBC. Overall, 256 eligible patients were assigned to systemic therapy based on patient and tumor characteristics. Those whose disease did not progress during 4 to 8 months of treatment were then randomly assigned to systemic therapy plus locoregional treatment with surgery and radiation for the intact primary breast tumor (n = 125) versus systemic therapy alone (n = 131). At a median follow-up of 59 months, investigators found no significant difference in OS between optimal systemic therapy plus locoregional therapy compared with optimal systemic therapy alone (3-year OS 68.4% vs 67.9%; hazard ratio 1.09; 90% CI 0.80–1.49; P = .63). The addition of locoregional therapy also failed to improve 3-year PFS. However, locoregional recurrence or progression was significantly higher in the systemic therapy–alone arm (25.6% vs 10.2%; P = .003). In addition, investigators in ECOG-ACRIN E2108 evaluated health-related quality of life using the FACT-B Trial Outcome Index, which measures factors such as depression, anxiety, and well-being. Results showed no quality-of-life advantage associated with locoregional therapy.

A separate study took place at a single center in Mumbai, India and included women younger than 65 years with untreated, de novo MBC. Patients assigned to chemotherapy (96% of patients) had to demonstrate an objective tumor response after 6 to 8 cycles before randomization. A total of 350 patients were randomly assigned (1:1) to systemic therapy plus locoregional treatment of the breast and axilla with surgery and radiation versus systemic therapy alone. After a median follow-up of 23 months, there was no difference in the primary OS end point (19.2 months in the locoregional group vs 20.5 months in the systemic therapy–alone group).[179] The third trial, known as MF07-01, was a Turkish study that included 274 patients with de novo MBC. Patients were randomly assigned to receive up-front locoregional treatment with surgery and radiation followed by systemic therapy versus systemic therapy alone. This study did show an OS benefit for up-front locoregional therapy, and median OS was 46 months versus 37 months for systemic therapy alone (hazard ratio 0.66; 95% CI 0.49–0.88). However, randomization was not stratified by ER/PR status or the presence or absence of visceral disease, resulting in unbalanced arms. The locoregional group was characterized by a higher percentage of ER/PR-positive disease, less TNBC, and more patients with bone-only metastases, potentially confounding the results.[180] The current practice at MDACC is to treat patients with de novo metastatic disease with systemic therapy alone. Breast and axillary surgery are considered for palliative purposes and for patients with low-volume, treatment-responsive, metastatic disease and significant locoregional disease. Breast and axillary surgery (and radiation) are also offered to patients with oligometastatic disease who are treated with curative intent. The decision to proceed with locoregional therapy for a patient with MBC must involve close collaboration and detailed discussions between the patient, medical oncologist, breast surgeon, and radiation oncologist.

INVESTIGATIONAL THERAPY

The pace of discovery for effective agents that improve clinical outcomes for patients with MBC is accelerating. Here, we outline several promising agents and

concepts without providing a comprehensive review. For ER-positive disease, fulvestrant remains a standard treatment both as monotherapy and in combination with newer agents (eg, CDK4/6 inhibitors, alpelisib). However, a major disadvantage of fulvestrant is its requirement for two large-volume gluteal intramuscular injections per month. An oral SERD, AZD9496, was recently tested in a phase 1 trial and proved safe with preliminary evidence of efficacy in heavily pretreated patients.[181] We expect that this agent or a related oral SERD will eventually prove comparable to fulvestrant, filling a longstanding void in the clinic. In addition, for ER-positive disease, results from the recent phase 2 FAKTION trial showed that the addition of the AKT inhibitor, capivasertib, to fulvestrant improved PFS compared with fulvestrant alone. A total of 140 patients with ER-positive MBC and progression on a prior AI were enrolled, and PFS was 10.3 months for the combination versus 4.8 months for fulvestrant alone (hazard ratio 0.58; 95% CI 0.39–0.84). Grade 3/4 hypertension, diarrhea, and rash were more common in the capivasertib arm and a phase 3 trial is now underway.[182]

Tucatinib and trastuzumab deruxtecan are recently approved agents for HER2-positive MBC and are reviewed in the main section. Interestingly, trastuzumab deruxtecan also has activity in breast cancers with low HER2 expression, possibly because of a high drug-to-antibody ratio and a cell bystander effect. In a phase 1b study that enrolled 54 patients with heavily pretreated MBC (median 7.5 prior lines) and low HER2 expression (IHC 1+ or 2+ and negative in situ hybridization), trastuzumab deruxtecan at 6.4 mg/kg achieved an ORR of 37% with a median duration of response of 10.4 months. Most patients (87%) had ER-positive disease. Comparable to the DESTINY-Breast01 trial, myelosuppression was the most common grade 3/4 event, and fatal ILD was reported in three patients.[183]

Immunotherapy is a major focus of investigation in mTNBC owing to the efficacy of atezolizumab. The KEYNOTE-355 trial is testing combination pembrolizumab plus standard chemotherapy (nab-paclitaxel, paclitaxel, or gemcitabine/carboplatin) versus standard chemotherapy alone as frontline therapy for patients with mTNBC. At the virtual ASCO 2020 meeting, the investigators reported that the trial met a co-primary end point in that patients with PD-L1–positive disease (combined positive score ≥10) experienced improved PFS with the addition of pembrolizumab (9.7 vs 5.6 months; hazard ratio 0.65; 95% CI 0.49–0.86). Analysis of survival data for KEYNOTE-355 is ongoing. Another strategy is to augment the tumor microenvironment and sensitize tumors to checkpoint blockade. The TONIC trial studied the effect of induction chemotherapy or radiation before nivolumab in mTNBC and found that short-term doxorubicin or cisplatin induction was associated with an improved RR to nivolumab and a more favorable tumor immune microenvironment.[184] There are ongoing clinical trials in patients with mTNBC combining checkpoint blockade with other immunotherapies including those targeting CTLA-4, 4-1BB, and OX40. It is our hope and expectation that the next decade of innovative breast cancer research will result in continued improvements in outcomes for patients with MBC.

MD ANDERSON PRACTICE TIPS

- We strongly agree with the recommendation to biopsy a metastatic disease site for HR and HER2 receptor testing regardless of the initial primary breast cancer subtype. Ideally, we concurrently utilize this tissue for assaying other biomarkers such as PD-L1 (TNBC).
- Once a diagnosis of MBC is confirmed, we prioritize discussing the goals of care early in the physician-patient relationship to allow patients autonomy in the ensuing treatment decisions that often span many years.
- For HR-positive MBC, we utilize endocrine therapy and a CDK4/6 inhibitor as standard frontline therapy, including in patients with significant visceral disease.
- We generally opt for continuous and sequential, single-agent chemotherapy rather than combination chemotherapy for most patients with MBC.
- We are aggressive in treating carefully selected patients with oligometastatic MBC with combination multimodal therapy, including surgery and radiation.
- We prioritize clinical trials for patients with MBC, including those in early treatment lines.

REFERENCES

1. DeSantis CE, Ma J, Gaudet MM, et al. Breast cancer statistics, 2019. *CA Cancer J Clin.* 2019;69(6):438-451.
2. Pan H, Gray R, Braybrooke J, et al. 20-year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. *N Engl J Med.* 2017;377(19):1836-1846.
3. Fraser Symmans W, Wei C, Gould R, et al. Long-term prognostic risk after neoadjuvant chemotherapy associated with residual cancer burden and breast cancer subtype. *J Clin Oncol.* 2017;35(10):1049-1060.
4. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet.* 2014;384(9938):164-172.
5. Welch HG, Gorski DH, Albertsen PC. Trends in metastatic breast and prostate cancer--lessons in cancer dynamics. *N Engl J Med.* 2015;373(18):1685-1687.
6. Caswell-Jin JL, Plevritis SK, Tian L, et al. Change in survival in metastatic breast cancer with treatment advances: meta-analysis and systematic review. *JNCI Cancer Spectr.* 2018;2(4):pky062.
7. Swain SM, Miles D, Kim S-B, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol.* 2020;21(4):519-530.
8. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *N Engl J Med.* 2018;379(22):2108-2121.
9. Kennecke H, Yerushalmi R, Woods R, et al. Metastatic behavior of breast cancer subtypes. *J Clin Oncol.* 2010;28(20):3271-3277.
10. Jain S, Fisher C, Smith P, et al. Patterns of metastatic breast cancer in relation to histological type. *Eur J Cancer.* 1993;29A(15):2155-2157.
11. Schrijver WAME, Suijkerbuijk KPM, van Gils CH, et al. Receptor conversion in distant breast cancer metastases: a systematic review and meta-analysis. *J Natl Cancer Inst.* 2018;110(6):568-580.
12. Lumachi F, Basso SMM, Camozzi V, et al. Bone turnover markers in women with early stage breast cancer who developed bone metastases. A prospective study with multivariate logistic regression analysis of accuracy. *Clin Chim Acta.* 2016;460:227-230.
13. Cortes J, Cescon DW, Rugo HS, et al. KEYNOTE-355: Randomized, double-blind, phase III study of pembrolizumab + chemotherapy versus placebo + chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer. *J Clin Oncol.* 2020;38(suppl 15):1000-1000.
14. André F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. *N Engl J Med.* 2019;380(20):1929-1940.
15. Sorscher S. Rationale for evaluating breast cancers of Lynch syndrome patients for mismatch repair gene expression. *Breast Cancer Res Treat.* 2019;178(2):469-471.
16. Bonneville R, Krook MA, Kautto EA, et al. Landscape of microsatellite instability across 39 cancer types. *JCO Precis Oncol.* 2017;2017. doi: 10.1200/PO.17.00073.
17. Davies H, Morganella S, Purdie CA, et al. Whole-genome sequencing reveals breast cancers with mismatch repair deficiency. *Cancer Res.* 2017;77(18):4755-4762.
18. Lassen U. How I treat NTRK gene fusion-positive cancers. *ESMO Open.* 2019;4(suppl 2):e000612.
19. Hanrahan EO, Broglio KR, Buzdar AU, et al. Combined-modality treatment for isolated recurrences of breast carcinoma: update on 30 years of experience at the University of Texas M.D. Anderson Cancer Center and assessment of prognostic factors. *Cancer.* 2005;104(6):1158-1171.
20. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet.* 2019;393(10185):2051-2058.
21. Khan SA, Zhao F, Solin LJ, et al. A randomized phase III trial of systemic therapy plus early local therapy versus systemic therapy alone in women with de novo stage IV breast cancer: a trial of the ECOG:ACRIN Research Group (E2108). ASCO Virtual Scientific Program 2020. *J Clin Oncol.* 2020;38(suppl):abstract LBA2.
22. Rosen LS, Gordon DH, Dugan W Jr, et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. *Cancer.* 2004;100(1):36-43.
23. Hortobagyi GN, Lipton A, Chew HK, et al. Efficacy and safety of continue zoledronic acid every 4 weeks versus every 12 weeks in women with bone metastasis from breast cancer: results of the OPTIMIZE-2 trial. *J Clin Oncol.* 2014;32;5s.
24. Stopeck AT, Lipton A, Body J-J, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol.* 2010;28(35):5132-5139.
25. Gobbini E, Ezzalfani M, Dieras V, et al. Time trends of overall survival among metastatic breast cancer patients in the real-life ESME cohort. *Eur J Cancer.* 2018;96:17-24.
26. VanArsdale T, Boshoff C, Arndt KT, Abraham RT. Molecular pathways: targeting the cyclin D-CDK4/6 axis for cancer treatment. *Clin Cancer Res.* 2015;21(13):2905-2910.
27. Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncol.* 2015;16(1):25-35.
28. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med.* 2016;375(20):1925-1936.
29. Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncol.* 2016;17(4):425-439.
30. Turner NC, Slamon DJ, Ro J, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. *N Engl J Med.* 2018;379(20):1926-1936.
31. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med.* 2016;375(18):1738-1748.
32. Hortobagyi GN, Stemmer SM, Burris HA, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. *Ann Oncol.* 2018;29(7):1541-1547.
33. Slamon DJ, Neven P, Chia S, et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3. *J Clin Oncol.* 2018;36(24):2465-2472.
34. Slamon DJ, Neven P, Chia S, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. *N Engl J Med.* 2020;382(6):514-524.
35. Tripathy D, Im S-A, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. *Lancet Oncol.* 2018;19(7):904-915.
36. Im S-A, Lu Y-S, Bardia A, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. *N Engl J Med.* 2019;381(4):307-316.
37. Johnston S, Martin M, Di Leo A, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. *NPJ Breast Cancer*, 2019;5:5.

38. Sledge GW Jr, Toi M, Neven P, et al. The effect of abemaciclib plus fulvestrant on overall survival in hormone receptor-positive, ERBB2-negative breast cancer that progressed on endocrine therapy-MONARCH 2: a randomized clinical trial. *JAMA Oncol.* 2019;6(1):116-124.
39. Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, a phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory HR(+)/HER2(-) metastatic breast cancer. *Clin Cancer Res.* 2017;23(17):5218-5224.
40. Selli C, Dixon JM, Sims AH. Accurate prediction of response to endocrine therapy in breast cancer patients: current and future biomarkers. *Breast Cancer Res.* 2016;18(1):118.
41. Buzdar AU. Current status of endocrine treatment of carcinoma of the breast. Semin Surg Oncol, 1990;6(2):77-82.
42. Cole MP, Jones CT, Todd ID. A new anti-oestrogenic agent in late breast cancer. An early clinical appraisal of ICI46474. *Br J Cancer.* 1971;25(2):270-275.
43. Klijn JG, Blamey RW, Boccardo F, et al. Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. *J Clin Oncol.* 2001;19(2):343-353.
44. Nabholtz JM, Buzdar A, Pollak M, et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. Arimidex Study Group. *J Clin Oncol.* 2000;18(22):3758-3767.
45. Bonneterre J, Buzdar A, Nabholtz JM, et al. Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma. *Cancer.* 2001;92(9):2247-2258.
46. Mouridsen H, Gershanovich M, Sun Y, et al. Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. *J Clin Oncol.* 2003;21(11):2101-2109.
47. Paridaens RJ, Dirix LY, Beex LV, et al. Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. *J Clin Oncol.* 2008;26(30):4883-4890.
48. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med.* 2012;366(6):520-529.
49. Di Leo A, Jerusalem G, Petruzelka L, et al. Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer. *J Clin Oncol.* 2010;28(30):4594-4600.
50. Mehta RS, Barlow WE, Albain KS, et al. Overall survival with fulvestrant plus anastrozole in metastatic breast cancer. *N Engl J Med.* 2019;380(13):1226-1234.
51. Jeselsohn R, Buchwalter G, De Angelis C, et al. ESR1 mutations-a mechanism for acquired endocrine resistance in breast cancer. *Nat Rev Clin Oncol.* 2015;12(10):573-583.
52. Hanker AB, Sudhan DR, Arteaga CL. Overcoming endocrine resistance in breast cancer. *Cancer Cell.* 2020;37(4):496-513.
53. Alvarez-Fernandez M, Malumbres M. Mechanisms of sensitivity and resistance to CDK4/6 inhibition. *Cancer Cell.* 2020;37(4):514-529.
54. Kornblum N, Zhao F, Manola J, et al. Randomized phase II trial of fulvestrant plus everolimus or placebo in postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer resistant to aromatase inhibitor therapy: results of PrE0102. *J Clin Oncol.* 2018;36(16):1556-1563.
55. Bachelot T, Bourgier C, Cropet C, et al. Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors: a GINECO study. *J Clin Oncol.* 2012;30(22):2718-2724.
56. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *N Engl J Med.* 2018;379(8):753-763.
57. Robson M, Im S-A, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *N Engl J Med.* 2017;377(6):523-533.
58. Giuliano M, Schettini F, Rognoni C, et al. Endocrine treatment versus chemotherapy in postmenopausal women with hormone receptor-positive, HER2-negative, metastatic breast cancer: a systematic review and network meta-analysis. *Lancet Oncol.* 2019;20(10):1360-1369.
59. Dear RF, McGeechan K, Jenkins MC, et al. Combination versus sequential single agent chemotherapy for metastatic breast cancer. *Cochrane Database Syst Rev.* 2013(12):CD008792.
60. Bishop JF, Dewar J, Toner GC, et al. Initial paclitaxel improves outcome compared with CMFP combination chemotherapy as front-line therapy in untreated metastatic breast cancer. *J Clin Oncol.* 1999;17(8):2355-2364.
61. Joensuu H, Holli K, Heikkinen M, et al. Combination chemotherapy versus single-agent therapy as first- and second-line treatment in metastatic breast cancer: a prospective randomized trial. *J Clin Oncol.* 1998;16(12):3720-3730.
62. Partridge AH, Rumble RB, Carey LA, et al. Chemotherapy and targeted therapy for women with human epidermal growth factor receptor 2-negative (or unknown) advanced breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol.* 2014;32(29):3307-3329.
63. Gennari A, Stockler M, Puntoni M, et al. Duration of chemotherapy for metastatic breast cancer: a systematic review and meta-analysis of randomized clinical trials. *J Clin Oncol.* 2011;29(16):2144-2149.
64. Claessens AKM, Erdkamp FLG, Lopez-Yurda M, et al. Secondary analyses of the randomized phase III Stop&Go study: efficacy of second-line intermittent versus continuous chemotherapy in HER2-negative advanced breast cancer. *Acta Oncol.* 2020:1-10.
65. Claessens AKM, Timman R, Busschbach JJ, et al. The influence on quality of life of intermittent scheduling in first- and second-line chemotherapy of patients with HER2-negative advanced breast cancer. *Breast Cancer Res Treat.* 2020;179(3):677-685.
66. Richards MA, Hopwood P, Ramirez AJ, et al. Doxorubicin in advanced breast cancer: influence of schedule on response, survival and quality of life. *Eur J Cancer.* 1992;28A(6-7):1023-1028.
67. Norris B, Pritchard KI, James K, et al. Phase III comparative study of vinorelbine combined with doxorubicin versus doxorubicin alone in disseminated metastatic/recurrent breast cancer: National Cancer Institute of Canada Clinical Trials Group Study MA8. *J Clin Oncol.* 2000;18(12):2385-2394.
68. Jain KK, Casper ES, Geller NL, et al. A prospective randomized comparison of epirubicin and doxorubicin in patients with advanced breast cancer. *J Clin Oncol.* 1985;3(6):818-826.
69. Chan S, Friedrichs K, Noel D, et al. Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. *J Clin Oncol.* 1999;17(8):2341-2354.
70. A prospective randomized phase III trial comparing combination chemotherapy with cyclophosphamide, fluorouracil, and either doxorubicin or epirubicin. French Epirubicin Study Group. *J Clin Oncol.* 1988;6(4):679-688.
71. O'Brien MER, Wigler N, Inbar M, et al. Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. *Ann Oncol.* 2004;15(3):440-449.

72. Sledge GW, Neuberg D, Bernardo P, et al. Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). *J Clin Oncol.* 2003;21(4):588-592.
73. Mauri D, Kamposioras K, Tsali L, et al. Overall survival benefit for weekly vs. three-weekly taxanes regimens in advanced breast cancer: a meta-analysis. *Cancer Treat Rev.* 2010;36(1):69-74.
74. Harvey V, Mouridsen H, Semiglazov V, et al. Phase III trial comparing three doses of docetaxel for second-line treatment of advanced breast cancer. *J Clin Oncol.* 2006;24(31):4963-4970.
75. Jones SE, Erban J, Overmoyer B, et al. Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. *J Clin Oncol.* 2005;23(24):5542-5551.
76. Valero V, Jones SE, Von Hoff DD, et al. A phase II study of docetaxel in patients with paclitaxel-resistant metastatic breast cancer. *J Clin Oncol.* 1998;16(10):3362-3368.
77. Gradishar WJ, Krasnojon D, Cheporov S, et al. Significantly longer progression-free survival with nab-paclitaxel compared with docetaxel as first-line therapy for metastatic breast cancer. *J Clin Oncol.* 2009;27(22):3611-3619.
78. Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol.* 2005;23(31):7794-7803.
79. Blum JL, Jones SE, Buzdar AU, et al. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. *J Clin Oncol.* 1999;17(2):485-493.
80. Oshaughnessy JA, Blum J, Moiseyenko V, et al. Randomized, open-label, phase II trial of oral capecitabine (Xeloda) vs. a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer. *Ann Oncol.* 2001;12(9):1247-1254.
81. Ambros T, Zeichner SB, Zaravinos J, et al. A retrospective study evaluating a fixed low dose capecitabine monotherapy in women with HER-2 negative metastatic breast cancer. *Breast Cancer Res Treat.* 2014;146(1):7-14.
82. Rashad N, Abdelhamid T, Shouman SA, et al. Capecitabine-based chemoendocrine combination as first-line treatment for metastatic hormone-positive metastatic breast cancer: phase 2 study. *Clin Breast Cancer.* 2020.
83. Blackstein M, Vogel CL, Ambinder R, et al. Gemcitabine as first-line therapy in patients with metastatic breast cancer: a phase II trial. *Oncology.* 2002;62(1):2-8.
84. Possinger K, Kaufmann M, Coleman R, et al. Phase II study of gemcitabine as first-line chemotherapy in patients with advanced or metastatic breast cancer. *Anticancer Drugs.* 1999;10(2):155-162.
85. Carmichael J, Possinger K, Phillip P, et al. Advanced breast cancer: a phase II trial with gemcitabine. *J Clin Oncol.* 1995;13(11):2731-2736.
86. Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet.* 2011;377(9769):914-923.
87. McIntyre K, et al. Phase 2 study of eribulin mesylate as first-line therapy for locally recurrent or metastatic human epidermal growth factor receptor 2-negative breast cancer. *Breast Cancer Res Treat.* 2014;146(2):321-328.
88. Kaufman PA, Awada A, Twelves C, et al. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. *J Clin Oncol.* 2015;33(6):594-601.
89. Jones S, Winer E, Vogel C, et al. Randomized comparison of vinorelbine and melphalan in anthracycline-refractory advanced breast cancer. *J Clin Oncol.* 1995;13(10):2567-2574.
90. Fumoleau P, Delgado FM, Delozier T, et al. Phase II trial of weekly intravenous vinorelbine in first-line advanced breast cancer chemotherapy. *J Clin Oncol.* 1993;11(7):1245-1252.
91. Martín M, Ruiz A, Muñoz M, et al. Gemcitabine plus vinorelbine versus vinorelbine monotherapy in patients with metastatic breast cancer previously treated with anthracyclines and taxanes: final results of the phase III Spanish Breast Cancer Research Group (GEICAM) trial. *Lancet Oncol.* 2007;8(3):219-225.
92. Perez EA, Lerzo G, Pivot X, et al. Efficacy and safety of ixabepilone (BMS-247550) in a phase II study of patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine. *J Clin Oncol.* 2007;25(23):3407-3414.
93. Roché H, Yelle L, Cognetti F, et al. Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, as first-line therapy in patients with metastatic breast cancer previously treated with anthracycline chemotherapy. *J Clin Oncol.* 2007;25(23):3415-3420.
94. Thomas E, Tabernero J, Fornier M, et al. Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, in patients with taxane-resistant metastatic breast cancer. *J Clin Oncol.* 2007;25(23):3399-3406.
95. Biganzoli L, Cufer T, Bruning P, et al. Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: The European Organization for Research and Treatment of Cancer 10961 Multicenter Phase III Trial. *J Clin Oncol.* 2002;20(14):3114-3121.
96. Nabholtz JM, Falkson C, Campos D, et al. Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: results of a randomized, multicenter, phase III trial. *J Clin Oncol.* 2003;21(6):968-975.
97. Nabholtz JN, Patterson A, Dirix L, et al. A phase III randomized trial comparing docetaxel (T), doxorubicin (A) and cyclophosphamide (C) (TAC) to FAC as first line chemotherapy (CT) for patients (Pts) with metastatic breast cancer (MBC). *Proc Am Soc Clin Oncol*. 2001;20:abstract 83.
98. Mackey J, Patterson A, Dirix L, et al. Final results of the phase III randomized trial comparing docetaxel (T), doxorubicin (A) and cyclophosphamide (C) to FAC as first line chemotherapy (CT) for patients (pts) with metastatic breast cancer (MBC). *Proc Am Soc Clin Oncol*. 2002;21:abstract 137.
99. O'Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol.* 2002;20(12):2812-2823.
100. Albain KS, Nag SM, Calderillo-Ruiz G, et al. Gemcitabine plus paclitaxel versus paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. *J Clin Oncol.* 2008;26(24):3950-3957.
101. Fountzilas G, Kalofonos HP, Dafni U, et al. Paclitaxel and epirubicin versus paclitaxel and carboplatin as first-line chemotherapy in patients with advanced breast cancer: a phase III study conducted by the Hellenic Cooperative Oncology Group. *Ann Oncol.* 2004;15(10):1517-1526.
102. Perez EA, Hillman DW, Stella PJ, et al. A phase II study of paclitaxel plus carboplatin as first-line chemotherapy for women with metastatic breast carcinoma. *Cancer.* 2000;88(1):124-131.
103. Mavroudis D, Alexopoulos A, Malamos N, et al. Salvage treatment of metastatic breast cancer with docetaxel and carboplatin. A multicenter phase II trial. *Oncology.* 2003;64(3):207-212.
104. Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med.* 2007;357(26):2666-2676.
105. Robert NJ, Diéras V, Glaspy J, et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. *J Clin Oncol.* 2011;29(10):1252-1260.

106. Thomas ES. Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. *J Clin Oncol.* 2007;25(33):5210-5217.
107. Sparano JA, Vrdoljak E, Rixe O, et al. Randomized phase III trial of ixabepilone plus capecitabine versus capecitabine in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. *J Clin Oncol.* 2010;28(20):3256-3263.
108. Ciruelos EM, Cortés J, Cortés-Funes H, et al. Gemcitabine and capecitabine in previously anthracycline-treated metastatic breast cancer: a multicenter phase II study (SOLTI 0301 trial). *Ann Oncol.* 2010;21(7):1442-1447.
109. Stemmler HJ, diGioia D, Freier W, et al. Randomised phase II trial of gemcitabine plus vinorelbine vs gemcitabine plus cisplatin vs gemcitabine plus capecitabine in patients with pretreated metastatic breast cancer. *Br J Cancer.* 2011;104(7):1071-1078.
110. Ross JS, Slodkowska EA, Fraser Symmans W, et al. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. *Oncologist.* 2009;14(4):320-368.
111. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med.* 2001;344(11):783-792.
112. Cobleigh MA, Vogel CL, Tripathy D, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. *J Clin Oncol.* 1999;17(9):2639-2648.
113. Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol.* 2005;23(19):4265-4274.
114. Moja L, Tagliabue L, Balduzzi S, et al. Trastuzumab containing regimens for early breast cancer. *Cochrane Database Syst Rev.* 2012(4):CD006243.
115. Baselga J, Cortés J, Kim S-B, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med.* 2012;366(2):109-119.
116. Wang R, Smyth LM, Iyengar N, et al. Phase II study of weekly paclitaxel with trastuzumab and pertuzumab in patients with human epidermal growth receptor 2 overexpressing metastatic breast cancer: 5-year follow-up. *Oncologist.* 2019;24(8):e646-e652.
117. Bachelot T, Ciruelos E, Schneeweiss A, et al. Preliminary safety and efficacy of first-line pertuzumab combined with trastuzumab and taxane therapy for HER2-positive locally recurrent or metastatic breast cancer (PERUSE). *Ann Oncol.* 2019;30(5):766-773.
118. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med.* 2012;367(19):1783-1791.
119. Diéras V, Miles D, Verma S, et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2017;18(6):732-742.
120. Perez EA, Barrios C, Eiermann W, et al. Trastuzumab emtansine with or without pertuzumab versus trastuzumab plus taxane for human epidermal growth factor receptor 2-positive, advanced breast cancer: primary results from the phase III MARIANNE study. *J Clin Oncol.* 2017;35(2):141-148.
121. Murthy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *N Engl J Med.* 2020;382(7):597-609.
122. Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med.* 2020;382(7):610-621.
123. Saura C, Oliveira M, Feng Y-H, et al. Neratinib + capecitabine versus lapatinib + capecitabine in patients with HER2+ metastatic breast cancer previously treated with ≥ 2 HER2-directed regimens: Findings from the multinational, randomized, phase III NALA trial. *J Clin Oncol.* 2019;37(suppl 15):1002-1002.
124. Freedman RA, Gelman RS, Anders CK, et al. TBCRC 022: a phase II trial of neratinib and capecitabine for patients with human epidermal growth factor receptor 2-positive breast cancer and brain metastases. *J Clin Oncol.* 2019;37(13):1081-1089.
125. Petrelli F, Ghidini M, Lonati V, et al. The efficacy of lapatinib and capecitabine in HER-2 positive breast cancer with brain metastases: a systematic review and pooled analysis. *Eur J Cancer.* 2017;84:141-148.
126. Schaller G, Fuchs I, Gonsch T, et al. Phase II study of capecitabine plus trastuzumab in human epidermal growth factor receptor 2 overexpressing metastatic breast cancer pretreated with anthracyclines or taxanes. *J Clin Oncol.* 2007;25(22):3246-3250.
127. Yamamoto D, Iwase S, Kitamura K, et al. A phase II study of trastuzumab and capecitabine for patients with HER2-overexpressing metastatic breast cancer: Japan Breast Cancer Research Network (JBCRN) 00 Trial. *Cancer Chemother Pharmacol.* 2008;61(3):509-514.
128. Bartsch R, Wenzel C, Altorjai G, et al. Capecitabine and trastuzumab in heavily pretreated metastatic breast cancer. *J Clin Oncol.* 2007;25(25):3853-3858.
129. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med.* 2006;355(26):2733-2743.
130. Blackwell KL, Burstein HJ, Storniolo AM, et al. Randomized study of lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. *J Clin Oncol.* 2010;28(7):1124-1130.
131. Sakaguchi K, Nakatsukasa K, Koyama H, et al. Phase II clinical trial of first-line eribulin plus trastuzumab for advanced or recurrent HER2-positive breast cancer. *Anticancer Res.* 2018;38(7):4073-4081.
132. Burstein HJ, Keshaviah A, Baron AD, et al. Trastuzumab plus vinorelbine or taxane chemotherapy for HER2-overexpressing metastatic breast cancer: the trastuzumab and vinorelbine or taxane study. *Cancer.* 2007;110(5):965-972.
133. Perez EA, López-Vega JM, Petit T, et al. Safety and efficacy of vinorelbine in combination with pertuzumab and trastuzumab for first-line treatment of patients with HER2-positive locally advanced or metastatic breast cancer: VELVET Cohort 1 final results. *Breast Cancer Res.* 2016;18(1):126.
134. O'Shaughnessy JA, Vukelja S, Marsland T, et al. Phase II study of trastuzumab plus gemcitabine in chemotherapy-pretreated patients with metastatic breast cancer. *Clin Breast Cancer.* 2004;5(2):142-147.
135. Robert N, Leyland-Jones B, Asmar L, et al. Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer. *J Clin Oncol.* 2006;24(18):2786-2792.
136. Murthy RK, Raghavendra AS, Hess KR, et al. Neoadjuvant pertuzumab-containing regimens improve pathologic complete response rates in stage II to III HER-2/neu-positive breast cancer: a retrospective, single institution experience. *Clin Breast Cancer.* 2018;18(6):e1283-e1288.
137. Schneeweiss A, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann Oncol.* 2013;24(9):2278-2284.
138. Denkert C, Chia S, Hickish T, et al. HER2 and ESR1 mRNA expression levels and response to neoadjuvant trastuzumab plus chemotherapy in patients with primary breast cancer. *Breast Cancer Res.* 2013;15(1):R11.

139. Ballinger TJ, Sanders ME, Abramson VG. Current HER2 testing recommendations and clinical relevance as a predictor of response to targeted therapy. *Clin Breast Cancer.* 2015;15(3):171-180.
140. Chumsri S, Li Z, Serie DJ, et al. Incidence of late relapses in patients with HER2-positive breast cancer receiving adjuvant trastuzumab: combined analysis of NCCTG N9831 (Alliance) and NRG Oncology/NSABP B-31. *J Clin Oncol.* 2019;37(35):3425-3435.
141. Gonzalez-Angulo AM, Litton JK, Broglio KR, et al. High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller. *J Clin Oncol.* 2009;27(34):5700-5706.
142. Guarneri V, Broglio K, Kau S-W, et al. Prognostic value of pathologic complete response after primary chemotherapy in relation to hormone receptor status and other factors. *J Clin Oncol.* 2006;24(7):1037-1044.
143. Kaufman B, Mackey JR, Clemens MR, et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. *J Clin Oncol.* 2009;27(33):5529-5537.
144. Rimawi M, Ferrero J-M, de la Haba-Rodriguez J, et al. First-line trastuzumab plus an aromatase inhibitor, with or without pertuzumab, in human epidermal growth factor receptor 2-positive and hormone receptor-positive metastatic or locally advanced breast cancer (PERTAIN): a randomized, open-label phase II trial. *J Clin Oncol.* 2018;36(28):2826-2835.
145. Johnston S, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. *J Clin Oncol.* 2009;27(33):5538-5546.
146. Johnston SRD, Pippen J Jr, Pivot X, et al. Phase III, randomized study of dual human epidermal growth factor receptor 2 (HER2) blockade with lapatinib plus trastuzumab in combination with an aromatase inhibitor in postmenopausal women with HER2-positive, hormone receptor-positive metastatic breast cancer: ALTERNATIVE. *J Clin Oncol.* 2018;36(8):741-748.
147. Hayashi N, et al. Adding hormonal therapy to chemotherapy and trastuzumab improves prognosis in patients with hormone receptor-positive and human epidermal growth factor receptor 2-positive primary breast cancer. *Breast Cancer Res Treat.* 2013;137(2):523-531.
148. Gianni L, Niikura N, Yamauchi H, et al. Neoadjuvant treatment with trastuzumab and pertuzumab plus palbociclib and fulvestrant in HER2-positive, ER-positive breast cancer (NA-PHER2): an exploratory, open-label, phase 2 study. *Lancet Oncol.* 2018;19(2):249-256.
149. O'Sullivan CC, Suman VJ, Goetz MP. The emerging role of CDK4/6i in HER2-positive breast cancer. *Ther Adv Med Oncol.* 2019;11:1758835919887665.
150. Howlader N, Cronin KA, Kurian AW, et al. Differences in breast cancer survival by molecular subtypes in the United States. *Cancer Epidemiol Biomarkers Prev.* 2018;27(6):619-626.
151. Bianchini G, Balko JM, Mayer IA, et al. Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease. *Nat Rev Clin Oncol.* 2016;13(11):674-690.
152. Denkert C, von Minckwitz G, Brase JC, et al. Tumor-infiltrating lymphocytes and response to neoadjuvant chemotherapy with or without carboplatin in human epidermal growth factor receptor 2-positive and triple-negative primary breast cancers. *J Clin Oncol.* 2015;33(9):983-991.
153. Loi S, Drubay D, Adams S, et al. Tumor-infiltrating lymphocytes and prognosis: a pooled individual patient analysis of early-stage triple-negative breast cancers. *J Clin Oncol.* 2019;37(7):559-569.
154. Adams S, Loi S, Toppmeyer D, et al. Pembrolizumab monotherapy for previously untreated, PD-L1-positive, metastatic triple-negative breast cancer: cohort B of the phase II KEYNOTE-086 study. *Ann Oncol.* 2019;30(3):405-411.
155. Dirix LY, Takacs I, Jerusalem G, et al. Avelumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase 1b JAVELIN Solid Tumor study. *Breast Cancer Res Treat.* 2018;167(3):671-686.
156. Nanda R, Chow LQM, Dees EC, et al. Pembrolizumab in patients with advanced triple-negative breast cancer: phase Ib KEYNOTE-012 study. *J Clin Oncol.* 2016;34(21):2460-2467.
157. Schmid P, Rugo HS, Adams S, et al. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2020;21(1):44-59.
158. Barroso-Sousa R, Keenan E, Pernas S, et al. Tumor mutational burden and PTEN alterations as molecular correlates of response to PD-1/L1 blockade in metastatic triple-negative breast cancer. *Clin Cancer Res*. 2020;26(11):2565-2572.
159. Bardia A, Mayer IA, Vahdat LT, et al. Sacituzumab govitecan-hziy in refractory metastatic triple-negative breast cancer. *N Engl J Med.* 2019;380(8):741-751.
160. Piccart-Gebhart MJ, Burzykowski T, Buyse M, et al. Taxanes alone or in combination with anthracyclines as first-line therapy of patients with metastatic breast cancer. *J Clin Oncol.* 2008;26(12):1980-1986.
161. Loibl S, O'Shaughnessy J, Untch M, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. *Lancet Oncol.* 2018;19(4):497-509.
162. von Minckwitz G, Schneeweiss A, Loibl S, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. *Lancet Oncol.* 2014;15(7):747-756.
163. Sikov WM, Berry DA, Perou CM, et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). *J Clin Oncol.* 2015;33(1):13-21.
164. Yardley DA, Coleman R, Conte P, et al. nab-Paclitaxel plus carboplatin or gemcitabine versus gemcitabine plus carboplatin as first-line treatment of patients with triple-negative metastatic breast cancer: results from the tnAcity trial. *Ann Oncol.* 2018;29(8):1763-1770.
165. Sorlie T, Tibshirani R, Parker J, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. *Proc Natl Acad Sci U S A.* 2003;100(14):8418-8423.
166. Isakoff SJ, Mayer EL, He L, et al. TBCRC009: a multicenter phase II clinical trial of platinum monotherapy with biomarker assessment in metastatic triple-negative breast cancer. *J Clin Oncol.* 2015;33(17):1902-1909.
167. Silver DP, Richardson AL, Eklund AC, et al. Efficacy of neoadjuvant cisplatin in triple-negative breast cancer. *J Clin Oncol.* 2010;28(7):1145-1153.
168. Zhang J, Lin Y, Sun XJ, et al. Biomarker assessment of the CBCSG006 trial: a randomized phase III trial of cisplatin plus gemcitabine compared with paclitaxel plus gemcitabine as first-line therapy for patients with metastatic triple-negative breast cancer. *Ann Oncol.* 2018;29(8):1741-1747.
169. O'Shaughnessy J, Schwartzberg L, Danso MA, et al. Phase III study of iniparib plus gemcitabine and carboplatin versus gemcitabine and carboplatin in patients with metastatic triple-negative breast cancer. *J Clin Oncol.* 2014;32(34):3840-3847.
170. Twelves C, Awada A, Cortes J, et al. Subgroup analyses from a phase 3, open-label, randomized study of eribulin mesylate versus capecitabine in pretreated patients with advanced or metastatic breast cancer. *Breast Cancer (Auckl)*. 2016;10:77-84.

171. Perez EA, Patel T, Moreno-Aspitia A. Efficacy of ixabepilone in ER/PR/HER2-negative (triple-negative) breast cancer. *Breast Cancer Res Treat.* 2010;121(2):261-271.
172. Rugo HS, Roche H, Thomas E, et al. Efficacy and safety of ixabepilone and capecitabine in patients with advanced triple-negative breast cancer: a pooled analysis from two large phase III, randomized clinical trials. *Clin Breast Cancer.* 2018;18(6):489-497.
173. Atchley DP, Albarracin CT, Lopez A, et al. Clinical and pathologic characteristics of patients with BRCA-positive and BRCA-negative breast cancer. *J Clin Oncol.* 2008;26(26):4282-4288.
174. Tutt A, Tovey H, Cheang MCU, et al. Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial. *Nat Med.* 2018;24(5):628-637.
175. Byrski T, Huzarski T, Dent R, et al. Pathologic complete response to neoadjuvant cisplatin in BRCA1-positive breast cancer patients. *Breast Cancer Res Treat.* 2014;147(2):401-405.
176. Abouharb S, Moulder S. Metaplastic breast cancer: clinical overview and molecular aberrations for potential targeted therapy. *Curr Oncol Rep*. 2015;17(3):431.
177. Rapiti E, Verkooijen HM, Vlastos G, et al. Complete excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis. *J Clin Oncol.* 2006;24(18):2743-2749.
178. Blanchard DK, Shetty PB, Hilsenbeck SG, et al. Association of surgery with improved survival in stage IV breast cancer patients. *Ann Surg.* 2008;247(5):732-738.
179. Badwe R, Hawaldar R, Nair N, et al. Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial. *Lancet Oncol.* 2015;16(13):1380-1388.
180. Soran A, Ozmen V, Ozbas S, et al. Randomized trial comparing resection of primary tumor with no surgery in stage IV breast cancer at presentation: protocol MF07-01. *Ann Surg Oncol.* 2018;25(11):3141-3149.
181. Hamilton EP, Patel MR, Armstrong AC, et al. A first-in-human study of the new oral selective estrogen receptor degrader AZD9496 for ER(+)/HER2(-) advanced breast cancer. *Clin Cancer Res.* 2018;24(15):3510-3518.
182. Jones RH, Casbard A, Carucci M, et al. Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive breast cancer (FAKTION): a multicentre, randomised, controlled, phase 2 trial. *Lancet Oncol.* 2020;21(3):345-357.
183. Modi S, Park H, Murthy RK, et al. Antitumor activity and safety of trastuzumab deruxtecan in patients with HER2-low-expressing advanced breast cancer: results from a phase Ib study. *J Clin Oncol.* 2020;38(17):1887-1896.
184. Voorwerk L, Slagter M, Horlings HM, et al. Immune induction strategies in metastatic triple-negative breast cancer to enhance the sensitivity to PD-1 blockade: the TONIC trial. *Nat Med.* 2019;25(6):920-928.

This page intentionally left blank

37

Management of Locally Advanced Breast Cancer, Including Inflammatory Breast Cancer

Bora Lim
Gabriel N. Hortobagyi

KEY CONCEPTS

- The major difference between early breast cancers and locally advanced breast cancers (LABCs) include the extent of disease involvement and associated poor survivals. Both inflammatory breast cancer (IBC) and noninflammatory LABC are rare yet contribute to high morbidity and mortality.
- Both IBC and noninflammatory LABC require multidisciplinary care including medical oncology, surgical oncology, and radiation oncology. Effective induction strategy starting with the neoadjuvant systemic therapy (NAST) followed by aggressive local therapy including surgery and radiation is the best approach to reverse the poor outcome of these diseases.
- The unique biological cause of LABC that distinguishes it from other types of breast cancer may not be fully elucidated in the near future. In contrast, in IBC, recent enhancement of methods of biological interrogation has led to novel insights and development of novel therapeutic; however, the practice change is yet to follow, emphasizing the importance of ongoing efforts to change the grim clinical outcome.
- Compared with other noninflammatory breast cancer, stage III noninflammatory breast cancer harbor worse event-free and overall survivals. Early recognition, distinction from other LABCs, and early/accurate intervention are critical in the treatment of this dismal disease. The local therapy approach for IBC is different from other LABCs, and adherence to aggressive multimodality therapy has been shown to improve survival.
- Various new strategies are being tested in clinical trial settings to improve the response to the NAST, yet no new systemic therapeutics have been approved by the FDA. We anticipate several agents (eg, anti-programmed cell death–1 agents) to be approved as part of standard care in this setting.
- Additional strategies (eg, alternative/additive adjuvant therapies along with integrated biomarkers such as liquid biopsy to monitor early relapse) should be considered as a next step to improve the outcome of these breast cancers.

Locally advanced breast cancer (LABC) metastasizes and recurs frequently and is associated with poor overall survival (OS). Inflammatory breast cancer (IBC) is a rare form of LABC associated with distinctly worse survival.[1] Timely diagnosis, aggressive neoadjuvant systemic therapy (NAST), surgery, and radiation therapy, combined with novel diagnostic and therapeutic approaches based on new biological insights and delivered by a well-trained and well-coordinated team, is critical to improving the survival of patients with these cancers. Here we present current treatment recommendations for LABC and IBC from a panel of experts at MDACC and discuss future directions in the development of novel therapies for these diseases.

LABC VERSUS IBC

LABC is breast cancer that extends beyond the breast to the chest wall and/or multiple levels of regional lymph nodes but has not spread to distant sites and therefore is curable (ie, stage III). Not all stage III breast cancer falls into the LABC category, but most do. LABC can result from aggressive, rapidly growing

breast cancers such as IBC or from more slowly growing breast cancers when appropriate medical care is not delivered in a timely manner. According to data in the Surveillance, Epidemiology, and End Results Program (SEER) registries, the incidence of non-IBC LABC was similar to that of IBC (2%–4% of all breast cancers).[2] Based on one study in younger women, the rate of stage III breast cancer ranged from 16% to 24% of all diagnosed cases; in older women, the rate of stage III breast cancer was much lower.[3] The 5-year OS of patients with stage III breast cancer is approximately 72%.[1]

IBC is a rare form of LABC that accounts for only 2% to 4% of all breast cancers. Despite its low incidence, IBC accounts for 7% to 10% of breast cancer deaths because of its aggressive nature.[4] The 5-year OS of patients with IBC is approximately 50% to 55%. Despite collaborative international research efforts, the survival of patients with IBC remains poor, owing to lack of effective systemic therapy. The differences in definitions of IBC and the lack of specificity associated with clinical identification of IBC limit the accurate estimation of IBC incidence. However, this issue is slowly resolving as a result of international collaboration. Approximately 30% of patients with IBC are found to have distant metastasis at diagnosis; the remaining 70% are classified as having LABC (stage III disease).[5]

RISK FACTORS AND EPIDEMIOLOGY

Age

According to an analysis of breast cancer cases in the SEER registries diagnosed between 1988 and 2000 (n = 180,224), IBC was diagnosed at a younger age than non-IBC breast cancers overall (median age at diagnosis, 57 vs 61.9 years).[2]

Ethnicity

Both LABC and IBC are more common among Black and Hispanic individuals than other ethnic groups. Data from the United States show that the incidence of IBC is higher among Blacks than among Caucasians (3.1 vs 2.2 cases per 100,000 woman-years; $P < .001$).[2] Even with the same stage, Black patients with IBC have a shorter survival than patients in other ethnic groups.[6]

Family History and Genetic Risk Factors

Approximately 12% of women with breast cancer have a family history of breast cancer in a first-degree relative,[7] but only 5% of breast cancers are directly attributed to inherited germline mutations.[8] A number of hereditary mutations have been identified that are associated with increased breast cancer risk, including mutations in *BRCA1*, *BRCA2*, *PALB2*, *CHK2*, and others.[9–12] To date, no separate studies have investigated the relationship between genetic factors and LABC risk. In a study comparing 68 patients with IBC and 143 patients with non-IBC seen at MDACC, 13% of the patients with IBC versus 8% of the patients with non-IBC had a family history of breast cancer, but the difference was not statistically significant.[13] In a study conducted in Pakistan, 20% of patients with IBC had a family history of breast cancer[13]; however, this rate of family history has not been found in other studies to date.[14]

Obesity

One of the risk factors most consistently associated with IBC is a high body mass index (BMI).[6,15] Especially in hormone receptor–positive (HR+) IBC, a decrease in BMI was associated with better recurrence-free survival and OS.[15] Schairer et al compared 617 patients with IBC with three reference groups: patients with LABC (n = 7600), patients with non-IBC without chest wall or skin involvement (n = 1151), and healthy individuals (n = 93,654), and showed that IBC was the only category associated with high BMI at diagnosis.[16] A retrospective study of 602 patients with LABC, including 111 patients (18%) with IBC, showed that patients with IBC had a higher BMI.[17]

Several groups have studied the association between BMI and the clinical outcome of patients with LABC and IBC. An analysis by Chang et al published in 1998 showed that among postmenopausal women with IBC, obese women had significantly worse survival than those with normal BMI (hazard ratio 1.86; 95% CI 1.02–3.40); however, this pattern was not observed in premenopausal women with IBC.[18] In the aforementioned retrospective study of 602 patients with LABC, obese patients had significantly worse OS, relapse-free survival, and rates of visceral metastasis than nonobese patients.[17]

Geographic Region

The incidences of LABC and IBC are consistently low across the United States. For example, SEER registries showed that from 1992 to 2002, rates of IBC ranged from 2.064 per 100,000 woman-years in San Jose–Monterey, California to 3.042 cases per 100,000 woman-years in Los Angeles, California.[19] However, other parts of the world may have higher incidences; studies showed that 6% of all breast cancers in Tunisia and 10% of all breast cancers in Egypt were IBC.[20,21]

Pregnancy and Lactation

Studies to date regarding the relationships between pregnancy and lactation and the incidences of LABC and IBC have produced inconsistent findings, although a recent study found that women not having breastfed was one of the risk factors for the incidence of IBC according to a multivariate Cox proportional hazard analysis.[6,22]

PATHOLOGY

Molecular Subtypes

Both LABC and IBC are divided into three molecular subtypes: HR+; HER2-positive (HER2+); and triple-negative breast cancer (TNBC), in which both HRs and HER2 are absent. The distribution of cases by molecular subtype differs between LABC and IBC. The exact distribution of molecular subtypes within LABC has not been completely reported, but it is suspected to be skewed toward the more aggressive molecular subtypes (HER2+ and TNBC). In IBC, the distribution of cases by molecular subtypes has been more extensively reported owing to focused research efforts. In IBC, it has been reported that approximately 65% to 70% of cases are HER2+ (35%–40%), 30% are triple-negative,[6] and approximately 30% are HR+.

Tumor Emboli

Microscopic lesions known as tumor emboli within lymphatic vessels are the pathologic hallmark of IBC and explain most of its clinical manifestations, including edema, swelling, and ridges in the skin. Tumor emboli are found in 75% of patients with IBC[23]; however, identification of such emboli is not mandatory for confirmation of the diagnosis.[24] Advanced (T4b) non-IBC LABC may also harbor tumor emboli blocking the lymphatic ducts; therefore, confirmation of tumor emboli is not pathognomonic for IBC. Tumor emboli in IBC usually appear early in the course of disease and migrate readily to distant organs. Although the metastatic potential and reduced survival of IBC have been attributed to the presence of tumor emboli,[25] the prognostic significance of dermal lymphatic invasion remains an area of controversy.

DIAGNOSIS

Distinguishing Between IBC and LABC

To offer the most appropriate therapeutic options, primary IBC must be distinguished from LABC. The major differentiation between IBC and LABC relates to the timing of progression from the initial onset of the signs and symptoms to the full-blown presentation of the breast change. This progression occurs within 3 to 6 months in IBC but often takes more than 6 months in LABC. Previous normal mammograms and a detailed medical history can help clarify the timeline. Often, patients with LABC have not been evaluated with annual mammography. Some patients with LABC do not seek medical care for more than 6 months from the time they first recognized the palpable mass or lymph node. In addition, not all cases of LABC are associated with T4b (secondary changes of the skin or chest wall) or T4d disease. Some cases of LABC are associated with extensive nodal disease; however, LABC tends to be associated with less extensive nodal disease than IBC. Without a detailed clinical history, including the timing of breast changes, differentiation of IBC from LABC may be challenging. Although the majority of patients with IBC present with erythema and edema of the skin, these are not common findings in non-IBC LABC. Conversely, ulcerations and disintegration of the skin are more commonly found in non-IBC LABC and not commonly in IBC during the early phase of the disease. Figure 37–1 shows representative photographs of LABC (Fig. 37–1A) and IBC (Fig. 37–1B).

Distinguishing Between IBC and Benign Breast Diseases

The clinical presentation of IBC is frequently confused with that of more common benign diseases, and accurate diagnosis of IBC requires a high index of suspicion on the part of the diagnosing physician. If IBC is suspected, the physician must obtain pathologic evidence of breast carcinoma to establish the presence of malignancy. Once evidence of breast carcinoma is obtained, the presence of dermal lymphatic invasion helps to confirm the diagnosis but is neither required nor sufficient to make the diagnosis. All other clinical criteria must be satisfied to make the diagnosis of IBC—including erythema and skin changes including peau d'orange and engorgement of the skin that involves more than one-third of the breast and presented within 3 months duration as reviewed in the previous section. Further, these changes in the skin are often accompanied by enlargement of the draining lymph nodes, frequently in the absence of a breast mass. This clinical picture closely mimics that of common inflammatory conditions of the breast, such as simple bacterial mastitis. As a result, many patients with IBC unnecessarily undergo repeated courses of antibiotics before focused imaging is performed and a diagnosis is made. Tumor emboli hiding in the lymphatic duct can make the IBC hard to detect; about



FIGURE 37-1 **Representative photographs of breasts affected by LABC and IBC. A. A woman presented with a mass on her left breast that she had first noticed 2 years earlier and for which she had not previously sought medical care. Biopsy of the mass confirmed invasive ductal carcinoma with 60% of cells positive for Ki-67. Skin punch biopsy showed invasive ductal carcinoma. The patient was found to have N2 nodal diseases but no distant metastasis (T4bN2M0 disease). B. A woman presented for evaluation of erythema of the left breast. She had noted a red streak around the nipple of the left breast after tennis practice 3 weeks earlier, and since that time the area of erythema had grown to cover more than 60% of the left breast. Biopsy of the area of architectural distortion and an axillary lymph node as well as infraclavicular lymph node biopsy all showed invasive ductal carcinoma with 90% of cells positive for Ki-67 (T4dN3M0 disease). Skin punch biopsy showed invasive ductal carcinoma.**

half of patients with IBC do not have a distinctly visible (or palpable) mass at diagnosis. Approximately 70% to 80% of patients with IBC have metastasis to the higher-level regional lymph nodes.[6]

IMAGING MODALITIES

Imaging modalities of the IBC-involved breast, chest wall, and lymph node areas are required to diagnose LABC or IBC. Imaging confirmation of IBC, however, can be tricky, as we review in detail below.

Mammography

Often the extent of LABC can be measured by standard mammography. However, the mammogram may not be able to capture the full involvement of the regional lymph nodes, especially in cases of advanced nodal disease. In such cases, complementary imaging modalities such as ultrasonography, magnetic resonance imaging (MRI), and computed tomography (CT) of the neck will likely be required. IBC commonly presents with tumor emboli in the lymphatic ducts and lacks a palpable breast mass. Skin thickening is a signature change seen on the mammograms of patients with IBC and is present in 92% of cases.[26] Other common radiologic findings in IBC include increased breast tissue density, trabecular and stromal thickening (in 62% of cases), breast swelling, axillary lymphadenopathy, and nipple retraction (Fig. 37–2A). These findings may be missed by less experienced radiologists and annotated as benign findings. Bilateral mammography is recommended as a standard imaging method in the diagnosis of IBC.[27]

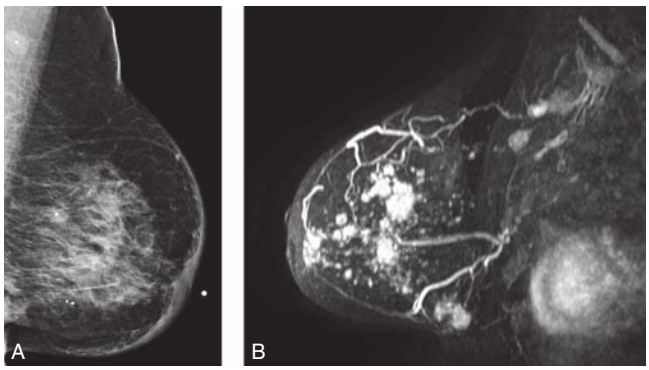


FIGURE 37–2 **Mammography and breast MRI findings in a woman newly diagnosed with IBC. A. Mammogram shows architectural distortion, including a mass-like lesion (marked as *), calcifications, and trabecular thickening. The mammogram also shows global skin thickening in approximately 50% of the central part of the breast. B. Breast MRI from the same patient clearly shows multiple mass-like lesions throughout the breast, engorgement of blood vessels, and locoregional lymph node metastases with high resolution that were not clearly shown on the mammogram. The areas with skin thickening shown on the mammogram exhibit parenchymal fluid accumulation on the breast MRI. Given its sensitivity, MRI is recommended as part of the initial evaluation for IBC. (Used with permission from Dr. Huong Le-Petross.)**

Ultrasonography

Locoregional lymph nodes assessment is critical in both LABC and IBC, and ultrasonography is much more sensitive than mammography in the detection of nodal disease. Thus, ultrasonography is a key part of the initial diagnostic workup in cases of suspected LABC and IBC. In addition, subtle changes such as architectural distortion, thickening of the skin, and trabecular thickening cannot be detected clearly on mammograms but can be detected on ultrasonography.[27] The sensitivity of ultrasonography in the detection of primary breast lesions in IBC is as high as 92% to 96%, whereas that of mammography is only 68%.[24,28]

Breast MRI

The role of breast MRI in the diagnosis of breast cancer in general is still being debated; however, there is no doubt about its sensitivity in detecting both primary breast lesions and locoregional lymph nodes, as well as mediastinal nodes.[29] MRI also depicts unique blood vessel patterns and skin and lymph node involvement. The sensitivity of MRI in the detection of primary breast lesions is the highest among all breast imaging modalities (up to 98%).[26] Findings on mammography and MRI in the same patient with IBC are shown in Fig. 37–2.

CT and PET/CT Scan

Both CT and positron emission tomography–CT (PET/CT) scans can detect distant metastasis in LABC. PET/CT scan offers a complete view of all visceral organs and bone, and it has the bonus of showing metabolic activity. When CT is used, a bone scan should be added to ensure full assessment of metastasis to the bone. In IBC, multiple studies have shown that PET/CT scan has higher sensitivity than conventional CT scan, not only in the detection of distant visceral or bone metastasis but also in the detection of distant lymph node metastases, and therefore it should be used instead of conventional CT whenever feasible.[30–33]

TREATMENT

Trimodality Therapy

Trimodality therapy, consisting of systemic therapy, surgery, and radiation therapy, is important in any breast cancer but is critical in the management of LABC, including IBC. Patients with IBC who did not undergo the recommended trimodality therapy had much worse outcomes than patients who did.[34] In an analysis of the National Cancer Database, underutilization of trimodality therapy was shown to reduce survival of patients with IBC, indicating that the need for this therapy should be taken seriously.[35] In both LABC and IBC, appropriate local therapy to prevent locoregional recurrence is critical, and the surgery and radiation oncology teams need to engage at the time of diagnosis to accurately assess the extent of disease, even though NAST is the first treatment for these breast cancers.

Systemic Therapy

Systemic therapeutic regimens for LABC and IBC, like therapeutic regimens for other types of breast cancer, are chosen on the basis of molecular subtype. However, despite having the same molecular subtypes as other types of breast cancer, LABC and IBC may respond differently to targeted therapy.

Chemotherapy

Anthracycline-Based Chemotherapy

Anthracycline-based regimens have been the cornerstone of systemic treatment of IBC since the 1970s. Although randomized trials of this approach are lacking, a pooled analysis of four prospective trials conducted at MDACC covering a 20-year period examined the outcome of neoadjuvant chemotherapy followed by local irradiation with or without mastectomy. In this analysis, patients who received anthracycline-based regimens had an overall response rate of 71% and 5- and 10-year OS rates of 40% and 33%, respectively.[36] The use of anthracycline-based regimens in patients with HER2+ LABC has declined in recent years given advances in effective anti-HER2 therapy.[37] In IBC, however, the use of anthracycline-based regimens is still strongly recommended given the accumulated data from retrospective studies.[38]

Taxane-Based Chemotherapy

In early studies after the introduction of taxanes at MDACC in 1994, among patients with estrogen receptor–negative tumors, the 3-year OS and progression-free survival rates were significantly higher in patients receiving paclitaxel-containing regimens than in those receiving anthracycline-based therapy without taxanes (OS 54 vs 32 months, $P = .03$; progression-free survival 27 vs 18 months, $P = .04$), and the pathologic complete response rate was 25% for paclitaxel-containing regimens and 10% for anthracycline-based therapy without taxanes ($P = .012$).[39]

Multiregimen Neoadjuvant Chemotherapy

A large, multicenter randomized trial (GeparTrio) prospectively examined the benefit of neoadjuvant docetaxel-and-anthracycline–containing regimens in different subtypes of breast cancer by comparing the outcomes of 194 patients with LABC and 93 patients with IBC with the outcomes of 1777 patients with operable breast cancers. Patients received four or six cycles of docetaxel, doxorubicin, and cyclophosphamide (TAC) or four cycles of TAC followed by four cycles of vinorelbine and capecitabine. In this study, tumor stage, including IBC status, was not an independent predictor of pathologic complete response in multivariate analysis (odds ratio 1.51; 95% CI 0.88–2.59; $P = .13$).[40]

Dawood et al analyzed SEER data from 2004 to 2007 and found that even with anthracycline-and-taxane-based chemotherapy, women with stage III IBC still had worse outcomes than women with stage III non-IBC. In this study, the 2-year breast cancer–specific survival rates in patients with IBC and non-IBC stage III breast cancer were 84% (95% CI 80–87) and 91% (95% CI, 90–91), respectively.[3] Patients with stage III IBC had a 43% increased risk of death from breast cancer compared with the risk in patients with stage III non-IBC. In a larger cohort of 398 patients with IBC diagnosed at MDACC between 1974 and 2005, patients with IBC treated with a taxane had a median survival time of 6.3 years compared with 3.8 years in patients not treated with a taxane.[41]

HER2-Targeted Therapy

As much as 35% to 40% of IBC tumors overexpress HER2, compared with approximately 25% of non-IBC tumors.[6] Trastuzumab has shown efficacy against HER2+ LABC and HER2+ IBC. Pertuzumab has been added as part of standard care in LABC regardless of IBC or non-IBC status and has contributed to an increased response rate in both LABC and IBC. HER2-targeted therapy in the form of trastuzumab or pertuzumab is an integral part of NAST for patients with HER2+ molecular subtype. If patients have large-volume residual disease after NAST, results of the KATHERINE study indicate that trastuzumab emtansine is the best choice for adjuvant therapy.[42] Neratinib, a pan-HER inhibitor, has also shown efficacy in terms of improving distant recurrence-free survival and thus can also be used for adjuvant therapy in patients who did not achieve pCR, and received trastuzumab but not the other adjuvant anti-HER2 therapeutics.[43] As noted, the benefit of alternative adjuvant HER2 therapy seems to be bigger in high-risk groups, thus these approaches should be considered for both non-IBC LABC and IBC without pCR after NAST. As noted, none of these studies was specifically designed for IBC and clinical applications of their results are extrapolated from studies that include small numbers of IBC cases, and thus should be considered cautiously. Further real-life retrospective review of benefit can aid this limitation, while several prospective studies are ongoing.

Surgery

Definitive surgical resection remains a fundamental part of treating IBC/LABC. In LABC, various forms of surgery can be considered, including breast-conserving surgery and sentinel lymph node biopsy, depending on the response to NAST. In some cases of slow-growing LABC, surgery can offer excellent local control if negative surgical margins can be obtained.[44] If breast-conserving surgery is not possible, different types of mastectomy can be applied, as long as negative margins can be achieved. In surgery for IBC, wide excision that includes all potential cancer-affected areas including skin is critical; therefore, modified radical mastectomy is the standard of care.[45,46] Skin- or nipple-sparing mastectomy produces suboptimal oncologic outcomes and should be avoided. When the response to NAST is poor, surgery to prevent local progression should be undertaken with speed and careful planning, given the potential for rapid progression during suspension of systemic therapy. Postmastectomy reconstruction, if undertaken, should be performed in delayed fashion to (1) ensure an appropriate duration of adjuvant therapy to prevent early local recurrence to the chest wall and skin, (2) allow for monitoring for early local recurrence, and (3) avoid poor outcomes as a result of the impact of radiation therapy on a reconstructed breast. Expander insertion may affect the delivery of radiation therapy and should be avoided.[38]

Radiation Therapy

Radiation therapy is delivered immediately after surgery to address the remaining cancer cells. Thus, the standard order of locoregional treatment is surgery followed by radiation therapy.[47] Preoperative radiation therapy may be delivered as part of a clinical trial but only after careful planning and interdisciplinary discussion. Postmastectomy radiation therapy should include the confirmed cancer-affected areas, such as the chest wall, skin, and lymph nodes, including supraclavicular and infraclavicular lymph nodes.[48–50] At MDACC, we prescribe an accelerated hyperfractionation schedule for patients at higher risk of recurrence, with a total dose of 66 Gy. A dose of 51 Gy is delivered in 34 fractions of 1.5 Gy, given twice daily at least 6 hours apart to the chest wall and undissected draining lymphatics, followed by a boost of 15 Gy to the chest wall

and any clinically involved undissected regional nodes, administered in twice-daily fractions of 1.5 Gy over 5 days. This twice-daily delivery of radiation therapy can cause increased fatigue and pose logistical challenges; however, data from retrospective studies support the efficacy of this approach in IBC, and therefore this is the standard of care at MDACC. Clinical trials are currently testing additional agents to improve the efficacy of radiation therapy, based on preclinical data using a poly(ADP-ribose) polymerase inhibitor[51] or capecitabine.[52]

Post-Therapy Surveillance and Follow-Up

After completion of trimodality therapy, patients should be evaluated with clinical examination every 3 to 6 months for 5 years and thereafter every year. Mammography of the contralateral breast should be performed annually.[38] Additional investigation may be requested according to clinical indications. As of this writing, additional modalities of post-therapy surveillance, including assessment for circulating tumor DNA or circulating tumor cells, are being actively developed for patients with a high risk of recurrence, such as patients with LABC and IBC.[53]

MANAGEMENT OF STAGE IV IBC

Approximately 6% of all breast cancers are stage IV at diagnosis. LABC, which by definition is stage III at diagnosis, often progresses to stage IV as a result of recurrence after an initial response or continuous progression caused by therapeutic resistance. When LABC involves the pectoralis muscle or nearby rib or lymph nodes more extensive than N2, local management becomes quite challenging.[54] In comparison, approximately one-third of IBC cases are stage IV at diagnosis. In patients with de novo stage IV IBC, chemotherapy alone resulted in a 5-year OS of less than 10%. The median breast cancer–specific survival was significantly lower for stage IV IBC than for stage IV non-IBC (1.75 years [range 0–15.7] vs 2.3 years [range 0–18.9]; $P < .0001$).[55]

The problem of stage IV IBC is unique and somewhat opposite from that of stage IV non-IBC LABC. The success of multimodality therapy in nonmetastatic IBC has encouraged exploration of a similar approach in metastatic IBC when an expert team is available to deliver trimodality therapy. In a series of patients with stage IV IBC treated with trimodality therapy, the 5-year OS was as high as 50%.[56] These results suggest that in selected patients with metastatic IBC, multimodality treatment, including surgery, may offer better local control and higher quality of life than surgery alone, radiation alone, or without local therapies. The role of definitive surgery to improve the survival in patients with breast cancer presenting with metastatic disease remains controversial, but relevant data are accumulating. Three randomized studies have not clearly shown either benefit or harm, thus specific treatment may need to be approached for individual cases.[57–59] Benefit in this situation may reflect a selection bias for patients who present with less advanced tumors, better performance status, or higher chemosensitivity.

SURVIVAL

Overall Survival

Overall, patients with LABC have worse OS than patients with early-stage (stage I–II) breast cancer regardless of molecular subtype, although OS of patients with LABC differs according to molecular subtype. The recently updated American Joint Committee on Cancer staging system for breast cancer reflects the contribution of molecular subtypes[60]; for example, LABC of less aggressive subtypes, eg, HR+ disease, will have a lower prognostic stage than LABC of more aggressive subtypes. The survival of patients with IBC is significantly worse than that of patients with non-IBC LABC; 5-year OS was 40.5% for IBC versus 63.2% for non-IBC LABC ($P < .0001$).[61] Interestingly, the survival of patients with stage III IBC does not differ by molecular subtypes, but the triple-negative subtype of IBC has the worst survival.[62]

Locoregional Recurrence-Free Survival

IBC has significantly higher rates of locoregional (skin and lymph nodes) and distant metastasis than do other forms of LABC. Furthermore, the absolute risk of subsequent diagnosis of contralateral breast cancer was higher in IBC than in other subtypes of LABC (4.9% vs 1.1% at 2 years), irrespective of age or hormonal status, and remained high even 15 years after initial diagnosis. The majority of IBC recurrences occurred within 2 to 23 months after initial diagnosis, suggesting that careful monitoring is required during the early follow-up period after adjuvant therapy.[16]

Distant Recurrence-Free Survival

The detailed pattern of distant recurrence in non-IBC LABC is not well established, but it is known that the distant recurrence rate is higher in LABC than in early-stage breast cancers. In a pooled analysis of 10 clinical trials conducted at MDACC, patterns of recurrence

were compared between 240 patients with IBC and 831 patients with stage-matched non-IBC.[61] In this study, 5-year recurrence-free survival for patients with IBC was 35% (95% CI 29.4–41.8).

NEW TARGETS AND BIOLOGICAL INSIGHTS

New Biological Targets

LABC may not exhibit unique biomarkers or biological features compared with other types of early-stage breast cancer, but when LABC occurs as a result of a treatment delay, de novo resistance to standard therapy may exist because of accumulative genetic changes. PAM50-based genomic discovery work to detect and diagnose IBC has led to identification of several gene signatures.[63] Unfortunately, these gene signatures were not successful in distinguishing IBC from non-IBC. Analysis of metastatic IBCs by next-generation sequencing showed that the most frequently altered genes based on DNA analysis overlapped with the most frequently altered genes in advanced breast cancer and included *TP53* (altered in about 60% of IBCs), *MYC* (32%), *PIK3CA* (28%), *HER2* (26%), and *FGFR1* (17%). Also shown to be altered in IBC are markers of epithelial-to-mesenchymal transition and stem cell markers, including zinc finger E-box-binding homeobox 1 and E-cadherin,[64] and the stem cell markers aldehyde dehydrogenase 1 and neurogenic locus notch homolog protein 3 (Notch 3).[65,66] Recent trials of neoadjuvant therapy that aimed to improve survival by assigning treatment on the basis of molecular features of the disease, eg, the ARTEMIS trial (NCT02276443), uncovered significant correlations of the molecular signatures and the response to standard therapy and metastatic progression. Nuclear receptors, transcription factors, including NF1, and androgen receptors have been recognized to be altered in advanced breast cancers, and inhibitors of these molecules are being tested as part of combination therapy in clinical trials. As another strategy, well-developed targeted therapies that are proven to be effective in metastatic breast cancer are also being tested in LABC. A CDK4/6-inhibitor combined with endocrine therapy has been tested in HR+ LABC and showed efficacy in terms of reducing the tumor volumes or number of Ki-67–positive cells.[67,68]

Tumor Microenvironment

Most genomic studies of IBC have focused on IBC tumor cells and have failed to identify mutations distinct from those in non-IBC; few genomic studies of IBC have investigated the role of the tumor microenvironment in IBC progression and resistance. International efforts to study IBC tumor cells by standard "bulk" transcriptomic and genomic analysis have failed to identify unique IBC-specific mutations.[63,69] As mentioned earlier in this chapter, unlike non-IBC tumors, which form distinct solid masses, IBC presents with scattered agglomeration of tumor cells and dermal lymphatic invasion, identified as tumor emboli, in 75% of cases.[70] Tumor emboli are thought to be the result of IBC tumor cells interacting with the aberrant immune system and vascular/lymphatic cell types in the microenvironment. Thus, an unbiased analysis of cell types in the IBC tumor microenvironment (TME) and tumor emboli may reveal novel targets.[71] Furthermore, detailed information about stromal and immune components in the IBC TME, including T lymphocytes, tumor-associated macrophages, and dendritic cells, need to be unraveled for effective targeting.[72,73] To date, most studies of the IBC TME have been conducted using targeted immunohistochemical markers such as CD68 for macrophages and CD3 for T-cells, which can only estimate the cell type frequencies without defining their transcriptionally reprogrammed cell states, which we plan to resolve with single-cell RNA sequencing.

CONCLUSION AND FUTURE DIRECTIONS

LABC and IBC both pose unique therapeutic challenges that require careful sequencing of treatment modalities. The major challenges include resistance to systemic therapy and the difficulty of achieving local control in many patients. Evolving systemic therapy and the integration of neoadjuvant systemic therapy followed by local therapy in the overall therapeutic strategy have improved the survival of LABC and IBC, yet there is much room for further improvement. The unique biological cause of LABC that distinguishes the LABC from other types of breast cancer may not be fully elucidated in the near future. In contrast, in IBC, recent enhancement of methods of biological interrogation has led to novel insights and development of novel therapeutics; however, the change in practice is yet to follow, emphasizing the importance of the ongoing efforts to improve the clinical outcome. Efforts to unravel the epigenetics, detailed genomics, proteomics, and circulating biomarkers of LABC and IBC need to continue, along with careful development of the precision therapeutic approach based on individual risk and precise biomarkers.

MD ANDERSON PRACTICE TIPS

- We recommend that practicing oncologists strongly consider the possibility of IBC when a patient presents with breast inflammation or clinical features suggestive of a breast infection. Distinguishing between IBC and noninflammatory LABC can be challenging, but IBC tends to have a short time (3 months) from onset of signs and symptoms to marked breast changes, whereas LABC tends to develop more slowly.
- For both LABC and IBC, we recommend early engagement of a multidisciplinary team to discuss and plan treatment.
- Systemic therapies for LABC and IBC, like systemic therapies for other types of breast cancer, are chosen on the basis of molecular subtypes, as the first treatment before local therapies: surgery and radiation.
- For IBC, modified radical mastectomy and axillary node dissection with resection of all gross disease whenever possible remains the gold standard for optimal local control. For LABC, modified radical mastectomy is not mandatory; breast-conserving surgery can be performed in certain cases at the surgeon's discretion.

REFERENCES

1. Dawood S, Ueno NT, Valero V, et al. Differences in survival among women with stage III inflammatory and noninflammatory locally advanced breast cancer appear early: a large population-based study. *Cancer*. 2011;117(9):1819-1826.
2. Hance KW, Anderson WF, Devesa SS, Young HA, Levine PH. Trends in inflammatory breast carcinoma incidence and survival: the surveillance, epidemiology, and end results program at the National Cancer Institute. *J Natl Cancer Inst*. 2005;97(13):966-975.
3. Thomas A, Rhoads A, Pinkerton E, et al. Incidence and survival among young women with stage I-III breast cancer: SEER 2000-2015. *JNCI Cancer Spectr*. 2019;3(3):pkz040.
4. Atkinson RL, El-Zein R, Valero V, et al. Epidemiological risk factors associated with inflammatory breast cancer subtypes. *Cancer Causes Control*. 2016;27(3):359-366.
5. Raghav K, French JT, Ueno NT, et al. Inflammatory breast cancer: a distinct clinicopathological entity transcending histological distinction. *PLoS One*. 2016;11(1):e0145534.
6. Fouad TM, Ueno NT, Yu RK, et al. Distinct epidemiological profiles associated with inflammatory breast cancer (IBC): a comprehensive analysis of the IBC registry at The University of Texas MD Anderson Cancer Center. *PLoS One*. 2018;13(9):e0204372.
7. Collaborative Group on Hormonal Factors in Breast Cancer. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. *Lancet*. 2001;358(9291):1389-1399.
8. Brewer HR, Jones ME, Schoemaker MJ, Ashworth A, Swerdlow AJ. Family history and risk of breast cancer: an analysis accounting for family structure. *Breast Cancer Res Treat*. 2017;165(1).
9. Antoniou AC, Casadei S, Heikkinen T, et al. Breast-cancer risk in families with mutations in PALB2. *N Engl J Med*. 2014;371(6):497-506.
10. Thompson ER, Rowley SM, Li N, et al. Panel testing for familial breast cancer: calibrating the tension between research and clinical care. *J Clin Oncol*. 2016;34(13):1455-1459.
11. Cragun D, Weidner A, Tezak A, Clouse K, Pal T. Cancer risk management among female BRCA1/2, PALB2, CHEK2, and ATM carriers. *Breast Cancer Res Treat*. 2020;182(2):421-428.
12. Zhou J, Wang H, Fangmeng F, et al. Spectrum of PALB2 germline mutations and characteristics of PALB2-related breast cancer: screening of 16,501 unselected patients with breast cancer and 5890 controls by next-generation sequencing. *Cancer*. 2020;126(14):3202-3208.
13. Anderson WF, Schairer C, Chen BE, Hance KW, Levine PH. Epidemiology of inflammatory breast cancer (IBC). *Breast Dis*. 2005;22:9-23.
14. Gutierrez Barrera AM, et al. BRCA mutations in women with inflammatory breast cancer. | Presented at the 2010 Breast Cancer Symposium. October 1-3, 2010; Suburban, Washington , DC. ASCO general poster abstract. 2010;abstract 192.
15. Kogawa T, Fujii T, Fouad TM, et al. Impact of change in body mass index during neoadjuvant chemotherapy and survival among breast cancer subtypes. *Breast Cancer Res Treat*. 2018;171(2):501-511.
16. Schairer C, Li Y, Frawley P, et al. Risk factors for inflammatory breast cancer and other invasive breast cancers. *J Natl Cancer Inst*. 2013;105(18):1373-1384.
17. Dawood S, Broglio K, Gonzalez-Angulo AM, et al. Prognostic value of body mass index in locally advanced breast cancer. *Clin Cancer Res*. 2008;14(6):1718-1725.
18. Chang S, Buzdar AU, Hursting SD. Inflammatory breast cancer and body mass index. *J Clin Oncol*. 1998;16(12):3731-3735.
19. Hirko KA, Soliman AS, Banerjee M, et al. Characterizing inflammatory breast cancer among Arab Americans in the California, Detroit and New Jersey Surveillance, Epidemiology and End Results (SEER) registries (1988-2008). *Springerplus*. 2013;2(1):3.
20. Mohamed HT, El-Shinawi M, Nouh MA, et al. Inflammatory breast cancer: high incidence of detection of mixed human cytomegalovirus genotypes associated with disease pathogenesis. *Front Oncol*. 2014;4:246.
21. Mejri N, Boussen H, Labidi S, et al. Inflammatory breast cancer in Tunisia from 2005 to 2010: epidemiologic and anatomoclinical transitions from published data. *Asian Pac J Cancer Prev*. 2015;16(3):1277-1280.
22. Levine PH, Veneroso C. The epidemiology of inflammatory breast cancer. *Semin Oncol*. 2008;35(1):11-16.
23. Levine PH, Portera CC, Hoffman HJ, et al. Evaluation of lymphangiogenic factors, vascular endothelial growth factor D and E-cadherin in distinguishing inflammatory from locally advanced breast cancer. *Clin Breast Cancer*. 2012;12(4):232-239.
24. Abeywardhana DY, Nascimento VC, Dissanayake D, et al. Review of ultrasound appearance in inflammatory breast cancer: a pictorial essay. *J Med Imaging Radiat Oncol*. 2016;60(1):83-87.
25. Arora J, Sauer SJ, Tarpley M, et al. Inflammatory breast cancer tumor emboli express high levels of anti-apoptotic proteins: use of a quantitative high content and high-throughput 3D IBC spheroid assay to identify targeting strategies. *Oncotarget*. 2017;8(16):25848-25863.
26. Le-Petross HT, Lim B. Role of MR imaging in neoadjuvant therapy monitoring. *Magn Reson Imaging Clin N Am*. 2018;26(2):207-220.
27. Yamauchi H, Woodward WA, Valero V, et al. Inflammatory breast cancer: what we know and what we need to learn. *Oncologist*. 2012;17(7):891-899.
28. Gunhan-Bilgen I, Ustun EE, Memis A. Inflammatory breast carcinoma: mammographic, ultrasonographic, clinical, and pathologic findings in 142 cases. *Radiology*. 2002;223(3):829-838.
29. O'Connor MK. Molecular breast imaging: an emerging modality for breast cancer screening. *Breast Cancer Manag*. 2015;4(1):33-40.
30. Al-Faham Z, Al-Katib S, Jaiyesimi I, Bhavnagri S. Evaluation of a case of inflammatory breast cancer with 18F-FDG PET/CT. *J Nucl Med Technol*. 2015;43(4):289-291.
31. Champion L, Lerebours F, Alberini JL, et al. 18F-FDG PET/CT to predict response to neoadjuvant chemotherapy and prognosis in inflammatory breast cancer. *J Nucl Med*. 2015;56(9):1315-1321.
32. Champion L, Lerebours F, Cherel P, et al. (1)(8)F-FDG PET/CT imaging versus dynamic contrast-enhanced CT for staging and prognosis of inflammatory breast cancer. *Eur J Nucl Med Mol Imaging*. 2013;40(8):1206-1213.
33. Alberini JL, Lerebours F, Wartski M, et al. 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) imaging in the staging and prognosis of inflammatory breast cancer. *Cancer*. 2009;115(21):5038-5047.
34. Denu RA, Hampton JM, Currey A, et al. Influence of patient, physician, and hospital characteristics on the receipt of guideline-concordant care for inflammatory breast cancer. *Cancer Epidemiol*. 2015;40:7-14.
35. Rueth NM, Lin HY, Bedrosian I, et al. Underuse of trimodality treatment affects survival for patients with inflammatory breast cancer: an analysis of treatment and survival trends from the National Cancer Database. *J Clin Oncol*. 2014;32(19):2018-2024.
36. Ueno NT, Buzdar AU, Singletary SE, et al. Combined-modality treatment of inflammatory breast carcinoma: twenty years of experience at M. D. Anderson Cancer Center. *Cancer Chemother Pharmacol*. 1997;40(4):321-329.
37. Baldini E, Gardin G, Evagelista G, Prochilo T, Collecchi P, Lionetto R. Long-term results of combined-modality therapy for inflammatory breast carcinoma. *Clin Breast Cancer*. 2004;5(5):358-363.
38. Ueno NT, Fernandez JRE, Cristofanilli M, et al. International Consensus on the Clinical Management of Inflammatory Breast Cancer from the Morgan Welch Inflammatory Breast

Cancer Research Program 10th Anniversary Conference. *J Cancer.* 2018;9(8):1437-1447.
39. Cristofanilli M, Buzdar AU, Sneige N, et al. Paclitaxel in the multimodality treatment for inflammatory breast carcinoma. *Cancer*. 2001;92(7):1775-1782.
40. Huober J, von Minckwitz G, Denkert C, et al. Effect of neoadjuvant anthracycline-taxane-based chemotherapy in different biological breast cancer phenotypes: overall results from the GeparTrio study. *Breast Cancer Res Treat*. 2010;124(1):133-140.
41. Tsai CJ, Li J, Gonzalez-Angulo AM, et al. Outcomes after multidisciplinary treatment of inflammatory breast cancer in the era of neoadjuvant HER2-directed therapy. *Am J Clin Oncol*. 2015;38(3):242-247.
42. von Minckwitz G, Huang C-S, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med.* 2019;380(7):617-628.
43. Chan A, Delaloge S, Holmes FA, et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2016;17(3):367-377.
44. Matro JM, Li T, Cristofanilli M, et al. Inflammatory breast cancer management in the National Comprehensive Cancer Network: the disease, recurrence pattern, and outcome. *Clin Breast Cancer*. 2015;15(1):1-7.
45. Kell MR, Morrow M. Surgical aspects of inflammatory breast cancer. *Breast Dis.* 2005;22:67-73.
46. Fleming RY, Asmar L, Buzdar AU, et al. Effectiveness of mastectomy by response to induction chemotherapy for control in inflammatory breast carcinoma. *Ann Surg Oncol*. 1997;4(6):452-461.
47. Bozzetti F, Saccozzi R, De Lena M, Salvadori B. Inflammatory cancer of the breast: analysis of 114 cases. *J Surg Oncol.* 1981;18(4):355-361.
48. Walker GV, Niikura N, Yang W, et al. Pretreatment staging positron emission tomography/computed tomography in patients with inflammatory breast cancer influences radiation treatment field designs. *Int J Radiat Oncol Biol Phys.* 2012;83(5):1381-1386.
49. Takiar V, Akay CL, Stauder MC, et al. Predictors of durable no evidence of disease status in de novo metastatic inflammatory breast cancer patients treated with neoadjuvant chemotherapy and post-mastectomy radiation. *Springerplus.* 2014;3:166.
50. Woodward WA. Postmastectomy radiation therapy for inflammatory breast cancer: is more better? *International Journal of Radiation Oncology Biology Physics*. 2014;89(5):1004-1005.
51. Michmerhuizen AR, Pesch AM, Moubadder L, et al. PARP1 inhibition radiosensitizes models of inflammatory breast cancer to ionizing radiation. *Mol Cancer Ther.* 2019;18(11):2063-2073.
52. Woodward WA, Fang P, Arriaga L, et al. A phase 2 study of capecitabine and concomitant radiation in women with advanced breast cancer. *Int J Radiat Oncol Biol Phys.* 2017;99(4):777-783.
53. Hall CS, Karhade M, Laubacher BA, et al. Circulating tumor cells and recurrence after primary systemic therapy in stage III inflammatory breast cancer. *J Natl Cancer Inst*. 2015;107(11):djv250.
54. Yalcin B. Overview on locally advanced breast cancer: defining, epidemiology, and overview on neoadjuvant therapy. *Exp Oncol.* 2013;35(4):250-252.
55. Schlichting JA, Soliman AS, Schairer C, Schottenfeld D, Merajver SD. Inflammatory and non-inflammatory breast cancer survival by socioeconomic position in the Surveillance, Epidemiology, and End Results database, 1990-2008. *Breast Cancer Res Treat*. 2012;134(3):1257-1268.
56. Akay CL, Ueno NT, Chisholm GB, et al. Primary tumor resection as a component of multimodality treatment may improve local control and survival in patients with stage IV inflammatory breast cancer. Cancer. 2014;120(9):1319-1328.
57. Khan SA, Zhao F, Solin LJ, et al. A randomized phase III trial of systemic therapy plus early local therapy versus systemic therapy alone in women with de novo stage IV breast cancer: a trial of the ECOG-ACRIN Research Group (E2108). ASCO20 Virtual Scientific Program. *J Clin Oncol*. 2020;38(suppl 18):abstract LBA2 2020.
58. Badwe R, Hawaldar R, Nair N, et al. Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial. *Lancet Oncol*. 2015;16(13):1380-1388.
59. Soran A, Ozmen V, Ozbas S, et al. A randomized controlled trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer: Turkish Study (Protocol MF07-01). *J Clin Oncol*. 2016;34(suppl);abstract 1005.
60. Weiss A, Chavez-MacGregor M, Lichtensztajn DY, et al. Validation study of the American Joint Committee on Cancer Eighth Edition Prognostic Stage Compared With the Anatomic Stage in Breast Cancer. *JAMA Oncol.* 2018;4(2):203-209.
61. Cristofanilli MC, Valero V, Buzdar AU, et al. Inflammatory breast cancer (IBC) and patterns of recurrence: understanding the biology of a unique disease. *Cancer*. 2007;110(7):1436-1444.
62. Masuda H, Baggerly KA, Wang Y, et al. Comparison of molecular subtype distribution in triple-negative inflammatory and non-inflammatory breast cancers. *Breast Cancer Res*. 2013;15(6):R112.
63. Van Laere SJ, Ueno NT, Finetti P, et al. Uncovering the molecular secrets of inflammatory breast cancer biology: an integrated analysis of three distinct affymetrix gene expression datasets. *Clin Cancer Res*. 2013;19(17):4685-4696.
64. Ye Y, Gao JX, Tian H, et al. Early to intermediate steps of tumor embolic formation involve specific proteolytic processing of E-cadherin regulated by Rab7. *Mol Cancer Res*. 2012;10(6):713-726.
65. Charafe-Jauffret E, Ginestier C, Iovino F, et al. Aldehyde dehydrogenase 1-positive cancer stem cells mediate metastasis and poor clinical outcome in inflammatory breast cancer. *Clin Cancer Res*. 2010;16(1):45-55.
66. Xiao Y, Ye Y, Zou X, et al. The lymphovascular embolus of inflammatory breast cancer exhibits a Notch 3 addiction. *Oncogene*. 2011;30(3):287-300.
67. Ma CX, Gao F, Luo J, et al. NeoPalAna: neoadjuvant palbociclib, a cyclin-dependent kinase 4/6 inhibitor, and anastrozole for clinical stage 2 or 3 estrogen receptor-positive breast cancer. *Clin Cancer Res*. 2017;23(15):4055-4065.
68. Prat A, Saura C, Pascual T, et al. Ribociclib plus letrozole versus chemotherapy for postmenopausal women with hormone receptor-positive, HER2-negative, luminal B breast cancer (CORALLEEN): an open-label, multicentre, randomised, phase 2 trial. *Lancet Oncol*. 2020;21(1):33-43.
69. Bertucci F, Ueno NT, Finetti P, et al. Gene expression profiles of inflammatory breast cancer: correlation with response to neoadjuvant chemotherapy and metastasis-free survival. *Ann Oncol*. 2014;25(2):358-365.
70. Silvera D, Schneider RJ. Inflammatory breast cancer cells are constitutively adapted to hypoxia. *Cell Cycle.* 2009;8(19):3091-3096.
71. Jolly MK, Boareto M, Debeb BG, et al. Inflammatory breast cancer: a model for investigating cluster-based dissemination. *NPJ Breast Cancer*. 2017;3:21.
72. Morrow RJ, Etemadi N, Yeo B, Ernst M. Challenging a misnomer? The role of inflammatory pathways in inflammatory breast cancer. *Mediators Inflamm.* 2017;2017:4754827.
73. Wolfe AR, Trenton NJ, Debeb BG, et al. Mesenchymal stem cells and macrophages interact through IL-6 to promote inflammatory breast cancer in pre-clinical models. *Oncotarget*. 2016;7(50):82482-82492.

This page intentionally left blank

38 Special Situations in Breast Cancer

Rachel M. Layman

KEY CONCEPTS

- Management of pregnancy-associated breast cancer requires careful multidisciplinary care and coordination for optimal outcomes.
- Pregnancy after a breast cancer diagnosis is not associated with worsened outcomes, based on retrospective data.
- Male breast cancer management is largely extrapolated from data on female breast cancer; however, tamoxifen is the preferred endocrine therapy agent.
- Combined hormone replacement therapy with estrogen and progesterone in postmenopausal women increases the risk of developing breast cancer, but risk is not clearly increased with estrogen-only therapy.
- Adjuvant endocrine therapy with tamoxifen or an aromatase inhibitor can be considered for estrogen receptor–positive ductal carcinoma in situ.
- Patients with pathogenic mutations in breast cancer susceptibility genes should be counseled regarding the risks and benefits of screening and prevention options.

BREAST CANCER DURING PREGNANCY

Epidemiology

Pregnancy-associated breast cancer (PABC) is defined as breast cancer diagnosed during pregnancy, the 12 months after delivery, or during lactation. Breast cancer is one of the most common cancers diagnosed during pregnancy. Because many women delay pregnancy, and age is a risk factor for breast cancer, the incidence of PABC appears to be rising. A Swedish National Health Registry study showed increased incidence from 16 to 37.4 per 100,000 deliveries between 1963 and 2002.[1] Factors associated with PABC included age 35 years or older, private insurance, and delivery in an urban teaching hospital.[2] Pregnancy itself is associated with a transient increase in breast cancer risk, followed by a reduced risk later in life.[3]

Diagnosis

PABC most commonly presents as a painless mass that is self-detected or noted on clinical examination. The duration of symptoms is often longer in patients with PABC compared with their nonpregnant counterparts. Physiologic changes in a pregnant woman's breast, especially in women older than 30 years, lack of physician familiarity with PABC, and socioeconomic and cultural factors may contribute to delays in diagnosis.[4]

Biopsy

Although the majority of breast masses during pregnancy are benign, a breast mass that does not resolve within 2 weeks requires further investigation.[5] Any clinically suspicious breast mass should be biopsied for a definitive diagnosis. Although a number of small studies have demonstrated diagnostic accuracy of fine-needle aspiration, a core or excisional biopsy is necessary to identify invasion (Fig. 38–1).[6]

Two large surgical series of pregnant patients who had general anesthesia for various medical problems failed to demonstrate an increased risk of congenital malformations compared with those not undergoing surgery.[7,8] Ultimately, the least invasive, but most technically accurate method(s) available are recommended to determine the nature of a breast mass in a pregnant woman.

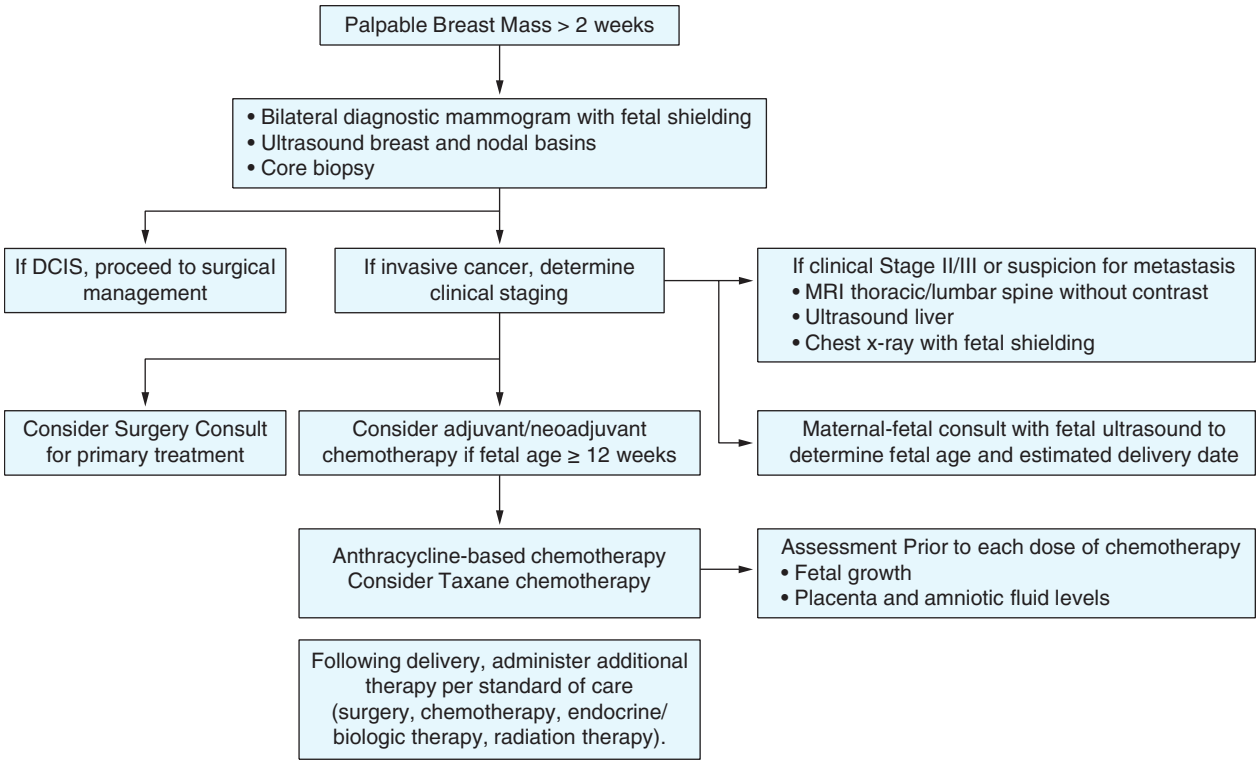


FIGURE 38–1 **Algorithm for the evaluation and treatment of a suspicious breast mass during pregnancy. DCIS, ductal carcinoma in situ; MRI, magnetic resonance imaging.**

Diagnostic Imaging

Mammography and Ultrasound

Mammography can be safely performed during pregnancy with abdominal shielding. The estimated fetal radiation exposure is <0.01 Gy, which is considered to cause minimal fetal risk (Table 38–1).[9] Ultrasound imaging is preferred because of its lack of radiation exposure and better sensitivity in young patients. Ultrasonography is also a valuable tool for nodal basin evaluation before treatment, and disease response monitoring during preoperative chemotherapy.[9]

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) for evaluation of breast masses in pregnant or lactating women has not been studied. Gadolinium crosses the placenta and causes fetal abnormalities in animal studies. As such, gadolinium is a FDA Class C drug in pregnancy (Table 38–2) and should not be routinely used during pregnancy.[5]

Table 38–1 Fetal Radiation Exposure

Background fetal radiation exposure through pregnancy	1 mGy
Threshold of acceptable fetal exposure	<50 mGy
Threshold for congenital fetal loss, congenital anomalies, intellectual effects	60–200 mGy
Mammogram 2 views	0.001–0.01 mGy
Chest radiograph	0.0005–0.001 mGy
Chest CT	0.01–0.66 mGy
Bone scan T99	4–5 mGy
Abdominal CT	1.3–3.5 mGy
Pelvic CT	10–50 mGy
Pet CT whole body	10–50 mGy

Adapted from Guidelines for Diagnostic Imaging During Pregnancy and Lactation. American College of Obstetrics and Gynecology, Committee Opinion 723, October 2017.
mGy, milligray; CT, computed tomography; T99, technetium-99m.
Data from Tremblay E, Thérasse E, Thomassin-Naggara I, et al: Quality initiatives: guidelines for use of medical imaging during pregnancy and lactation, Radiographics May-Jun 2012;32(3):897-911.

Pathologic Features of Breast Cancer During Pregnancy

The most common subtype of PABC is invasive ductal carcinoma. In an MDACC case series of patients with breast cancer treated with chemotherapy during pregnancy, PABC was diagnosed at a more advanced stage, had more lymph node involvement, and poorer histologic and prognostic features, including high Ki67 and estrogen receptor (ER) and progesterone receptor (PR) negativity. HER2-positive tumors comprised 28% of the specimens. The authors observed that the features

Table 38–2 FDA Pregnancy Category Definition

A. Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester, and the possibility of fetal harm appears remote.
B. Animal studies do not indicate a risk to the fetus and there are no controlled human studies or animal studies to show an adverse effect on the fetus, but well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.
C. Studies have shown that the drug exerts animal teratogenic or embryocidal effects, but there are no controlled studies in women, or no studies are available in either animals or women.
D. Positive evidence of human fetal risk exists, but benefits in certain situations (eg, life-threatening situations or serious diseases for which safer drugs cannot be used or are ineffective) may make use of the drug acceptable despite its risks.
X. Studies in animals or humans have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience, or both, and the risk clearly outweighs any positive benefit.

Reproduced with permission from Litton JK, Theriault RL. Breast cancer and pregnancy: current concepts in diagnosis and treatment, *Oncologist* 2010;15(12):1238-1247.

were similar to those reported in young nonpregnant women, concluding that age, rather than pregnancy, may be the determinant of tumor biology.[10]

Staging

The American Joint Committee on Cancer's tumor-node-metastasis system is used for staging in PABC. Because stage at diagnosis may have significant treatment and psychosocial implications, accurate staging is important.

A complete history and physical examination and laboratory work, including complete blood cell counts and metabolic panel, is recommended before treatment. Locoregional imaging should include mammography and ultrasonography of the breast and draining lymphatics. Because women with PABC often present with advanced-stage disease, the major sites of metastatic disease (lung, liver, and bone) should be evaluated in patients with concerning symptoms or stage II or higher disease, with modifications for fetal protection. Evaluation includes chest radiography with abdominal shielding, liver ultrasonography, and MRI of the spine without contrast. A transthoracic echocardiogram before initiation of anthracycline chemotherapy is recommended.[5]

Treatment of Breast Cancer During Pregnancy

The goals of treatment in both pregnant and nonpregnant women are the same: control of locoregional and systemic disease. Although the treatment strategies are similar, the impact of the treatment on the fetus and pregnancy outcome should be considered in PABC.

Local Therapy

As previously discussed, anesthesia during pregnancy is not associated with an increased risk of fetal malformation.[7,8] Often, surgery is delayed until the end of the first trimester to minimize the risk of spontaneous abortion. Most reports show that women largely undergo total mastectomy with axillary staging, possibly reflecting treatment practice during that time period, later stage at diagnosis, or concern about the need for radiation with breast-conserving surgery (BCS). Fortunately, surgical therapies have evolved, even in women with PABC. Breast radiation is generally contraindicated during pregnancy given the risk of fetal radiation exposure. As modern practices recommend systemic therapy and surgery as initial treatment strategies, radiation therapy can usually be delayed until after delivery.[5,11]

In a MDACC series of 67 women with PABC who received chemotherapy during pregnancy before surgery, 47 had mastectomy and 20 had BCS. Of six postoperative complications (four with mastectomy, two with BCS), all could be managed in the outpatient setting. The authors concluded that BCS is feasible with no increased complication rates.[12]

A report from the Cancer and Pregnancy Registry of 130 women with PABC showed that 95 patients had surgery while pregnant: 38 in the first trimester, 48 in the second, and nine in the third. Fifty-four patients had mastectomy, 34 had lumpectomy, and 15 had an excisional biopsy with no additional surgery. The miscarriage rate in the first trimester was not increased compared with the general population.[13]

There are limited data on the use of sentinel lymph node biopsy (SLNB) in pregnant patients. Isosulfane blue dye is not recommended because of reports of anaphylaxis as well as concerns for fetal safety.[5] Radiolabeled sulfur colloid appears to be safe for SLNB in pregnancy, with a very low fetal radiation absorption[14,15] and has demonstrated accurate mapping.[16] However, the data are very limited, consisting of reports of small case series, and should be interpreted with caution.

Systemic Therapy

The indications for systemic therapy in a pregnant patient with breast cancer are similar to those in the nonpregnant patient. Most of the chemotherapy agents used in pregnancy are Category D (Table 38–2). There are limited data on the pharmacokinetics of antineoplastic agents in the setting of the physiologic changes of pregnancy. Retrospective data of pregnant cancer patients treated with chemotherapy for a variety of malignancies demonstrated that the 14% to 19% incidence of fetal malformations in the first trimester exposure dropped to 1.3% with exposure in the second and third trimesters.[17] Another series reported an overall 3.8% rate of congenital malformations, which is not increased compared with the general population.[13]

Chemotherapy

A prospective cohort study of 81 patients with PABC treated with systemic chemotherapy during the second and third trimesters was performed at MDACC.[18] Chemotherapy with FAC (5-fluorouracil 500 mg/m^2 intravenous [IV] on days 1 and 4; doxorubicin 50 mg/m^2 IV continuous infusion over 72 hours; and cyclophosphamide 500 mg/m^2 IV on day 1; every 21–28 days) was administered for a median of four cycles. Chemotherapy was held after 35 weeks to avoid maternal neutropenia at the time of delivery. All women had live births, one child had Down syndrome, and two children had congenital anomalies (clubfoot; ureteral reflux). Based on collected survey data, at a median age of 7 years, the children with prior exposure to chemotherapy in utero did not exhibit an increased rate of serious medical problems than that expected in the general population.

The European registry published a report detailing outcomes of 413 women who received systemic chemotherapy during pregnancy. Multiple regimens were used, including taxanes, cyclophosphamide/methotrexate/fluorouracil (CMF), and anthracyclines. Obstetric complications were more common in women receiving chemotherapy compared with those who did not (17% and 9%, respectively). At the same gestational age, infants exposed to chemotherapy in utero had lower birth weights, deemed to be clinically insignificant by the authors, and had an increased risk of complications compared with infants not exposed. Most complications were observed in premature infants and the authors concluded that continuing pregnancy to term delivery is crucial to decrease the risk of infant complications.[19]

A systematic review of 50 women with PABC who received various taxane regimens after the first trimester revealed that 77% of the neonates were healthy at birth, and 90% of the children were completely healthy at their 16-month follow-up. One child had recurrent otitis media, another had immunoglobulin A deficiency and constipation, and one had delayed speech.[20] Safety may be related, in part, to fetal protection from excessive taxane exposure through high placental P-glycoprotein expression, and increased taxane clearance during the third trimester.[21] An international consensus meeting concluded that taxane chemotherapy is reasonable during the second and third trimesters, with small maternal and fetal risk.[22]

At MDACC, pregnant women with breast cancer are treated with anthracycline-based and taxane chemotherapy. Administration of methotrexate is not recommended because it is teratogenic and associated with spontaneous abortion.[23]

Endocrine Therapy

Tamoxifen use during pregnancy is contraindicated given animal data suggesting that it could be teratogenic. In addition, case reports in humans describe congenital malformations, including Goldenhar syndrome, ambiguous genitalia, vaginal bleeding, and spontaneous abortions.[5,22]

Biologic Agents

Trastuzumab use in pregnancy is not recommended given multiple reports of oligohydramnios and anhydramnios in the literature.[5,24] Lapatinib exposure during pregnancy was described in one patient who received lapatinib until 11 weeks of gestation, followed by drug discontinuation and an uneventful pregnancy, with eventual delivery of a healthy baby.[25] However, lapatinib is not recommended given insufficient safety data. Accordingly, inadequate data exist to guide the use of pertuzumab or ado-trastuzumab-emtansine during pregnancy.

Prognosis

The literature regarding PABC prognosis is mixed. A large meta-analysis of 30 studies included 3628 PABC and 37,100 control cases.[26] Overall, women with PABC were at increased risk for death with hazard ratio (HR) of 1.44 (95% CI 1.27–1.63). Outcomes were worse for patients diagnosed after pregnancy (HR 1.84, 95% CI 1.28–2.65), whereas women diagnosed during pregnancy were not clearly at increased risk (HR 1.29, 95% CI 0.74–2.24). A cohort study of 311 European women with PABC revealed no significant difference in disease-free survival (DFS) or overall survival (OS) when compared with a cohort of nonpregnant women.[27]

Data from MDACC showed no difference in locoregional recurrence, distant metastasis, or OS between 104 young women 35 years old or younger with PABC and their 564 nonpregnant counterparts, treated between 1973 and 2006.[28] In addition, data on 75 patients treated for PABC in a controlled setting on

a MDACC protocol with FAC chemotherapy during the second and third trimesters revealed improved DFS and OS compared with age- and stage-matched nonpregnant control patients.[29] Therefore, a multidisciplinary approach to the management of PABC is able to provide patients with at least as favorable outcomes as their nonpregnant counterparts.

Monitoring the Pregnancy

The pregnant patient with breast cancer should be referred to a high-risk obstetrician skilled in maternal-fetal medicine, who will be charged with monitoring the health of the mother and fetus while undergoing cancer therapy.

Ultrasonography for fetal viability, gestational age, and expected date of delivery is important for treatment planning. Ideally, ultrasonography is performed before every chemotherapy dose for fetal growth and development assessment. Amniocentesis may be recommended if the fetus is thought to be at higher-than-average risk for karyotype abnormalities or based on concerning ultrasound findings. Although not part of the routine evaluation, amniocentesis may also be necessary to assess fetal lung maturity, particularly if early induction of labor is being considered.

Timing of delivery should be optimized with relation to systemic treatment, ideally occurring no less than 3 weeks after the last dose of chemotherapy to minimize the risk of cytopenias.[22] Planned inductions of labor and cesarean deliveries are often performed to minimize pregnancy-associated complication risk.[11]

Breastfeeding

Many cancer therapeutic agents are excreted in breast milk and can carry risk to the infant. Therefore, breastfeeding should be avoided during the administration of chemotherapy, biologic agents, endocrine therapy (ET), and radiation therapy.

Long-Term Implications for the Offspring

MDACC reported on 81 children born to mothers who underwent chemotherapy in the second or third trimesters. Surveys performed by parents/guardians of children exposed to anthracycline-based chemotherapy in utero assessed the child's health, development, and school performance. Developmental delays were reported in 12% of the children, similar to the reported prevalence of 10% in the general population.[18] At the time of the most recent survey, the median age was 7 years (range <1–21). Allergies and eczema were the only reported long-term health problems that were more common than those expected in the general population. However, longer follow-up is needed to evaluate possible late side effects, such as cognitive impairment and fertility problems. Another study described similar outcomes for children born to mothers who received chemotherapy for hematologic malignancies during pregnancy.[30] Eighty-one children had cardiac evaluation by clinical evaluation and echocardiography every 5 years after birth until 29 years of age (mean 17.1 y) with no evidence of cardiac dysfunction.[30]

A multicenter case-control study evaluated 129 children who were in utero while their mothers had cancer and were compared with matched controls.[31] A nonsignificant increase in small-for-gestational-age infants was seen in the cancer cohort compared with controls, 22% versus 15.2% (P = .16). Premature birth, regardless of receipt of cancer therapy, was associated with decreased cognitive outcomes, again emphasizing the importance of avoiding early delivery in patients with PABC. A large international cohort study published the outcomes of 1170 women who had cancer while pregnant, 39% of whom had breast cancer.[32] Overall, 21% of neonates were small for gestational age. A trend for chemotherapy association with small-for-gestational-age infants was reported; however, the relationship was most convincing with platinum chemotherapies and it is difficult to draw conclusions for other agents. Prematurity was common, representing almost half of births, with the vast majority of premature births, 88%, being iatrogenic.

Pregnancy Termination

A number of case series do not support the previously held belief that pregnancy termination improves the survival with PABC. In contrast, there appears to be a trend toward shorter survival with termination of pregnancy.[33] Patients must be made fully aware of the evidence, or lack thereof, regarding pregnancy termination and survival. In situations of known or suspected fetal teratogenesis, or if maternal health is in jeopardy, pregnancy termination may be an appropriate medical recommendation.

PREGNANCY AFTER A DIAGNOSIS OF BREAST CANCER

Epidemiology

Of the women in the United States diagnosed with breast cancer from 2012 to 2016, 1% were 20 to 29 years old, 4% were 30 to 39 years, and 14% were 40 to 49 years.[34] In 2017, the mean age of first-time mothers in the United States was 26.8 years,[35] and data from the National Center for Health Statistics demonstrates the trend of women bearing children at later ages.[35,36] The first birth rates in women aged 35 to 44 have

increased, but have decreased in women younger than 30, especially in the age group younger than 20.[35,36] Thus, younger women diagnosed with breast cancer may not have completed childbearing at the time of their diagnosis and may seek to do so after their treatment is complete.

Chemotherapy-Related Amenorrhea

Chemotherapy-related amenorrhea (CRA) is variable defined as cessation of menstruation for 3 to 12 months in women with chemotherapy exposure.[37] The incidence of CRA varies with age, cytotoxic agent used, and cumulative cytotoxic dose.[37] A study of 183 women who underwent systemic therapy, including chemotherapy and tamoxifen, for breast cancer revealed that age and chemotherapy were the primary predictors of menopause.[38] Taxanes may result in a higher CRA rate in the first year, but after two years, the rates of CRA are similar regardless of taxane administration. Women older than 40 also had higher rates of CRA.[39]

The preferred fertility preservation approach recommended by the American Society of Clinical Oncology (ASCO) is controlled ovarian stimulation followed by oocyte or embryo cryopreservation.[40] Concurrent administration of an aromatase inhibitor (AI) can be used to decrease estrogen exposure during ovarian stimulation. A prospective study revealed no significant difference in DFS compared with women who did not undergo ovarian stimulation, based on short follow-up of approximately 2 years.[41] A large retrospective study evaluated the outcomes of assisted reproductive technology by query of the Society for Assisted Reproductive Technology Clinic Outcome Reporting System database. Although women with a history of breast cancer had successful pregnancies, the live birth rate was significantly lower compared with women without a history of cancer. Use of autologous oocytes in women diagnosed with breast cancer 6 months to 5 years prior had a 23.3% live birth rate. However, birth rate improved to 62.5% with donor oocytes, similar to women without cancer.[42]

Unfortunately, cryopreservation is not practical for many women, in which case, ovarian suppression by a gonadotropin-releasing hormone analogue (GnRHa) can be offered. However, evidence of efficacy is inconsistent and ovarian suppression should not be considered as a replacement for proven techniques. GnRHa used to reduce CRA risk has been evaluated in clinical trials. For example, a study that randomly assigned 60 premenopausal women with hormone receptor–negative (HR–) breast cancer to chemotherapy with or without goserelin revealed no significant difference in amenorrhea at 6 months, and only one patient did not have resumption of regular menses at 2 years.[43]

The PROMISE-GIM6 (Prevention of Menopause Induced by Chemotherapy: A Study in Early Breast Cancer Patients-Gruppo Italiano Mammella 6) trial randomly assigned 281 women with stage I–III breast cancer to chemotherapy with or without triptorelin. Women treated with triptorelin were more likely to regain ovarian function with resumption of menses (age-adjusted HR 1.48, 95% CI 1.12–1.95; $P = .006$),[44] and there was no significant difference in 5-year DFS. In the ER-positive population, outcomes were very similar with 5-year DFS—85.1% in the triptorelin arm compared with 85.2% with control[44]; however, the study was not adequately powered for this exploratory end point.

The POEMS/SWOG (Southwest Oncology Group) 0230 trial randomly assigned 257 premenopausal women with stage I–IIIA HR– breast cancer to receive cyclophosphamide-containing chemotherapy with or without goserelin. There was a decrease in premature ovarian failure (POF) at 2 years (8% vs 22%) and more successful pregnancies in the goserelin arm.[45] A meta-analysis revealed a significant decrease in POF (odds ratio [OR] 0.43, 95% CI 0.22–0.84; $P = .013$) in patients receiving GnRHa.[46]

Impact of Pregnancy After Breast Cancer

Meta-analysis[47] and a number of reviews have concluded that pregnancy after a breast cancer diagnosis does not worsen survival.[48–50] In a retrospective case-control study, data from three Surveillance, Epidemiology, and End Results (SEER) populations were linked to vital records data to identify women with breast cancer who were younger than 45 years at diagnosis and who had live births 10 months or more after diagnosis. When matched with nonpregnant women with a history of breast cancer, women who became pregnant had a decreased risk of dying (relative risk [RR] 0.54, 95% CI 0.41–0.71).[51,52] Another retrospective cohort study that matched breast cancer patients by multiple factors, including ER status, revealed similar DFS and improved OS in patients who had pregnancy. Although OS was improved in the women with ER– tumors (HR 0.57, 95% CI 0.36–0.90; $P = .01$), but not in ER+ tumors (HR 0.84, 95% CI 0.60–1.18, $P = .32$),[52,53] this demonstrated that that pregnancy was not harmful with history of ER+ breast cancer. The improved survival noted in this and other studies may reflect a "healthy-mother effect," whereby women who become pregnant may have already been at decreased risk of recurrence.

Women considering pregnancy after a breast cancer diagnosis should understand that most data derive from retrospective case-control studies in different populations and with different data collection techniques. Patients must be aware of their personal risk

of recurrence and should weigh this against their desire to have a child. In addition, patients should not become pregnant while receiving anticancer therapy. Although it has been suggested that women should wait 2 years after their breast cancer diagnosis before becoming pregnant, there are no data suggesting that a pregnancy in the first 2 years increases the risk of recurrence; rather, data indicate that this is the period of increased recurrence regardless of pregnancy.[54] Patients with ER+ breast cancer receive adjuvant ET; the risk of interruption of therapy for pregnancy is unknown and is being evaluated in clinical trials.

Infant outcomes may also need to be considered. A retrospective study using the North Carolina Central Cancer Registry and vital statistics revealed that breast cancer patients who received chemotherapy, and women with delivery less than 2 years from diagnosis had higher rates of preterm birth, low-birth-weight infants, and small-for-gestational-age infants.[55] Another study using data from the FUCHSIA Women's Study also revealed increased risk of preterm birth and low birth weight in infants of breast cancer patients who become pregnant less than 1 year after completion of chemotherapy with or without radiation.[56]

MALE BREAST CANCER

Epidemiology

Male breast cancer is rare, accounting for less than 1% of male cancers and less than 1% of all breast cancers. It was estimated that 2670 new cases of male breast cancer would be diagnosed in the United States in 2019 and that 500 would die of the disease.[57] Despite its rarity, the incidence is increasing.[58,59] As with women, incidence increases with age, but men diagnosed with breast cancer are older compared with women, with the average age of diagnosis being approximately 5 years higher.[59]

Genetic mutations can influence the risk of breast cancer developing in men. BRCA mutation is a known risk factor, with a lifetime risk of 4% to 16% with *BRCA2* and up to 4% for *BRCA1*.[60] A study evaluating 1939 families using the National Cancer Institute's Cancer Genetics Network revealed that the estimated cumulative risk of breast cancer in men by age 70 was 6.8% for *BRCA2* carriers and 1.2% *for BRCA1*.[61] Other genetic mutations, such as *CHEK2*, *PALB2*, and *PTEN* may also increase the risk.[59,60] It is estimated that more than 20% of male patients with breast cancer will have detectible genetic mutations; therefore, genetic counseling is recommended for all men with breast cancer, per ASCO and National Comprehensive Cancer Network (NCCN) guidelines.[60,62]

Other risk factors include positive family history, radiation exposure, and increasing age. Elevated estrogen levels increase the risk of male breast cancer, which can occur in conjunction with liver disease, testicular abnormalities, obesity, gynecomastia, and Klinefelter syndrome.[59] There is a doubling in risk in men with a first-degree relative with breast cancer.[63]

Diagnosis and Staging

The most common presenting symptom of breast cancer in men is a painless lump, often in the retro-areolar location. Other symptoms include nipple retraction, local pain, skin ulceration, nipple bleeding or discharge, or axillary lymphadenopathy.[59] The mean age of diagnosis is 68 years and diagnosis below the age of 40 is rare.[64] Men are more likely to have a delay in diagnosis compared with women and, accordingly, tend to be diagnosed in a later stage of the disease.[65,66] Although this may, in part, account for observations of worse prognosis in men, a study evaluating outcomes from the SEER database demonstrated increased mortality compared with women in a multivariate analysis that controlled for major risk factors, such as stage and hormone receptor status (HR 1.43, 95% CI 1.26–1.61).[65] Another study utilizing the National Cancer Database also demonstrated worsened prognosis in men, which could partially be accounted for by lower administration of appropriate standard treatment in the male population.[66]

Breast imaging with mammography and/or ultrasonography of any suspicious breast mass is recommended, followed by biopsy, if indicated. If breast cancer is diagnosed, staging evaluation appropriate for the given tumor stage should be performed.

Pathologic Features of Male Breast Cancer

Approximately 85% of male breast cancers are infiltrating ductal carcinoma, with only 1% to 2% being invasive lobular.[64,67] The rarity of lobular carcinoma may be the result of little terminal lobule development in men.[10,59,64] Breast cancers in men are primarily hormone receptor–positive (HR+) with a low rate of HER2 positivity. Most are positive for androgen receptor (AR). Central pathology assessment of 1054 early-stage male breast cancers from the International Male Breast Cancer Program database revealed that 99% were ER+, 82% PR+, 8.7% HER2+, and 97% AR+ (Fig. 38–2B).[64] Small studies suggest that genomic profiles may also differ between male and female breast cancers. For example, male breast cancers are more likely to be Luminal B (Fig. 38–2A).[64,68] Genomic analysis has detected lower rates of somatic mutations in *PIK3CA*, PI3K/AKT/mTOR pathway genes, and *TP53* in men with ER+, HER2– breast cancer compared with

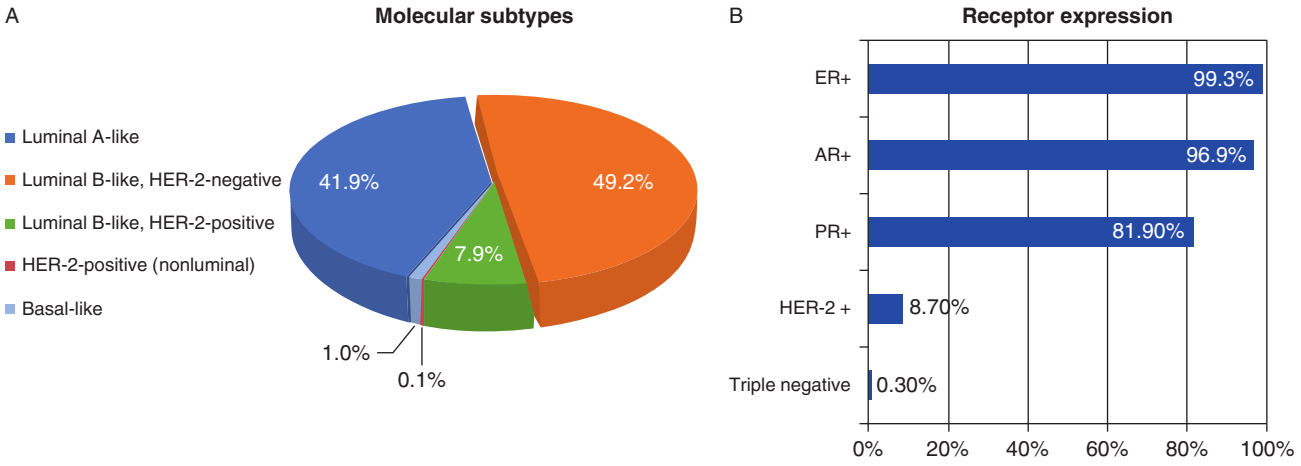


FIGURE 38–2 **A. Molecular subtypes of 1483 male breast cancer tumors based on the 2013 St Gallen Consensus definition.[64] B. Relative proportion of biomarker expression in a cohort of 1054 male breast cancers.[64] ER+, estrogen receptor–positive; AR+, androgen receptor–positive; PR+, progesterone receptor–positive. (Reproduced with permission from Leon-Ferre RA, Giridhar KV, Hieken TJ, et al: A contemporary review of male breast cancer: current evidence and unanswered questions, *Cancer Metastasis Rev* 2018 Dec;37(4):599-614.)**

breast cancers in postmenopausal women, but there was an increase in DNA repair pathway mutations.[68]

Surveillance

There is a lack of evidence to inform standard surveillance in male breast cancer, and so men are treated similarly to women. Consensus-based recommendations based on expert opinion offer some guidance. ASCO guidelines recommend yearly ipsilateral mammography in men who have BCS.[60] The relative risk of developing a subsequent contralateral breast cancer (CBC) is increased, with the highest risk in men younger than 50 years at initial diagnosis, but the absolute risk is low, approximately 0.1% per year.[69] Given this, the NCCN guidelines state that routine mammography is not required in men.[70] The ASCO guidelines recommend consideration of yearly contralateral mammography in men with a predisposing genetic mutation, but consensus was not met for men without mutations.[60] Both NCCN and ASCO recommend monitoring of bone mineral density in men taking GnRHa therapy.[60,70]

Treatment of Male Breast Cancer

The goals of treatment are the same as for women: local and systemic disease control. Although some randomized clinical trial data are available to guide systemic therapy in men, data for locoregional therapy does not exist. Many treatment decisions are made based on extrapolation of data in women.

Surgery

There are no randomized trials comparing surgical interventions for male breast cancer. Clinical practice is based on retrospective data as well as extrapolation from female breast cancer. Although total mastectomy and BCS are both appropriate, historically, most men have mastectomy; scant breast tissue nonpermissive for appropriate surgical margins and a tendency for central tumor location may contribute to this trend.[64,71] SEER data in men with T1–2N0 breast cancer yield similar 5-year cause-specific survival in patients who had BCS compared with mastectomy[72] and a separate analysis of men with T1N0 breast cancer revealed no difference in OS.[73]

As in women with breast cancer, evaluation of the axilla with SLNB or axillary lymph node dissection, as indicated, is considered part of standard of care.[59] Interrogation of SEER registry data reveals that axillary lymph node removal and examination in male patients with breast cancer is associated with improved OS.[73] Retrospective data demonstrate that SLNB is feasible and accurate[74,75] and appears to be reasonable in appropriately selected patients.

Radiation Therapy

Although no randomized studies have been conducted to inform on the benefit of locoregional radiation in men, treatment should be based on standards of care for female breast cancer.[59] Of concern, published data suggest that radiation is often inappropriately omitted in male patients with breast cancer, even with BCS.[64,73]

A study of 81 male patients with breast cancer between 1977 and 2006 revealed that locoregional therapy consisted of mastectomy for 26 patients and mastectomy with postmastectomy radiation therapy (PMRT) for 46 patients. There was no difference in OS between the two groups; however, there was a significant decrease in locoregional recurrence in the PMRT group, with benefit primarily observed in patients with high-risk features.[76] Another study used the SEER database to evaluate the benefit of PMRT in men who had modified radical mastectomy, demonstrating improved OS in patients with lymph node involvement.[77] A German cancer registry study revealed improved OS with PMRT in men with stage III breast cancer at 20 years of follow-up.[78]

Adjuvant Systemic Therapy

As with women, men with HR+ breast cancer also benefit from adjuvant systemic therapy. At MDACC, between 1944 and 2001,135 men with early-stage breast cancer were evaluated and treated; 51 received adjuvant systemic therapy: 13 received chemotherapy alone, 19 received ET alone, and 19 received both. There was a significant increase in time to recurrence (HR 0.49, 95% CI 0.27–0.9) and survival (HR 0.45, 95% CI 0.25–0.84) in patients receiving ET.[79] Additional retrospective data also indicate mortality benefit in men with HR+ breast cancer treated with adjuvant tamoxifen.[80]

The role of AIs in the adjuvant setting of male breast cancer is currently limited. A German Cancer Registry retrospective study of 257 male patients with breast cancer treated with adjuvant tamoxifen (n = 207) or an AI (n = 50) revealed survival benefit with tamoxifen. On multivariate analysis, AI was associated with increased mortality compared with tamoxifen (HR 1.55, 95% CI 1.13–2.13; P = .007).[81] Retrospective SEER data also demonstrate mortality benefit with adjuvant tamoxifen, but not with AI.[80] The poor performance of AI therapy may be related to lack of GnRH inhibition. AI administration in men results in an increase in testosterone, luteinizing hormone, and follicle-stimulating hormone, and a decrease in estradiol; however, complete estradiol suppression is not attained.[59] Further, estradiol levels with AI therapy are much higher in men compared with postmenopausal women. The finding is likely related to feedback from the pituitary and conversion of testosterone to estradiol, which can be circumvented with concurrent administration of a GnRHa.[59,60] Accordingly, the ASCO guidelines recommend tamoxifen as the preferred adjuvant ET agent; however, AI combined with a GnRHa is appropriate for men with a contraindication to tamoxifen.[60]

At a median follow-up of 3.9 years, 53% of men treated with tamoxifen experienced at least one toxicity, according to a review from MDACC. The most common side effects were weight gain and sexual dysfunction; 20% of men prematurely stopped tamoxifen because of side effects.[82] A study evaluating tamoxifen adherence in men with HR+ breast cancer revealed 65% adherence at year 1, decreasing to 18% at year 5. Five- and 10-year DFS and OS were significantly worsened in the low-adherence group.[83] Therefore, assessment and management of side effects with appropriate counseling on the importance of therapy compliance is necessary to optimize outcomes in male patients with breast cancer.

Although there is a lack of randomized data, male patients with breast cancer should generally be treated with (neo)adjuvant chemotherapy and HER2-directed therapy as indicated for women.[59] Nonrandomized prospective[84] and retrospective studies[85,86] suggest benefit from chemotherapy in men with breast cancer. As with women, molecular profiling assays can offer important prognostic information for male patients and can assist in identifying men most likely to benefit from chemotherapy. A study interrogating the SEER database confirmed that Oncotype Dx recurrence score in men correlated with prognosis. However, differences compared with women were observed, such as a greater number of very low (<11) and high (≥31) recurrence scores in men.[87]

Therapy for Metastatic Disease

As in early-stage breast cancer, strategies for management of metastatic breast cancer in men are largely derived from those in female patients. ET is favored as frontline treatment for men with HR+, HER2– metastatic breast cancer in most cases.[60] The recommended use of chemotherapy and therapies targeted to HER2, PIK3CA mutations, programmed death ligand 1 (PD-L1), and germline *BRCA1* and *BRCA2* mutations are the same as for women with metastatic breast cancer.[60]

The ASCO guidelines offer tamoxifen, AIs, preferably with a GnRHa, and fulvestrant as appropriate ET.[60] Although data in men are limited, the improved outcomes observed with ET combined with CDK4/6 inhibitors[88,89] and mTOR inhibitors[90] in women warrants similar use in men.[59,60] Case reports and series of AI therapy with or without GnRHa have been published.[91–94] One study showed an overall response rate of 40% in 15 patients with metastatic breast cancer receiving AI monotherapy.[93] Unfortunately, a phase 2 SWOG trial investigating anastrozole and goserelin for the treatment of male patients with metastatic or recurrent HR+ breast cancer closed in 2007 because of lack of enrollment. Available data on fulvestrant in men, administered at the previously approved 250-mg dose, include a pooled analysis of 23 male patients, revealing partial response in 26% and stable disease in 48%.[95]

THE RISKS AND BENEFITS OF HORMONE REPLACEMENT THERAPY

Postmenopausal Hormone Replacement Therapy

A great debate occurred over several years regarding the value of hormone replacement therapy (HRT) in women as a cardiovascular protective agent when weighed against the risk of developing breast cancer. The combined estrogen and progesterone arm of the Women's Health Initiative (WHI), a large, randomized clinical trial designed to evaluate HRT for primary prevention of coronary artery disease, demonstrated an increased risk of breast cancer and ischemic stroke without a decrease in cardiovascular events.[96] Combined HRT failed to improve cognitive function and health-related quality of life, although there was an improvement in vasomotor symptoms and sleep disturbances.[97,98] Combined HRT was effective at increasing bone mineral density and decreasing fractures in healthy postmenopausal women.[99] Given the WHI data, recommendation for combined HRT for vasomotor symptoms of menopause or bone health must be carefully considered by weighing the risks and benefits for the individual.

The estrogen-only arm of the WHI study closed for a lack of improvement in cardiovascular health.[100] Although there was a non–statistically significant decrease in breast cancer in women randomly assigned to the estrogen arm, the risks and benefits for the individual patient need to be taken into account when deciding whether to recommend estrogen-only HRT.

A Cochrane review, last updated in 2012, evaluated the effect of long-term HRT by reviewing 19 trials involving 41,904 women.[101] Continuous combined HRT significantly increased the risk of breast cancer, among other conditions. However, continuous estrogen-only HRT did not significantly increase breast cancer risk. HRT was only effective at decreasing the incidence of fractures. Therefore, HRT is not indicated for the routine management of chronic disease at this time, and more evidence is needed regarding its safety.

Hormone Replacement Therapy in Breast Cancer Survivors

The HABITS (Hormone Replacement After Breast Cancer—Is It Safe?) trial[102] is a randomized, non–placebo-controlled, noninferiority trial that evaluated the new breast cancer risk in women with a history of breast cancer and subsequent HRT use. Of the planned recruitment of 1300 subjects, 447 women were randomly assigned: 221 women received HRT and 221 women acted as controls. The study was terminated early after the results of the WHI trials became available. At a median follow-up of 4 years, the risk of developing a new breast cancer with HRT (HR 2.4, 95% CI 1.3–4.2), as was the cumulative incidence of breast cancer at 5 years (22.2% vs 8%).[102]

Given the available data, one must carefully consider the use of HRT for postmenopausal breast cancer survivors. Among postmenopausal women without a history of breast cancer in the WHI cohort, combination HRT increased the risk of breast cancer and was most beneficial for the treatment of vasomotor symptoms and the prevention of bone loss and fracture. Accordingly, in women with a history of breast cancer, other pharmacologic therapies for bone health or vasomotor symptoms are strongly preferred over HRT.

DUCTAL CARCINOMA IN SITU

Epidemiology

Ductal carcinoma in situ (DCIS), or intraductal carcinoma, is a noninvasive breast histologic entity whose incidence rose from 5.8 to 32.5 per 100,000 women between 1975 and 2004.[103] Because DCIS most commonly presents with an abnormal mammogram demonstrating suspicious microcalcifications,[104] increased incidence is likely secondary to screening mammography and better detection of lower-grade lesions. The incidence of noncomedo DCIS had increased up to the late 1990s when it began to level off, whereas the rate of comedo DCIS, a more aggressive subtype, has remained fairly stable.[105] The primary goal of therapy for DCIS is prevention of invasive breast cancer because the prognosis of DCIS with no invasion is excellent, with risk of distant metastasis or death far less than 1%.[106]

Pathologic Features

Pathologic assessment of DCIS includes the architectural pattern (solid, papillary, micropapillary, or cribriform), the presence or absence of comedonecrosis, and nuclear grade (low, intermediate, or high) (Fig. 38–3).[104] DCIS classification can correlate with the extent of disease. For example, micropapillary DCIS is more likely to involve more than one quadrant, 71% of cases in one series,[107] whereas the solid DCIS subtype is most likely to be fully excised at surgery.[107]

ER expression should be assessed in patients for whom adjuvant ET would be considered.[108] In general, ER expression is inversely correlated with nuclear grade, and ER-negative DCIS is associated with worse prognosis and higher rates of recurrence.[109] Some studies suggest that HER2+ DCIS is associated with higher grade and worse prognosis; however, results have

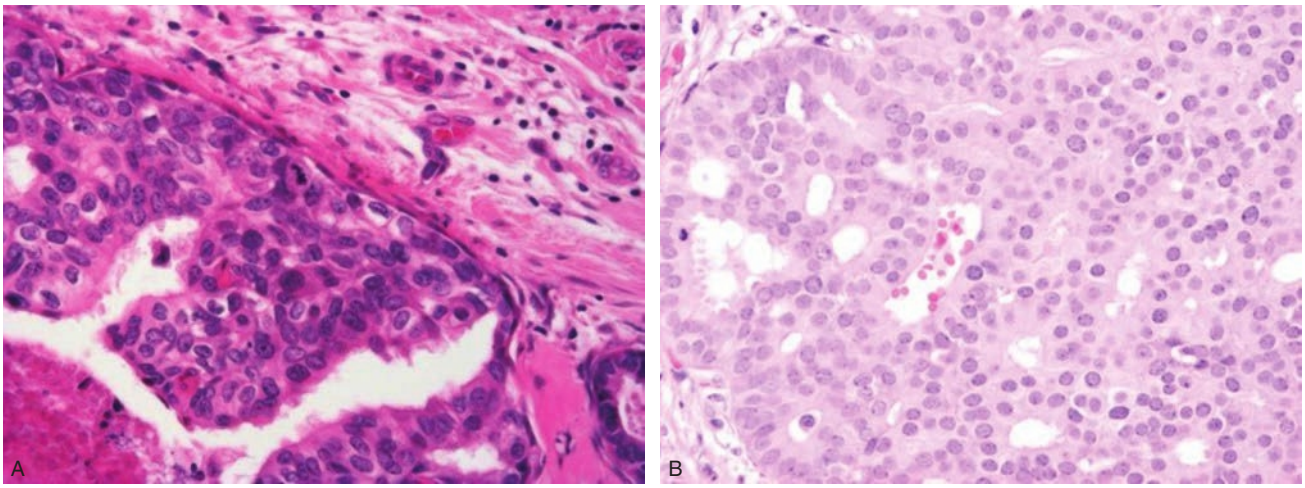


FIGURE 38–3 **High-grade and low-grade DCIS. A. High-grade ductal carcinoma in situ (DCIS) seen as neoplastic cells more than 2.5 erythrocytes in diameter with clumped chromatin, some with multiple, prominent nucleoli. Central comedo-type necrosis is also present (bottom left). B. Low-grade DCIS of cribriform architecture. Small nuclei (predominantly 1.5–2 erythrocytes in diameter), some with prominent nucleoli, are seen with mild pleomorphism. (Reproduced with permission from Pinder SE: Ductal carcinoma in situ (DCIS): pathological features, differential diagnosis, prognostic factors and specimen evaluation, *Mod Pathol* 2010 May;23 Suppl 2:S8-S13.)**

been mixed.[109] At this time, HER2 assessment is not standardly performed.[110]

For DCIS diagnosed by core-needle biopsy, invasive carcinoma is subsequently identified in approximately 10% to 15% of surgical resection specimens.[111] The chance of invasive disease increases with the extent of DCIS.[104] When invasive or microinvasive disease is detected, further management should be based on guidelines for invasive breast cancer.[104] Microinvasion is diagnosed if the invasive component is less than or equal to 1 mm in its greatest dimension.[112] With multiple foci of microinvasion, the size of the largest area is used.[112]

Treatment

Local Therapy

The options for the surgical management of DCIS range from BCS to mastectomy; SLNB can also be performed in select cases. Mastectomy achieves excellent outcomes, with risk of locoregional recurrence of approximately 1%.[113] SEER registry data reveal lower ipsilateral invasive recurrence with mastectomy compared with lumpectomy, but mastectomy does not offer significant Breast Cancer Specific Survival benefit.[114] With BCS, consensus guidelines recommend at least 2-mm margins to minimize the risk of recurrence in the ipsilateral breast.[115] Although mastectomy is highly effective, it may be an excessive approach for patients who are candidates for BCS.

Although axillary lymph node dissection or SLNB is not the standard of care for all women presenting with DCIS, a small proportion have axillary lymph node involvement. A NCDB review of almost 11,000 women with DCIS who had lymph node dissection between 1985 and 1991 found axillary metastases in 3.7%.[116] Two studies investigating pure DCIS without microinvasion reported 0.98% (1/102)[117] and 6% (5/87)[118] rates of sentinel lymph node positivity. Another study revealed positive sentinel lymph nodes in 12% (9/76) of patients with high-risk DCIS and 10% (3/31) with DCIS with microinvasion.[119] Currently, routine lymph node evaluation is not recommended for all patients with DCIS. However, SLNB may be considered for those undergoing a simple mastectomy for DCIS because the opportunity for SLNB is lost if invasive or microinvasive disease is detected because the tumor bed is no longer in place.[120,121]

The addition of adjuvant radiation therapy to BCS has been extensively evaluated. Radiation primarily reduces the risk of an ipsilateral/in-breast recurrence. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 study compared lumpectomy with or without radiation for women with primarily small-volume DCIS (≤2 cm) and negative resection margins. Through 8 years of follow-up, the use of radiation therapy significantly reduced noninvasive breast recurrence from 13.4% to 8.2% and that of invasive disease from 13.4% to 3.9%.[122] Of interest, degree of comedonecrosis was found to be an independent predictor for ipsilateral breast tumor recurrence.[123] Long-term outcomes were assessed in a combined analysis of the B-17 and B-24 studies. Radiation therapy was associated with a significant decrease in invasive ipsilateral breast recurrences (HR 0.48, 95% CI 0.33–0.69; $P < .001$), but did not impact the risk of contralateral

breast cancer, OS, or breast cancer–related mortality.[124] Patients who had an invasive ipsilateral breast recurrence, but not DCIS, had a higher risk of death (HR 1.75, 95% CI 1.24–2.45) and breast cancer–related death (HR 7.06, 95% CI 4.14–12.03).[124]

The European Organisation for Research and Treatment of Cancer) 10853 trial randomly assigned more than 1000 women with DCIS 5 cm or smaller to no further treatment or radiation therapy. At 10 years, 85% of patients assigned to radiation were free from local recurrence compared with 74% of those without radiation (HR 0.53, 95% CI 0.4–0.7; $P < .0001$).[125] Multivariate analysis identified risk factors significantly associated with local recurrence risk, including age 40 years or younger, symptomatic detection, intermediate/poor differentiation, cribriform or solid growth pattern, involved or close margins, and treatment with local excision alone. The beneficial impact of radiation therapy was consistent throughout all assessed risk factors.[125]

Cochrane meta-analysis confirmed the reduction in ipsilateral breast events (IBE) with the addition of radiation therapy to BCS for DCIS (HR 0.49, 95% CI 0.41–0.58; $P < .00001$), with reduction in both invasive and DCIS recurrences.[126] More recent retrospective SEER data suggest that radiation may be associated with a small survival benefit, which is most evident in patients with high-risk factors.[127,128] A patient prognostic score based on grade, patient age, and tumor size correlates to survival benefit.[128] Another analysis revealed greater improvement in breast cancer mortality with radiation in Black women who were younger than 50 years or who had ER- DCIS.[127] Therefore, additional studies evaluated the omission of radiation in certain patients.

ECOG-ACRIN E5194 is a prospective study that observed two cohorts of patients with DCIS treated with lumpectomy with more than or equal to 3-mm margins without radiation. Approximately 30% of patients received adjuvant tamoxifen.[129] Cohort 1 included patients with low/intermediate grade DCIS with tumor small than or equal to 2.5 cm (median tumor size 6 mm); cohort 2 included patients with high-grade DCIS measuring 1.0 cm or smaller (median tumor size 7 mm).[130] At 5 years, IBE occurred in 6.1% of patients in cohort 1 and in 15.3% of patients in cohort 2.[129] At 12 years, the risk was 14.4% and 24.6%, respectively.[130] Increasing size also correlated with increased risk of IBE.[130] There was no significant difference in OS or CBC events between the two cohorts.[130]

The RTOG 9804 study randomly assigned 636 of the planned 1790 patients who had lumpectomy for good-risk DCIS to radiation versus observation. Eligibility characteristics of DCIS included screen or incidental detection, low/intermediate nuclear grade, unicentric, tumor size less than 2.5 cm, and margins 3 mm or larger. Tamoxifen was permitted and was administered in 62% of patients.[131] At 7 years, ipsilateral local failure was 0.9% with radiation and 6.7% with observation (HR 0.11, 95% CI 0.03–0.47; $P = .001$).[131] There was no significant impact of radiation on OS, DFS, or CBC.[131]

Gene expression assays, such as Oncotype Dx DCIS, may also assist in risk stratification regarding benefit of radiation after BCS.[132] Overall, the cumulative data demonstrate that patients with low-risk DCIS based on various factors have a lower risk of IBEs compared with those with higher-risk features. However, even with low-risk DCIS, radiation does decrease the risk of IBE, albeit without benefit in OS or CBC.[130,131] Therefore, it may be reasonable to omit radiation in certain patients after a discussion of the risks and benefits, because some patients will find that the risk of IBE without radiation is acceptable. Patient life expectancy and comorbidities need to be considered when making this treatment decision.

Systemic Therapy

The goal of systemic ET for DCIS is to reduce the risk of IBE or CBC. As such, treatment in patients who have had ipsilateral mastectomy is controversial, because systemic therapy will only serve as chemoprevention to reduce the risk of CBC. Systemic therapy is not indicated for patients with DCIS who have had bilateral mastectomies (Table 38–3).

Tamoxifen is the most extensively studied systemic therapy for DCIS. In the NSABP B-24 study, 1804 women with DCIS treated with lumpectomy and radiation therapy were randomly assigned to tamoxifen 10 mg by mouth twice per day for 5 years or placebo. At 5 years, tamoxifen resulted in 5.2% absolute risk reduction of all breast cancers.[133] The benefit was mainly the result of decreased ipsilateral invasive disease and contralateral noninvasive disease, whereas the risk of regional or distant metastases was not significantly different among the two study arms. Serious but rare side effects of tamoxifen were deep venous thrombosis (1%), nonfatal pulmonary embolism (0.2%), and uterine cancer (~0.1%).[133] Subsequent analysis of available tumor tissue was performed to evaluate the impact of ER status on tamoxifen benefit.[134] Tamoxifen improved outcomes in women with ER+ DCIS. In ER– DCIS, tamoxifen did not improve IBE, but there was a nonsignificant decrease in CBC events (HR 0.46, 95% CI 0.12–1.80; $P = .35$).[134] The number of ER– DCIS cases was small in this subanalysis, precluding definitive conclusions.

The UK, Australia, and New Zealand (UK/ANZ) DCIS trial randomly assigned women who had BCS for DCIS with negative margins to receive additional treatment with radiation, tamoxifen, both, or none; 1576 women were randomly assigned to tamoxifen versus no tamoxifen.[135] At median follow-up of 12.7

Table 38–3 Systemic Therapy for DCIS Phase 3 Clinical Trials

	NSABP B-24[133]	UK/ANZ[135]	NSABP B-35[139]
Study Treatment[a] (n)	Tamoxifen (899) vs placebo (899)	Tamoxifen (794) vs none (782)[b]	Anastrozole (1552) vs tamoxifen (1552)
Patient population	DCIS BCS + RT Pre/Postmenopausal	DCIS BCS +/– RT Pre/Postmenopausal	HR + DCIS BCS + RT Postmenopausal
Median follow-up	5 y	12.7 y	9.0 y
Breast cancer events (all)	HR 0.63 *P* = .009	HR 0.71 *P* = .002	HR 0.73 *P* = .0234
Ipsilateral events	HR 0.70 *P* = .04	HR 0.78 *P* = .04	HR 0.83 *P* = .34
Contralateral events	HR 0.48 *P* = .01	HR 0.44 *P* = .005	HR 0.64 *P* = .0322
Invasive breast cancer	HR 0.57 *P* = .004	HR 0.81 *P* = .2	HR 0.62 *P* = .0123
DCIS	HR 0.69 *P* = .08	HR 0.67 *P* = .008	HR 0.88 *P* = .52

[a]All treatments given for 5 years.
[b]2 × 2 factorial randomization: radiation vs none; tamoxifen vs none.
BCS, breast-conserving surgery; DCIS, ductal carcinoma in situ; HR, hazard ratio; HR+, hormone receptor–positive; RT, radiation therapy.

years, breast cancer events (ipsilateral and contralateral) were reduced with tamoxifen (HR 0.71, 95% CI 0.58–0.88; *P* = .002), but subset analysis revealed benefit only in patients who did not receive radiation. For IBE, tamoxifen significantly reduced DCIS, but not invasive cancers. Tamoxifen treatment significantly reduced CBC (HR 0.44, 95% CI 0.25–0.77; *P* = .005).[135]

A Cochrane meta-analysis analyzed data on 3375 patients from the phase 3 B-24 and UK/ANZ DCIS trials.[136] Five years of adjuvant tamoxifen decreased the risk of both ipsilateral (HR 0.75, 95% CI 0.61–0.92; *P* = .006) and contralateral DCIS (RR 0.50, 95% CI 0.28–0.87; *P* = .01). Reduction in invasive CBC events was observed, whereas invasive IBE neared statistical significance. Tamoxifen did not improve all-cause mortality (RR 1.11, 95% CI 0.89–1.39). It was determined that 15 patients need to be treated with tamoxifen to prevent one breast cancer event.[136]

Although tamoxifen has demonstrated benefit in patients with DCIS, treatment does not improve mortality and is associated with significant side effects. Therefore, a phase 3 study evaluated tamoxifen treatment at a lower dose of 5 mg daily over a shorter time period of 3 years. The study randomly assigned 500 women with HR+/unknown DCIS, atypical ductal hyperplasia, or lobular carcinoma in situ, of whom 346 (69%) had DCIS.[137] At median follow-up of 5 years, low-dose tamoxifen reduced the rate of invasive breast cancer and DCIS (HR 0.48, 95% CI 0.26–0.92; *P* = .02). In the tamoxifen arm, one patient developed a deep venous thrombosis, and one was diagnosed with stage I endometrial cancer; one patient on placebo had a pulmonary embolism. The number needed to treat with low-dose tamoxifen to prevent one breast cancer was 22, and the number needed to harm was 218 based on observed serious adverse events.[137]

Anastrozole is an AI currently approved for the treatment HR+ invasive breast cancer. The IBIS II trial assessed the efficacy and safety of anastrozole for the prevention of breast cancer in high-risk postmenopausal women. Of the 3864 women randomly assigned, 326 were treated with ipsilateral mastectomy for ER+ DCIS and had reduction in subsequent breast cancer with anastrozole, which did not meet statistical significance (HR 0.44, 95% CI 0.17–1.15).[138] Subsequently, the NSABP B-35 phase 3 study randomly assigned more than 3000 postmenopausal women with HR+ DCIS treated with lumpectomy and radiation to 5 years of adjuvant ET with tamoxifen versus anastrozole.[139] Anastrozole treatment resulted in decreased breast cancer–free interval (ipsilateral/contralateral breast cancer or recurrence in regional or distant sites) with HR 0.73 (95% CI 0.56–0.96; *P* = .0234) at median follow-up of 9 years. Notably, improvement was not observed until more than 5 years of follow-up and was primarily seen in women younger than 60 years of age. CBC was decreased with anastrozole (HR 0.64, 95% CI 0.43–0.96; *P* = .0322), but IBE was similar in the two treatment arms.[139]

At MDACC, ET is recommended for patients with ER+ DCIS who have had BCS, but not for those with ER– DCIS. Tamoxifen administered 20 mg daily for a 5-year course is approved adjuvant ET for DCIS. Based on available data, AI therapy with anastrozole is at

least as effective as tamoxifen and can be considered in postmenopausal women, especially those younger than 60 years or those at risk for thrombosis. An individual patient's comorbidities and preferences should be taken into account when choosing a drug given the differing toxicity profiles.

HIGH-DOSE CHEMOTHERAPY WITH TRANSPLANTATION

The efficacy of more aggressive chemotherapeutic regimens, including high-dose chemotherapy with bone marrow or stem cell support has been investigated in women with poor-prognosis, early-stage, or metastatic breast cancer. Despite encouraging initial results, two meta-analyses failed to show a survival benefit.[140,141] Thus, HDC with stem cell support is not used in the management of breast cancer at MDACC.

RISK REDUCTION STRATEGIES FOR PATIENTS WITH MUTATIONS IN *BRCA1, BRCA2,* AND OTHER BREAST CANCER SUSCEPTIBILITY GENES

Although family history of breast cancer, especially in a first-degree relative, has been identified as a risk factor for the development of breast cancer, most women with breast cancer do not have a significant family history.[142] Approximately 3% to 4% of women with breast cancer have inheritance of highly penetrant germline mutations in the *BRCA1* or *BRCA2* genes; the risk is higher, approximately 10% to 20%, with triple-negative breast cancer.[143] Women with BRCA mutations have a cumulative lifetime risk of invasive breast cancer of approximately 70% (range 50%–90%),[143,144] ovarian cancer risk of 40% to 44%, and 17% to 18%[144,145] for *BRCA1* and *BRCA2* mutations, respectively.

Mutations also increase the risk of breast cancer in males with lifetime risk to age 70 to 80 of 1.2% to 1.8% with *BRCA1* mutations and 7% to 8% with *BRCA2*, much higher than the approximately 0.1% lifetime risk in men without a mutation.[61] BRCA mutations are also associated with increased risk of malignancies other than breast cancer and are described further in other chapters. Likewise, risk-reduction strategies for malignancies other than breast cancer are described elsewhere. NCCN criteria for testing for breast cancer susceptibility genes are summarized in Table 38–4.

Pathogenic mutations in other high- and moderate-penetrance genes have also been associated with an increased risk of breast cancer; however, data guiding management for these patients are much less robust compared with those on BRCA mutations. Mutations in *TP53*, which causes Li Fraumeni syndrome, and *PTEN*, causing Cowden syndrome, are considered to be highly penetrant. However, there are limited data on breast cancer risk-reduction strategies with these mutations and clinical management is primarily based on data extrapolated from patients with BRCA mutations, with considerations regarding competing risks of other malignancies.[62,143] An important concern in patients with *TP53* mutations is the need for avoidance of radiation when formulating breast cancer treatment plans.[62,143] Other moderately to highly penetrant genes associated with increased breast cancer risk include *PALB2*, *ATM*, *CHEK2*, *CDH1*, *NBN*, *STK11*, and *NF1*.[62,143] Again, the evidence to guide risk management strategies in these patients is lacking. The list of breast cancer susceptibility genes, associated risks, and recommended management is constantly changing as new data become available.

Screening

The NCCN guidelines recommend intensified breast cancer screening in women with BRCA mutations, including encouragement of breast awareness at 18 years of age or older, clinical breast examination one to two times per year at 25 years of age or older, yearly breast MRI at 25 to 29 years of age, and the addition of annual mammography with consideration of tomosynthesis at

Table 38–4 Genetic Testing Criteria for Breast Cancer Susceptibility Genes[a]

Personal History of Breast Cancer
45 years
50 years: second breast cancer diagnosis; unknown/limited family history; breast cancer in a close relative[b]
60 years: triple-negative breast cancer
Any Age: Male breast cancer; Ashkenazi Jewish ancestry; breast cancer at <50 years or ovarian, pancreatic, or prostate cancer[0] in >1 close relative[b]; >3 breast cancer diagnoses in patient and/or close relative[b]
Personal History of Other Cancer
Ovarian cancer, epithelial
Pancreatic cancer, exocrine
Prostate cancer[c]
Family history of cancer
Criteria above in a first- or second-degree relative
>5% probability of *BRCA1/2* pathogenic mutation[d]
Family history of pathogenic/likely pathogenic mutation

[a]Based on National Comprehensive Cancer Network Genetic/Familial High-Risk Assessment Guidelines.[62]
[b]First-, second-, and third-degree blood relatives on the same side of the family.
[c]Metastatic or intraductal prostate cancer and some high-grade prostate cancers.
[d]Based on prior probability models (such as Tyrer-Cuzick, BRCApro, Penn II).

30 to 75 years; recommendations are similar for women with other high-penetrance genes.[62] In women with moderate-penetrance gene mutations, annual mammography is generally initiated when the estimated risk of breast cancer within 5 years is higher than 1%, and screening with breast MRI starting when risk is higher than 2.2%.[62] Recommendations often require individualization based on family history, including the age of diagnosis and gene mutation variants.

When deciding on appropriate screening and prevention strategies for individual patients with pathogenic mutations, it is important to discuss the risks and benefits with the patient and consider multiple factors, including the patient's age, life expectancy, comorbid medical conditions, and quality of life preferences.

Chemoprevention

The benefit of tamoxifen for risk reduction among women with *BRCA1/BRCA2* mutations is based on limited data. The P1 breast cancer prevention trial randomly assigned patients to tamoxifen or placebo for breast cancer chemoprevention. A subgroup analysis of mutation carriers among the 288 patients in whom breast cancer developed was performed, but only 19 patients (6.6%) tested positive for deleterious *BRCA1* or *BRCA2* mutations.[146] Of the *BRCA1* mutation carriers (n = 8), 5 patients were randomly assigned to tamoxifen and three to placebo (RR 1.67, 95% CI 0.32–10.7). However, among the *BRCA2* mutation carriers (n = 11), three received tamoxifen and eight received placebo (RR 0.38, 95% CI 0.06–1.56). In this very small subset of patients, tamoxifen reduced breast cancer incidence only in *BRCA2* carriers; the 62% risk reduction was similar to that observed for ER+ breast cancer when all women in the study are considered. The findings may be related to the higher incidence of ER+ breast cancer in *BRCA2* carriers compared with *BRCA1*. Cumulative data reveal that 76% of breast cancers were ER+ in patients with *BRCA2* mutations, compared with 17% in *BRCA1* mutation carriers.[146]

The Hereditary Breast Cancer Clinical Study Group performed a matched case-control study of 1504 women with *BRCA1* or *BRCA2*. Tamoxifen was used in 331 (22%) of the women and was associated with decreased CBC in both *BRCA1* (OR 0.58, 95% CI 0.39–0.85) and *BRCA2* (OR 0.39, 95% CI 0.19–0.83) mutation carriers.[147] The impact of tamoxifen duration was also assessed. Interestingly, the strongest protective effect was observed in women who received 1 year or more of tamoxifen (OR 0.37, 95% CI 0.20–0.69; P = .001), followed by 1 to 4 years (OR 0.53, 95% CI 0.32–0.87; P = .01), and was nonsignificant in women who received 4 years or more of tamoxifen (OR 0.83, 95% CI 0.44–1.55; P = .55).[147] The authors concluded that a short-term course of tamoxifen for primary prevention might be as effective as a conventional 5-year treatment course in BRCA mutation carriers. Of caution, the data on tamoxifen duration were determined through interviews with study participants, in which accuracy and reporting of data is subject to bias.

Available data in women with BRCA mutations are insufficient to determine the most effective chemoprevention strategy, optimal duration of use, and the appropriate age to begin therapy. For patients who prefer to avoid prophylactic mastectomy, it is reasonable to offer primary prevention with a regimen similar to patients at high risk of breast cancer without a mutation.

Prophylactic Mastectomies

Women with BRCA mutations should be counseled regarding the potential role of prophylactic mastectomy in reducing the future risk of breast cancer. Regardless of the specific surgical procedure chosen, a small amount of residual breast tissue remains after prophylactic mastectomy, and so does not achieve 100% efficacy in preventing subsequent breast cancer. Although discussion of surgical options for the individual patient is recommended, recent data suggest that nipple-sparing prophylactic mastectomy may be an appropriate option based on limited follow-up.[143,148]

A retrospective study examined prophylactic mastectomy efficacy among women at increased risk of breast cancer. In the moderate-risk group, 4 breast cancers were diagnosed, compared with 37.4 predicted by the Gail model, an 89.5% risk reduction. In the high-risk group, 214 women who underwent bilateral prophylactic mastectomies (BPMs) were compared with their sisters who did not. At a median follow-up of 14 years, the incidence of breast cancer in the women who underwent surgery was 1.4% and was 38.7% in their sisters.[149] The investigators then genotyped 176 of the women who had BPM and 26 were found to carry germline mutations in *BRCA1* or *BRCA2*; breast cancer developed in none over a median follow-up of 13 years.[150]

A case-control study performed by the PROSE study group followed 483 women with *BRCA* mutations, of whom 105 underwent BPM and 378 did not, serving as matched controls. At a mean follow-up of 6.4 years, 1.9% of women in the surgery group were diagnosed with breast cancer, compared with 48.7% in the control group, a more than 90% risk reduction.[151]

Although randomized studies are not feasible, BPM results in significant benefit in these and other studies.[152,153] A meta-analysis including 2555 women without prior cancer revealed significant reduction in breast cancer risk with BPM (RR 0.114, 95% CI 0.041–0.317).[154] Benefit was observed both in patients with *BRCA1* (RR 0.134, 95% CI 0.019–0.937) and *BRCA2* mutations (RR 0.183, 95% CI 0.072–0.468). However, all-cause mortality benefit did not reach statistical significance

(HR 0.226, 95% CI 0.05–1.016). In 1672 women with a history of breast cancer and mastectomy, contralateral prophylactic mastectomy resulted in significant risk reduction in CBC (RR 0.072, 95% CI 0.035–0.148) and improved all-cause mortality (HR 0.226, 95% CI 0.05–0.016).[154] Although the available data are valuable, they are based on nonrandomized studies, and so results may be influenced by selection bias.

At MDACC, women with a known deleterious mutation in either *BRCA1* or *BRCA2* are evaluated and counseled by our genetic counselors and breast surgeons regarding the potential breast cancer risk reduction of BPM or bilateral mastectomies in patients who already carry a diagnosis of breast cancer.

Risk-Reduction Bilateral Salpingo-Oophorectomies

In addition to decreasing the risk of gynecologic cancer among women with a known BRCA mutation, risk-reduction bilateral salpingo-oophorectomy (RRSO) may decrease the risk of breast cancer developing; however, the risk for primary peritoneal cancer remains. A large, prospective, multicenter study followed 1079 women 30 years of age or older with deleterious *BRCA* mutations who chose RRSO or surveillance.[155] Of patients assessable for breast cancer, RRSO reduced the risk of breast cancer in *BRCA2* mutation carriers (HR 0.28, 95% CI 0.08–0.92; P = .036), but not in those with *BRCA1* mutations (HR 0.61, 95% CI 0.30–1.22; P = .16), and was protective against ER+, but not ER– breast cancer. A reduced risk of gynecologic cancer was also observed with RRSO (HR 0.12, 95% CI 0.03–0.41; P = .001); however, the benefit was primarily in *BRCA1* mutation carriers.[155]

A prospective analysis performed by the Hereditary Breast Cancer Clinical Study Group followed 3722 women with BRCA mutations for a mean of 5.6 years. RRSO significantly reduced the risk of breast cancer only in the subgroup of patients with *BRCA2* mutation who were younger than 50 years old (HR 0.18, 95% CI 0.05–0.63; P = .007) and was especially successful in preventing ER+ breast cancers (HR 0.10, 95% CI 0.01–0.82; P = .03).[156] In contrast, another large prospective cohort study revealed that RRSO was associated with a lower risk of first breast cancer diagnosis in both *BRCA1* and *BRCA2* mutation carriers; however, in women with *BRCA1* mutations, the benefit was primarily seen in those younger than 50 years old. RRSO also significantly improved all-cause mortality, breast cancer–specific mortality, and ovarian cancer–specific mortality.[153]

Results from a meta-analysis of 10 studies in *BRCA-mutation* carriers showed that RRSO was associated with a decreased risk of breast cancer (HR 0.49, 95% CI 0.37–0.65), with similar risk reduction in the *BRCA1* and *BRCA2* subgroups. Reduction in *BRCA*-associated gynecologic cancers with HR 0.21 (95% CI 0.12–0.39) was also observed.[157] Another meta-analysis revealed similar improvements in breast cancer risk with RRSO (RR 0.552, 95% CI 0.448–0.682).[154] In women without a prior history of breast cancer, RRSO significantly improved all-cause mortality (HR 0.349, 95% CI 0.190–0.639) but not breast cancer–specific mortality (HR 0.27, 95% CI 0.05–1.33). However, both all-cause mortality (HR 0.432, 95% CI 0.318–0.588) and breast cancer–specific mortality (HR 0.337, 95% CI 0.190–0.598) were improved in women with prior breast cancer.[154]

Our patients with germline BRCA mutations are counseled by qualified professionals on the risks and benefits of RRSO. Although the procedure decreases the risk of malignancy, fertility is clearly impaired. It is important to counsel premenopausal patients regarding the physiologic changes that may be associated with premature menopause, including bone loss and psychosocial changes, such as changes in mood and sexual function.

MD ANDERSON PRACTICE TIPS

- Diagnostic imaging to evaluate for distant metastasis in the pregnant woman with breast cancer can include: MRI of the thoracic/lumbar spine without contrast, liver ultrasonography, and chest radiograph with fetal shielding.
- In men, estradiol is not completely suppressed with AIs, and therefore the addition of a gonadotropin-releasing hormone analogue is favored with aromatase inhibitor therapy.
- HRT is discouraged in women with a history of breast cancer; other pharmacologic therapies for symptoms of estrogen deficiency are preferred.
- Adjuvant ET is not indicated for patients with DCIS who have had bilateral mastectomies, and benefit is limited to chemoprevention to reduce contralateral breast cancer risk in patients with ipsilateral mastectomy.
- High-dose chemotherapy with stem cell/bone marrow support is not recommended for treatment of breast cancer.
- Although risk-reduction salpingo-oophorectomy decreases the risk of gynecologic malignancy in women with BRCA mutations, the procedure may also reduce breast cancer risk, especially in younger women.

REFERENCES

1. Andersson TM, Johansson ALV, Hsieh C-C, Cnattingius S, Lambe M. Increasing incidence of pregnancy-associated breast cancer in Sweden. *Obstet Gynecol.* 2009;114(3):568-572.
2. Abenhaim HA, Azoulay L, Holcroft CA, et al. Incidence, risk factors, and obstetrical outcomes of women with breast cancer in pregnancy. *Breast J.* 2012;18(6):564-568.
3. Lambe M, Hsieh C, Trichopoulos D, et al. Transient increase in the risk of breast cancer after giving birth. *N Engl J Med.* 1994;331(1):5-9.
4. Gwyn K, Theriault R. Breast cancer during pregnancy. *Oncology (Williston Park).* 2001;15(1):39-46; discussion 46, 49-51.
5. Litton JK, Theriault RL. Breast cancer and pregnancy: current concepts in diagnosis and treatment. *Oncologist.* 2010;15(12):1238-1247.
6. Gupta RK, Naran S, Dowle CS, Simpson JS. The diagnostic impact of needle aspiration cytology of the breast on clinical decision making with an emphasis on the aspiration cytodiagnosis of male breast masses. *Diagn Cytopathol.* 1991;7(6):637-639.
7. Duncan PG, Pope WD, Cohen MM, Greer N. Fetal risk of anesthesia and surgery during pregnancy. *Anesthesiology.* 1986;64(6):790-794.
8. Mazze RI, Kallen B. Reproductive outcome after anesthesia and operation during pregnancy: a registry study of 5405 cases. *Am J Obstet Gynecol.* 1989;161(5):1178-1185.
9. Yang WT, Dryden MJ, Gwyn K, et al. Imaging of breast cancer diagnosed and treated with chemotherapy during pregnancy. *Radiology.* 2006;239(1):52-60.
10. Middleton LP, Amin M, Gwyn K, et al. Breast carcinoma in pregnant women: assessment of clinicopathologic and immunohistochemical features. *Cancer.* 2003;98(5):1055-1060.
11. Loibl S, von Minckwitz G, Gwyn K, et al. Breast carcinoma during pregnancy. International recommendations from an expert meeting. *Cancer.* 2006;106(2):237-246.
12. Dominici LS, Kuerer HM, Babiera G, et al. Wound complications from surgery in pregnancy-associated breast cancer (PABC). *Breast Dis.* 2010;31(1):1-5.
13. Cardonick E, Dougherty R, Grana G, et al. Breast cancer during pregnancy: maternal and fetal outcomes. *Cancer J.* 2010;16(1):76-82.
14. Keleher A, et al. The safety of lymphatic mapping in pregnant breast cancer patients using Tc-99m sulfur colloid. *Breast J.* 2004;10(6):492-495.
15. Gentilini O, Cremonesi M, Trifirò G, et al. Safety of sentinel node biopsy in pregnant patients with breast cancer. *Ann Oncol.* 2004;15(9):1348-1351.
16. Gropper AB, Calvillo KZ, Dominici L, et al. Sentinel lymph node biopsy in pregnant women with breast cancer. *Ann Surg Oncol.* 2014;21(8):2506-2511.
17. Doll DC, Ringenberg QS, Yarbro JW. Antineoplastic agents and pregnancy. *Semin Oncol.* 1989;16(5):337-346.
18. Murthy RK, Theriault RL, Barnett CM, et al. Outcomes of children exposed in utero to chemotherapy for breast cancer. *Breast Cancer Res.* 2014;16(6):500.
19. Loibl S, Han SN, von Minckwitz G, et al. Treatment of breast cancer during pregnancy: an observational study. *Lancet Oncol.* 2012;13(9):887-896.
20. Zagouri F, Sergentanis TN, Chrysikos D, et al. Taxanes for breast cancer during pregnancy: a systematic review. *Clin Breast Cancer.* 2013;13(1):16-23.
21. Mir O, Berveiller P, Goffinet F, et al. Taxanes for breast cancer during pregnancy: a systematic review. *Ann Oncol.* 2010;21(2):425-426.
22. Amant F, Deckers S, Van Calsteren K, et al. Breast cancer in pregnancy: recommendations of an international consensus meeting. *Eur J Cancer.* 2010;46(18):3158-3168.
23. Ebert U, Loffler H, Kirch W. Cytotoxic therapy and pregnancy. *Pharmacol Ther.* 1997;74(2):207-220.
24. Zagouri F, Sergentanis TN, Chrysikos D, et al. Trastuzumab administration during pregnancy: a systematic review and meta-analysis. *Breast Cancer Res Treat.* 2013;137(2):349-357.
25. Kelly H, Graham M, Humes E, et al. Delivery of a healthy baby after first-trimester maternal exposure to lapatinib. *Clin Breast Cancer.* 2006;7(4):339-341.
26. Azim HA Jr, Santoro L, Russell-Edu W, et al. Prognosis of pregnancy-associated breast cancer: a meta-analysis of 30 studies. *Cancer Treat Rev.* 2012;38(7):834-842.
27. Amant F, von Minckwitz G, Han SN, et al. Prognosis of women with primary breast cancer diagnosed during pregnancy: results from an international collaborative study. *J Clin Oncol.* 2013;31(20):2532-2539.
28. Beadle BM, Woodward WA, Middleton LP, et al. The impact of pregnancy on breast cancer outcomes in women<or=35 years. *Cancer.* 2009;115(6):1174-1184.
29. Litton JK, Warneke CL, Hahn KM, et al. Case control study of women treated with chemotherapy for breast cancer during pregnancy as compared with nonpregnant patients with breast cancer. *Oncologist.* 2013;18(4):369-376.
30. Aviles A, Neri N. Hematological malignancies and pregnancy: a final report of 84 children who received chemotherapy in utero. *Clin Lymphoma.* 2001;2(3):173-177.
31. Amant F, Vandenbroucke T, Verheecke M, et al. Pediatric outcome after maternal cancer diagnosed during pregnancy. *N Engl J Med.* 2015;373(19):1824-1834.
32. de Haan J, Verheecke M, Van Calsteren K, et al. Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. *Lancet Oncol.* 2018;19(3):337-346.
33. Clark RM, Chua T. Breast cancer and pregnancy: the ultimate challenge. *Clin Oncol (R Coll Radiol).* 1989;1(1):11-18.
34. DeSantis CE, Ma J, Gaudet MM, et al. Breast cancer statistics, 2019. *CA Cancer J Clin.* 2019;69(6):438-451.
35. Martin JA, Hamilton BE, Osterman MJK, et al. Births: final data for 2017. *Natl Vital Stat Rep.* 2018;67(8):1-50.
36. Matthews TJ, Hamilton BE. First births to older women continue to rise. *NCHS Data Brief.* 2014;(152):1-8.
37. Bines J, Oleske DM, Cobleigh MA. Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer. *J Clin Oncol.* 1996;14(5):1718-1729.
38. Goodwin PJ, Ennis M, Pritchard KI, et al. Risk of menopause during the first year after breast cancer diagnosis. *J Clin Oncol.* 1999;17(8):2365-2370.
39. Han HS, Ro J, Lee KS, et al. Analysis of chemotherapy-induced amenorrhea rates by three different anthracycline and taxane containing regimens for early breast cancer. *Breast Cancer Res Treat.* 2009;115(2):335-342.
40. Oktay K, Harvey BE, Partridge AH, et al. Fertility preservation in patients with cancer: ASCO Clinical Practice Guideline Update. *J Clin Oncol.* 2018;36(19):1994-2001.
41. Azim AA, Costantini-Ferrando M, Oktay K. Safety of fertility preservation by ovarian stimulation with letrozole and gonadotropins in patients with breast cancer: a prospective controlled study. *J Clin Oncol.* 2008;26(16):2630-2635.
42. Luke B, Brown MB, Missmer SA, et al. Assisted reproductive technology use and outcomes among women with a history of cancer. *Hum Reprod.* 2016;31(1):183-189.
43. Gerber B, von Minckwitz G, Stehle H, et al. Effect of luteinizing hormone-releasing hormone agonist on

ovarian function after modern adjuvant breast cancer chemotherapy: the GBG 37 ZORO study. *J Clin Oncol.* 2011;29(17):2334-2341.
44. Lambertini M, Boni L, Michelotti A, et al. Ovarian suppression with triptorelin during adjuvant breast cancer chemotherapy and long-term ovarian function, pregnancies, and disease-free survival: a randomized clinical trial. *JAMA.* 2015;314(24):2632-2640.
45. Moore HC, Unger JM, Phillips K-A, et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. *N Engl J Med.* 2015;372(10):923-932.
46. Del Mastro L, Ceppi M, Poggio F, et al. Gonadotropin-releasing hormone analogues for the prevention of chemotherapy-induced premature ovarian failure in cancer women: systematic review and meta-analysis of randomized trials. *Cancer Treat Rev.* 2014;40(5):675-683.
47. Azim HA Jr, Santoro L, Pavlidis N, et al. Safety of pregnancy following breast cancer diagnosis: a meta-analysis of 14 studies. *Eur J Cancer.* 2011;47(1):74-83.
48. Surbone A, Petrek JA. Childbearing issues in breast carcinoma survivors. *Cancer.* 1997;79(7):1271-1278.
49. Upponi SS, Ahmad F, Whitaker IS, Purushotham AD. Pregnancy after breast cancer. *Eur J Cancer.* 2003;39(6):736-741.
50. Morrow PK, Theriault RL. Pregnancy after the diagnosis of breast cancer. *Clin Breast Cancer.* 2006;7(2):173-175.
51. Mueller BA, Simon MS, Deapen D, et al. Childbearing and survival after breast carcinoma in young women. *Cancer.* 2003;98(6):1131-1140.
52. Azim HA Jr, Kroman N, Paesmans M, et al. Prognostic impact of pregnancy after breast cancer according to estrogen receptor status: a multicenter retrospective study. *J Clin Oncol.* 2013;31(1):73-79.
53. Lambertini M, Kroman N, Ameye L, et al. Long-term safety of pregnancy following breast cancer according to estrogen receptor status. *J Natl Cancer Inst.* 2018;110(4):426-429.
54. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet.* 2005;365(9472):1687-1717.
55. Black KZ, Nichols HB, Eng E, Rowley DL. Prevalence of preterm, low birthweight, and small for gestational age delivery after breast cancer diagnosis: a population-based study. *Breast Cancer Res.* 2017;19(1):11.
56. Hartnett KP, Mertens AC, Kramer MR, et al. Pregnancy after cancer: does timing of conception affect infant health? *Cancer.* 2018;124(22):4401-4407.
57. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin.* 2019;69(1):7-34.
58. Giordano SH, Cohen DS, Buzdar AU, et al. Breast carcinoma in men: a population-based study. *Cancer.* 2004;101(1):51-57.
59. Giordano SH. Breast cancer in men. *N Engl J Med.* 2018;378(24):2311-2320.
60. Hassett MJ, Somerfield MR, Baker ER, et al. Management of male breast cancer: ASCO Guideline. *J Clin Oncol.* 2020:JCO1903120.
61. Tai YC, Domchek S, Parmigiani P, et al. Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. *J Natl Cancer Inst.* 2007;99(23):1811-1814.
62. National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic (Version 1.2020); 2019. Accessed 5/17/2020. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf
63. Brinton LA, Richesson DA, Gierach GL, et al. Prospective evaluation of risk factors for male breast cancer. *J Natl Cancer Inst.* 2008;100(20):1477-1481.
64. Cardoso F, Bartlett JMS, Slaets L, et al. Characterization of male breast cancer: results of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program. *Ann Oncol.* 2018;29(2):405-417.
65. Liu N, Johnson KJ, Ma CX. Male Breast Cancer: An Updated Surveillance, Epidemiology, and End Results Data Analysis. *Clin Breast Cancer.* 2018;18(5):e997-e1002.
66. Wang F, Shu X, Meszoely I, et al. Overall mortality after diagnosis of breast cancer in men vs women. *JAMA Oncol.* 2019;5(11):1589-1596.
67. Chavez-Macgregor M, Clarke CA, Lichtenztajn D, et al. Male breast cancer according to tumor subtype and race: a population-based study. *Cancer.* 2013;119(9):1611-1617.
68. Piscuoglio S, Ng CKY, Murray MP, et al. The genomic landscape of male breast cancers. *Clin Cancer Res.* 2016;22(16):4045-4056.
69. Auvinen A, Curtis RE, Ron E. Risk of subsequent cancer following breast cancer in men. *J Natl Cancer Inst.* 2002;94(17):1330-1332.
70. National Comprehensive Cancer Network. Breast Cancer (Version 2.2020). 2020. Accessed 3/10/2020. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
71. Golshan M, Rusby J, Dominguez F, Smith BL. Breast conservation for male breast carcinoma. *Breast.* 2007;16(6):653-656.
72. Zaenger D, Rabatic BM, Dasher B, Mourad WF. Is breast conserving therapy a safe modality for early-stage male breast cancer? *Clin Breast Cancer.* 2016;16(2):101-104.
73. Leone JP, Leone J, Zwenger AO, et al. Locoregional treatment and overall survival of men with T1a,b,cN0M0 breast cancer: a population-based study. *Eur J Cancer.* 2017;71:7-14.
74. Gentilini O, Chagas E, Zurrida S, et al. Sentinel lymph node biopsy in male patients with early breast cancer. *Oncologist.* 2007;12(5):512-515.
75. Flynn LW, Park J, Patil SM, et al. Sentinel lymph node biopsy is successful and accurate in male breast carcinoma. *J Am Coll Surg.* 2008;206(4):616-621.
76. Yu E, Suzuki H, Younus J, et al. The impact of post-mastectomy radiation therapy on male breast cancer patients--a case series. *Int J Radiat Oncol Biol Phys.* 2012;82(2):696-700.
77. Abrams MJ, Koffer PP, Wazer DE, Hepel JT. Postmastectomy radiation therapy is associated with improved survival in node-positive male breast cancer: a population analysis. *Int J Radiat Oncol Biol Phys.* 2017;98(2):384-391.
78. Eggemann H, Ignatov A, Stabenow R, et al. Male breast cancer: 20-year survival data for post-mastectomy radiotherapy. *Breast Care (Basel).* 2013;8(4):270-275.
79. Giordano SH, Perkins GH, Broglio K, et al. Adjuvant systemic therapy for male breast carcinoma. *Cancer.* 2005;104(11):2359-2364.
80. Harlan LC, Zujewski JA, Goodman MT, Stevens JL. Breast cancer in men in the United States: a population-based study of diagnosis, treatment, and survival. *Cancer.* 2010;116(15):3558-3568.
81. Eggemann H, Ignatov A, Smith BJ, et al. Adjuvant therapy with tamoxifen compared to aromatase inhibitors for 257 male breast cancer patients. *Breast Cancer Res Treat.* 2013;137(2):465-470.
82. Pemmaraju N, Munsell MF, Hortobagyi GN, Giordano SH. Retrospective review of male breast cancer patients: analysis of tamoxifen-related side-effects. *Ann Oncol.* 2012;23(6):1471-1474.
83. Xu S, Yang Y, Tao W, et al. Tamoxifen adherence and its relationship to mortality in 116 men with breast cancer. *Breast Cancer Res Treat.* 2012;136(2):495-502.
84. Walshe JM, Berman AW, Vatas U, et al. A prospective study of adjuvant CMF in males with node positive breast cancer: 20-year follow-up. *Breast Cancer Res Treat.* 2007;103(2):177-183.
85. Patel HZ 2nd, Buzdar AU, Hortobagyi GN. Role of adjuvant chemotherapy in male breast cancer. *Cancer.* 1989;64(8):1583-1585.
86. Yildirim E, Berberoglu U. Male breast cancer: a 22-year experience. *Eur J Surg Oncol.* 1998;24(6):548-552.

87. Massarweh SA, Sledge GW, Miller DP, et al. Molecular characterization and mortality from breast cancer in men. *J Clin Oncol.* 2018;36(14):1396-1404.
88. Rugo HS, Dinn RS, Diéras V, et al. Palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer with extended follow-up. *Breast Cancer Res Treat.* 2019;174(3):719-729.
89. Slamon DJ, Neven P, Chia S, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. *N Engl J Med.* 2020;382(6):514-524.
90. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med.* 2012;366(6):520-529.
91. Giordano SH, Valero V, Buzdar AU, Hortobagyi GN. Efficacy of anastrozole in male breast cancer. *Am J Clin Oncol.* 2002;25(3):235-237.
92. Giordano SH, Hortobagyi GN. Leuprolide acetate plus aromatase inhibition for male breast cancer. *J Clin Oncol.* 2006;24(21):e42-3.
93. Doyen J, Italiano A, Largillier R, et al. Aromatase inhibition in male breast cancer patients: biological and clinical implications. *Ann Oncol.* 2010;21(6):1243-1245.
94. Zagouri F, Sergentanis TN, Koutoulidis V, et al. Aromatase inhibitors with or without gonadotropin-releasing hormone analogue in metastatic male breast cancer: a case series. *Br J Cancer.* 2013;108(11):2259-2263.
95. Zagouri F, Sergentanis TN, Chrysikos D, et al. Fulvestrant and male breast cancer: a pooled analysis. *Breast Cancer Res Treat.* 2015;149(1):269-275.
96. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;288(3):321-333.
97. Hays J, Ockene JK, Brunner RL, et al. Effects of estrogen plus progestin on health-related quality of life. *N Engl J Med.* 2003;348(19):1839-1854.
98. Rapp SR, Espeland MA, Shumaker SA, et al. Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA.* 2003;289(20):2663-2672.
99. Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA.* 2003;290(13):1729-1738.
100. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA.* 2004;291(14):1701-1712.
101. Marjoribanks J, Farquhar C, Roberts H, Lethaby A. Long term hormone therapy for perimenopausal and postmenopausal women. *Cochrane Database Syst Rev.* 2012(7):CD004143.
102. Holmberg L, Iversen O-E, Rudenstam CM, et al. Increased risk of recurrence after hormone replacement therapy in breast cancer survivors. *J Natl Cancer Inst.* 2008;100(7):475-482.
103. Virnig BA, Tuttle TM, Shamliyan T, Kane RL. Ductal carcinoma in situ of the breast: a systematic review of incidence, treatment, and outcomes. *J Natl Cancer Inst.* 2010;102(3):170-178.
104. Burstein HJ, Polyak K, Wong JS, Lester SC, Kaelin CM. Ductal carcinoma in situ of the breast. *N Engl J Med.* 2004;350(14):1430-1441.
105. Li CI, Daling JR, Malone KE. Age-specific incidence rates of in situ breast carcinomas by histologic type, 1980 to 2001; *Cancer Epidemiol Biomarkers Prev.* 2005;14(4):1008-1011.
106. Roses RE, Arun BK, Lari SA, et al. Ductal carcinoma-in-situ of the breast with subsequent distant metastasis and death. *Ann Surg Oncol.* 2011;18(10):2873-2878.
107. Bellamy CO, McDonald C, Slater DM, et al. Noninvasive ductal carcinoma of the breast: the relevance of histologic categorization. *Hum Pathol.* 1993;24(1):16-23.
108. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol.* 2010;28(16):2784-2795.
109. Lari SA, Kuerer HM. Biological Markers in DCIS and Risk of Breast Recurrence: A Systematic Review. *J Cancer.* 2011;2:232-261.
110. Wolff AC, Hammond ME, Hicks DG, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *J Clin Oncol.* 2007;25(1):118-145.
111. Darling ML, Smith DN, Lester SC, et al. Atypical ductal hyperplasia and ductal carcinoma in situ as revealed by large-core needle breast biopsy: results of surgical excision. *AJR Am J Roentgenol.* 2000;175(5):1341-1346.
112. Amin MB, Edge SB, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. Springer; 2017.
113. Owen D, Tyldesley S, Alexander C, et al. Outcomes in patients treated with mastectomy for ductal carcinoma in situ. *Int J Radiat Oncol Biol Phys.* 2013;85(3):e129-34.
114. Narod SA, Ibal J, Giannakeas V, Sopik V, Sun P. Breast cancer mortality after a diagnosis of ductal carcinoma in situ. *JAMA Oncol.* 2015;1(7):888-896.
115. Morrow M, Van Zee KJ, Solin LJ, et al. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Ductal Carcinoma In Situ. *J Clin Oncol.* 2016;34(33):4040-4046.
116. Winchester DP, Menck HR, Osteen RT, Kraybill W. Treatment trends for ductal carcinoma in situ of the breast. *Ann Surg Oncol.* 1995;2(3):207-213.
117. Zavagno G, Carcoforo P, Marconato R, et al. Role of axillary sentinel lymph node biopsy in patients with pure ductal carcinoma in situ of the breast. *BMC Cancer.* 2005;5:28.
118. Pendas S, Dauway E, Giuliano R, et al. Sentinel node biopsy in ductal carcinoma in situ patients. *Ann Surg Oncol.* 2000;7(1):15-20.
119. Klauber-DeMore N, Tan LK, Liberman L, et al. Sentinel lymph node biopsy: is it indicated in patients with high-risk ductal carcinoma-in-situ and ductal carcinoma-in-situ with microinvasion? *Ann Surg Oncol.* 2000;7(9):636-642.
120. Lyman GH, Giuliano AE, Somerfield MR, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. *J Clin Oncol.* 2005;23(30):7703-7720.
121. Lyman GH, Somerfield MR, Giuliano AE. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol.* 2017;35(5):561-564.
122. Fisher B, Dignam J, Wolmark N, et al. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17. *J Clin Oncol.* 1998;16(2):441-452.
123. Fisher ER, Dignam J, Tan-Chiu E, et al. Pathologic findings from the National Surgical Adjuvant Breast Project (NSABP) eight-year update of Protocol B-17: intraductal carcinoma. *Cancer.* 1999;86(3):429-438.
124. Wapnir IL, Dignam JJ, Fisher B, et al. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. *J Natl Cancer Inst.* 2011;103(6):478-488.
125. EORTC Breast Cancer Cooperative Group; EORTC Radiotherapy Group; Bijker N, Meijnen P, Peterse JL, et al. et al.

Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853--a study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. *J Clin Oncol.* 2006;24(21):3381-3387.
126. Goodwin A, Parker S, Ghersi D, Wolcken N. Post-operative radiotherapy for ductal carcinoma in situ of the breast. *Cochrane Database Syst Rev.* 2009(4):CD000563.
127. Giannakeas V, Sopik V, Narod SA. Association of radiotherapy with survival in women treated for ductal carcinoma in situ with lumpectomy or mastectomy. *JAMA Netw Open*. 2018;1(4):e181100.
128. Sagara Y, freedman RA, Vaz-Luis I, et al. Patient prognostic score and associations with survival improvement offered by radiotherapy after breast-conserving surgery for ductal carcinoma in situ: a population-based longitudinal cohort study. *J Clin Oncol.* 2016;34(11):1190-1196.
129. Hughes LL, Wang M, Page DL, et al. Local excision alone without irradiation for ductal carcinoma in situ of the breast: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol.* 2009;27(32):5319-5324.
130. Solin LJ, Gray R, Hughes LL, et al. Surgical excision without radiation for ductal carcinoma in situ of the breast: 12-year results from the ECOG-ACRIN E5194 study. *J Clin Oncol.* 2015;33(33):3938-3944.
131. McCormick B, Winter K, Hudis C, et al. RTOG 9804: a prospective randomized trial for good-risk ductal carcinoma in situ comparing radiotherapy with observation. *J Clin Oncol.* 2015;33(7):709-715.
132. Solin LJ, Gray R, Baehner FL, et al. A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast. *J Natl Cancer Inst.* 2013;105(10):701-710.
133. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. *Lancet.* 1999;353(9169):1993-2000.
134. Allred DC, Anderson SJ, Paik S, et al. Adjuvant tamoxifen reduces subsequent breast cancer in women with estrogen receptor-positive ductal carcinoma in situ: a study based on NSABP protocol B-24. *J Clin Oncol.* 2012;30(12):1268-1273.
135. Cuzick J, Sestak I, Pinder SE, et al. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. *Lancet Oncol.* 2011;12(1):21-29.
136. Staley H, McCallum I, Bruce J. Postoperative tamoxifen for ductal carcinoma in situ. *Cochrane Database Syst Rev.* 2012;10:CD007847.
137. DeCensi A, Puntoni M, Guerrieri-Gonzaga A, et al. Randomized placebo controlled trial of low-dose tamoxifen to prevent local and contralateral recurrence in breast intraepithelial neoplasia. *J Clin Oncol.* 2019;37(19):1629-1637.
138. Cuzick J, Sestak I, Forbes JF, et al. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. *Lancet.* 2014;383(9922):1041-1048.
139. Margolese RG, Cecchini RS, Julian TB, et al. Anastrozole versus tamoxifen in postmenopausal women with ductal carcinoma in situ undergoing lumpectomy plus radiotherapy (NSABP B-35): a randomised, double-blind, phase 3 clinical trial. *Lancet.* 2016;387(10021):849-856.
140. Berry DA, et al. High-dose chemotherapy with autologous stem-cell support as adjuvant therapy in breast cancer: overview of 15 randomized trials. *J Clin Oncol.* 2011;29(24):3214-3223.
141. Berry DA, Ueno NT, Johnson MM, et al. High-dose chemotherapy with autologous hematopoietic stem-cell transplantation in metastatic breast cancer: overview of six randomized trials. *J Clin Oncol.* 2011;29(24):3224-3231.
142. Collaborative Group on Hormonal Factors in Breast Cancer. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. *Lancet.* 2001;358(9291):1389-1399.
143. Tung NM, Boughey JC, Pierce LJ, et al. Management of hereditary breast cancer: American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Guideline. *J Clin Oncol.* 2020:JCO2000299.
144. Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. *JAMA.* 2017;317(23):2402-2416.
145. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. *J Clin Oncol.* 2007;25(11):1329-1333.
146. King MC, Wieand S, Hale K, et al. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. *JAMA.* 2001;286(18):2251-2256.
147. Gronwald J, Robidoux A, Kim-sing C, et al. Duration of tamoxifen use and the risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. *Breast Cancer Res Treat.* 2014;146(2):421-427.
148. Jakub JW, Peled AW, Gray RJ, et al. Oncologic safety of prophylactic nipple-sparing mastectomy in a population with BRCA mutations: a multi-institutional study. *JAMA Surg.* 2018;153(2):123-129.
149. Hartmann LC, Schaid DJ, Woods JE, et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. *N Engl J Med.* 1999;340(2):77-84.
150. Hartmann LC, Sellers TA, Schaid DJ, et al. Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 gene mutation carriers. *J Natl Cancer Inst.* 2001;93(21):1633-1637.
151. Rebbeck TR, Friebel T, Lynch HT, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. *J Clin Oncol.* 2004;22(6):1055-1062.
152. Meijers-Heijboer H, van Geel B, van Putten WL, et al. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med.* 2001;345(3):159-164.
153. Domchek SM, Friebel TM, Singer CF, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. *JAMA.* 2010;304(9):967-975.
154. Li X, You R, Wang X, et al. Effectiveness of prophylactic surgeries in BRCA1 or BRCA2 mutation carriers: a meta-analysis and systematic review. *Clin Cancer Res.* 2016;22(15):3971-3981.
155. Kauff ND, Domchek SM, Friebel TM, et al. Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. *J Clin Oncol.* 2008;26(8):1331-1337.
156. Kotsopoulos J, Huzarski T, Gronwald J, et al. Bilateral oophorectomy and breast cancer risk in BRCA1 and BRCA2 mutation carriers. *J Natl Cancer Inst.* 2017;109(1).
157. Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. *J Natl Cancer Inst.* 2009;101(2):80-87.

Section VIII

Gynecologic Malignancies

Section Editor: Karen H. Lu

39 Ovarian Cancer

40 Tumors of the Uterine Corpus

41 Tumors of the Uterine Cervix

42 Gestational Trophoblastic Disease

This page intentionally left blank

39 Ovarian Cancer

Roni Nitecki
Lauren P. Cobb
Amir A. Jazaeri
J. Alejandro Rauh-Hain

KEY CONCEPTS

- Over the past decade, there has been increasing recognition that epithelial ovarian cancers (EOCs) represent a heterogeneous group of malignancies secondary to distinct pathogenic pathways and molecular alterations associated with the development of different histologic subtypes. Although some types are thought to arise from the ovarian surface epithelium, the fallopian tube is the likely origin of high-grade serous cancer. This understanding heralded the practice of risk-reducing salpingo-oophorectomy in women at high risk for development of ovarian cancer
- Stage of disease at the time of diagnosis is an important prognostic indicator. Five-year survival rates among women with localized, regional, and distant disease at the time of diagnosis are 92%, 72%, and 27%, respectively. Early-stage ovarian cancer is discovered in fewer than 30% of patients.
- In advanced EOC, surgery and chemotherapy are both used in initial management; however, there remains debate regarding the sequence of these interventions. Historically, patients have been candidates for neoadjuvant chemotherapy if they have multiple medical comorbidities, poor performance status, or extensive disease on imaging that is not felt to be amenable to upfront surgery. Despite this, there is no current consensus regarding which patients should have upfront cytoreduction or neoadjuvant chemotherapy.
- High risk of recurrent disease after treatment of advanced-stage EOC has prompted an intensive search for maintenance strategies, and poly (adenosine diphosphate [ADP]-ribose) polymerase inhibitors have been found to be particularly efficacious in this setting. Recent trials have yielded multiple indications: olaparib for patients with germline or somatic *BRCA1/2* mutations, niraparib for all-comers, and the combination of olaparib and bevacizumab for those with homologous-recombination deficiency.
- Over the last 5 years, a number of trials have assessed the efficacy of programmed cell death protein 1/programmed cell death ligand 1 immune checkpoint inhibitors in patients with recurrent EOC. The efficacy results can be summarized as an observed response rate of 10% to 15%, with another 20% to 40% of patients experiencing stable disease.
- Malignant ovarian germ cell tumors (MOGCTs) recapitulate normal embryonic and extraembryonic cells and structures and are derived from the primitive germ cells of the embryonic gonad. The MOGCTs comprise 2% to 3% of all ovarian malignancies, and they usually develop in girls, adolescents, and women of reproductive age. Advances in chemotherapy have yielded cure in the vast majority of patients with these tumors, and modifications in surgical technique have allowed fertility preservation in most patients.

EPITHELIAL OVARIAN CANCER

Epidemiology

Ovarian cancer is the second most common cancer of the female genital tract in developed countries, with approximately 21,750 cases expected in the United States in 2020.[1] Epithelial tumors comprise 95% of ovarian cancers, and the most common histologic subtype is high-grade serous carcinoma, followed by endometrioid, clear cell, and mucinous tumors. Ovarian cancer remains the number one cause of death from gynecologic cancers in the United States, accounting for 13,940 deaths expected this year.

Among women, ovarian cancer is the fifth most common cancer-related cause of death in the United States.[1] The lifetime risk of a woman in the United States developing ovarian cancer is approximately 1 in 70 (1.37%).[2] Incidence rates are higher among White women compared with Black, Hispanic, or Asian American women in the United States, although the differences are narrowing. In most parts of Europe and North America, the incidence of ovarian cancer was constant during the decades before the 1990s. However, incidence rates have been falling on average 2.3% each year over the last 10 years. In addition, death rates have been falling on average 2.3% each year from 2007 through 2016.[2]

This cancer is predominantly a cancer of the perimenopausal and the postmenopausal period, with 80% to 90% of cases occurring after the age of 40 years. The incidence is higher in older women, and the median age at diagnosis is 63 years.[2]

Mortality

Ovarian cancer accounts for 5.4% of the deaths from cancer that occur in women between 60 and 79 years of age.[1] Prognosis among women with ovarian cancer is dependent on the stage of disease at the time of diagnosis. Five-year survival rates among women with localized, regional, and distant disease at the time of diagnosis are 92%, 72%, and 27%, respectively.[1] Relative survival rates for ovarian cancer have improved substantially over the last decade by an average of 2.3% per year, and the modern 5-year survival estimate is 47.6%.[2] A large study leveraging the Surveillance, Epidemiology, and End Results (SEER) database showed that among 35,868 patients, age above 70 years, marital status, Black race, and higher stage were strongly associated with worse 3-year mortality, but these characteristics had a declining impact the longer patients survived.[3] An additional study using SEER data demonstrated that compared with non-Hispanic White women, non-Hispanic Black women were at a 28% increased risk of death, and Hispanic women had equivalent survival to non-Hispanic White women, with Asian women experiencing the lowest risk of mortality.[4] Between 1995 and 2004, non-Hispanic Black women had a 31% increase in mortality compared with White women. This disparity remained consistent between the years 2005 and 2015, whereas there was a 6% reduction in the risk of mortality among White women.[4] It has been hypothesized that poorer survival in Black women may be mediated by lack of access to appropriate guideline-adherent care, with multiple studies revealing that Black women are less likely to receive surgery[4–6] and chemotherapy[5–7] for ovarian cancer.

Etiology

Over the past decade, there has been increasing recognition that epithelial ovarian cancers (EOCs) represent a heterogeneous group of malignancies. This heterogeneity is the product of distinct pathogenic pathways and molecular alterations associated with the development of different histologic subtypes. Specifically, serous malignancies are now further subdivided into two separate groups: high-grade serous carcinomas (HGSCs) and low-grade serous carcinomas (LGSCs).[8]

Historically, HGSC was thought to arise from the ovarian surface epithelium because it is often associated with ovarian masses.[9] However, over the past two decades, advancement in knowledge defined the fallopian tube as the likely origin of HGSC. The understanding that HGSC is often characterized by *TP53* mutations and subsequent defects in DNA repair mechanisms via loss of *BRCA* gene function[10] heralded the practice of risk-reducing salpingo-oophorectomy (RRSO) in women at high risk for developing ovarian cancer (such as those with *BRCA 1* and *BRCA 2* germline mutations). In women undergoing RRSO, it is now standard-of-care practice to section and extensively examine the fimbriated end of the fallopian tubes (SEE-FIM protocol). Even if overt malignancy is not present, this examination may reveal areas of marked cytologic atypia and disorganized growth within the fimbria. These aberrations have been called serous tubal intraepithelial carcinoma or tubal dysplasia and are characterized by cytologic atypia, positive p53 immunostaining (which correlates with mutations in the *TP53* gene), abnormal proliferation (as evident by Ki67 staining), and DNA damage (Fig. 39–1).[8–13] Older studies found the risk of occult tubal carcinoma in high-risk patients undergoing RRSO to be approximately 5% to 10%.[14–16] A recent systematic review of 27 studies found that the pooled prevalence was lower at 1.19%, though this study included women at risk based on family history alone in addition to women with germline *BRCA* mutations.[17] The discovery of fallopian tube carcinoma in the absence of ovarian carcinoma led to the hypothesis that precursor lesions for HGSC arise in the fallopian tube and share identical *TP53* mutations.[18]

Based on their distinct molecular features and clinicopathologic characteristics, other carcinogenesis models have been proposed for endometrioid, clear cell, mucinous, and low-grade serous ovarian cancers. Endometrioid and clear cell tumors have an epidemiologic link with endometriosis,[19] and there is accumulating evidence that they may arise via activation of *KRAS*, and *PI3K,* and inactivation of *PTEN* and *ARID1A*,[20] though the rate of malignant transformation is low[21] and endometriosis is not considered a precursor lesion. The origin of the rare mucinous ovarian tumors

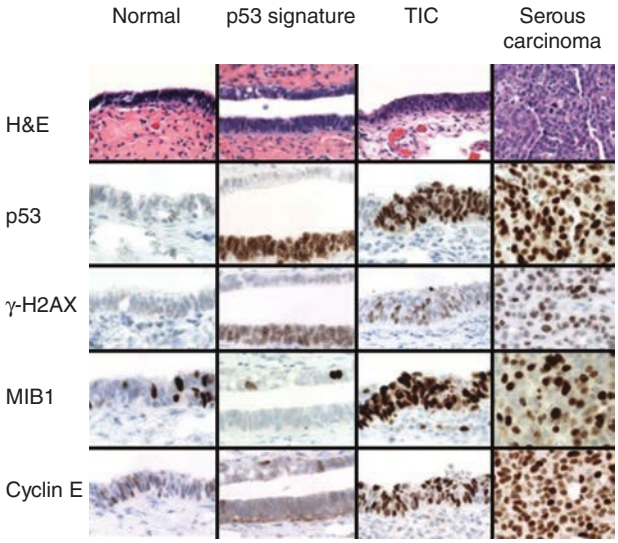


FIGURE 39–1 Overview of co-localization of p53, γ-H2AX, MIB1, and cyclin E in normal mucosa, p53 signature, tubal intraepithelial carcinoma, and serous carcinoma. H&E, hematoxylin and eosin. (Reproduced with permission from Lee Y, Miron A, Drapkin R, et al. A candidate precursor to serous carcinoma that originates in the distal fallopian tube, *J Pathol* 2007 Jan;211(1):26-35.)

is not fully elucidated, possibly because in the past many "mucinous ovarian cancers" were misdiagnosed metastases of gastrointestinal origin.[22] A study using genetic analysis found evidence for a stepwise progression from borderline precursors initiated by a KRAS or CDKN2A event to high-grade invasive Müllerian ovarian cancer driven by *TP53* mutation and copy number aberrations.[23] LGSCs are characterized by KRAS and BRAF mutations,[8] absence of TP53 mutations, and lack of a known precursor in the fallopian tube. They are thought to arise from ectopic cortical inclusion cysts and a stepwise progression from benign lesion to borderline neoplasm to LGSC has been described. This remains a controversial area with ongoing research efforts focusing on understanding the pathophysiology of these differing EOC subtypes.

Risk Factors

Numerous studies have attempted to demonstrate possible links between the risk of developing ovarian cancer and environmental, dietary, reproductive, endocrine, viral, and hereditary factors. These factors are summarized in Table 39–1.

The strongest risk factor for ovarian cancer is a genetic predisposition. A contemporary prospective study of 9856 women with *BRCA1* and *BRCA2* mutations demonstrated a 46% (95% CI 35–53) and 17% (95% CI 11–25) cumulative lifetime risk[24] of developing ovarian cancer, respectively, which is 18 to 36 times higher than that of the general population. Similar to *BRCA1* and *BRCA2* mutations, variants in other genes in the Fanconi anemia pathway have been implicated in the development of EOC, such as *RAD51C*, *RAD51D*, *PALB2*, and *BARD1*. Notably, these genes are less penetrant than variants in *BRCA* genes.[25] A smaller proportion of cases of familial ovarian cancer are associated with mutations in mismatch repair genes (*MLH1*, *MSH2*, *MHS6*, *PMS2*) related to Lynch syndrome. Patients with Lynch syndrome can demonstrate varying lifetime risk of ovarian cancer depending on the mutated gene. Patients with germline mutations in *MLH1* and *MSH2* seem to be at the highest risk for ovarian cancer compared with patients with

Table 39–1 Risk Factors for Developing Ovarian Cancer

Increased	Decreased	Indeterminate
Hereditary Family history of ovarian cancer Personal history of breast cancer *BRCA1* or *BRCA2* mutation Lynch syndrome Other gene mutations: *BRIP1* *RAD51C* *RAD51D*	*Reproductive* Multiparity Breastfeeding	Fertility drugs Exercise Cigarette smoking
Reproductive Advanced age Nulligravity Infertility	*Hormonal* Oral contraceptives Progestins	
Hormonal Early menarche Late age at natural menopause Hormone replacement therapy Estrogen Androgens	*Surgery* Hysterectomy Tubal ligation	
Inflammatory Endometriosis Pelvic inflammatory disease		
Lifestyle Obesity		
Geography Extremes in latitude		

Adapted with permission from Hunn J, Rodriguez GC.Ovarian cancer: etiology, risk factors, and epidemiology. *ClinObstet Gynecol*. 2012 Mar;55(1):3-23.

MSH6 and *PMS2* mutations. Ovarian cancer risk can range from 5% to 20% in patients with MLH1 mutations, 10% to 38% in patients with MSH2 mutations, and 1% to 11% in patients with MSH6 mutations. More data are needed to determine ovarian cancer risk in patients with PMS2 mutations.[26–30] Identifying women at risk for development of ovarian cancer from a heritable cause is currently the only successful method for ovarian cancer prevention. Thus, National Comprehensive Cancer Network (NCCN) guidelines have recommended genetic testing for patients with a history of ovarian cancer since at least 2010, not only to determine their risk for developing concurrent malignancies and identify treatment options, but also to identify family members who may be at risk and could benefit from preventive measures.

Other factors associated with an increased risk of ovarian cancer include age, early menarche, late menopause, and obesity.[31–33] Protective factors that have been shown to reduce the risk of ovarian cancer include the use of oral contraceptives, multiparity, breastfeeding, hysterectomy, and tubal ligation.[34] Other factors, including exercise, infertility treatment, and use of postmenopausal hormone replacement therapy, have not been definitively shown to alter a woman's risk of development of ovarian cancer.

Screening

Stage I ovarian cancer is associated with excellent survival; however, more than two-thirds of patients are diagnosed with stage III or IV disease. These observations have provided a compelling rationale in support of screening for early-stage disease. The most commonly used screening strategies include a combination of serum cancer antigen 125 (CA 125) levels and pelvic sonography. Although several large trials have demonstrated that screening can detect cancer in asymptomatic women, there are concerns regarding the poor positive predictive value for these strategies and lack of proven survival benefit. In fact, screening average-risk women can cause potential harm. With the low prevalence of ovarian cancer, there is a high risk of obtaining false-positive results with patients possibly undergoing unnecessary surgical evaluation, risk from surgery and anesthesia, psychological stress, and associated cost. The findings of four key trials are summarized in Table 39–2.[35–40] The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) evaluated more than 200,000 postmenopausal average-risk women and randomly assigned them to (1) multimodal screening (utilizing the Risk of Ovarian Cancer time series algorithm to interpret CA 125 with transvaginal ultrasound), (2) annual transvaginal ultrasound screening, or (3) no screening in a 1:1:2 ratio. There was no significant reduction in ovarian cancer–related mortality in their primary analysis.[40] As of this writing, the US Preventive Services Task Force as well as the American College of Obstetricians and Gynecologists and the Society of Gynecologic Oncology recommend against screening for ovarian cancer in asymptomatic women of average risk.

The Molecular Landscape of Epithelial Ovarian Cancer

Molecular Biology

Although the different subtypes of EOC possess unique molecular aberrations (Table 39–3) and transcriptional signatures, their morphologic features resemble the specialized epithelia of the reproductive tract that derive from the Müllerian ducts.

As noted, accumulating evidence points to the distal fallopian tube epithelium as the tissue of origin for most HGSCs. The most common molecular alterations in serous carcinomas are mutations in *TP53*, which are nearly ubiquitous. The Cancer Genome Atlas project has also significantly advanced our understanding of other molecular and genetic alterations in HGSC. In addition to the expected *TP53* mutations in 96% of tumors, low-prevalence, recurrent somatic mutations in *NF1*, *BRCA1*, *BRCA2*, *RB1*, and *CDK12* were also observed. Serous carcinomas are also characterized by a high degree of chromosomal instability (gene copy number amplifications and deletions), and both total and regional instability are associated with tumor grade and altered patient outcomes.[41] Somatic copy number analysis performed as part of The Cancer Genome Atlas also confirmed 8 and 22 chromosomal regions of recurrent gain and loss, respectively. Five of the gains and 18 of the losses occurred in more than half of the tumors. Although such aberrant areas of DNA frequently carry multiple genes, it is presently thought that only a limited number of genes are "key drivers" of the process. These key drivers are thought to be the most critical markers and potential treatment targets. Candidate drivers at areas of copy number gain and loss are frequently proposed. For example, it has been suggested that 45% of HGSCs harbor altered phosphatidylinositol 3-kinase (PI3K)/RAS signaling mediated by multiple copy number alterations, including *PTEN* deletion and *PIK3CA*, *KRAS*, *AKT1*, and *AKT2* amplification. LGSCs have been found to have alterations in the mitogen-activated protein kinase pathway. Approximately 20% to 40% of LGSC tumors have a *KRAS* mutation, although a smaller proportion of tumors demonstrate mutations in *BRAF*, accounting for 5% of LGSCs.[42]

Clear cell and endometrioid cancers are epidemiologically and molecularly linked to endometriosis. Frequent somatic mutations of *PIK3CA* and ARID1A

Table 39–2 Summary of Major Trials in Ovarian Cancer Screening

Study Name Recruitment Years	RCT	Location	No. of Women	Screening Method	Aim	Outcome	Limitations/Strengths
Kentucky study[39]	No	Kentucky, USA	37,293 screened	Annual TVS	5-year OC survival	Screened (74.8±6.6%) vs Unscreened (53.7±2.3%) $P < .001$ Hard to interpret true effects of screening on disease mortality in non-RCT	Single center Unscreened controls were diagnosed with OC in the center but not part of the study Lead time effect Healthy volunteer effect
SCSOCS[38] 1985–1999	Yes	Shizuoka, Japan 212 hospitals	82,487 total (41,688 screened) (40,799 control)	Annual CA 125 (>35 U/mL) Annual TVS	Early stage I/II diagnosis	Screened (63%) vs control (38%) $P = .23$	—
PLCO[37] 1993–2001	Yes	USA 10 sites	78,216 total (34,253 screened) (34,304 usual care)	Annual CA 125 (>35 U/mL) (6 years) Annual TVS (first 4 years)	All-cause mortality: for invasive EOC, tubal and peritoneal cancer	12.4-year risk ratio (1.18, 95% CI 0.91–1.54) 14.7-year risk ratio (1.01, 95% CI 0.97–1.05)	High surgical complication rate (15%) Lack of stage shift (22.2%)
UKCTOS[40] 2001–2005	Yes	UK 13 sites	202,638 total (50,639 USS) (50,640 MMS) (101,359 control)	MMS	Mortality reduction: for invasive EOC, tubal and peritoneal cancer Early stage I/II diagnosis	**Primary analysis:** Mortality reduction over years 0–14 was: MMS 15% (95% CI –3 to 20; $P = .10$) USS 11% (–7 to 27; $P = .21$) **Analysis excluding prevalent cases:** Overall mortality reduction 20% (–2 to 40; $P = .021$) with reduction of 8% (–27 to 43) over years 0–7 And 28% (–3 to 49) mortality reduction over years 7–14 in favor of MMS Stage I/II shift with MMS of 36.1% stage I/II vs control 23.9%, but not with USS ($P = .0001$)	Screening group had higher worry and lower pleasure scores when >2 TVS performed vs no TVS Good PPV of 4.4 surgeries per cancer detected
NROSS[a] 2001–2011	No	USA 7 sites	4051 total	MMS	Specificity and PPV of OC screening in PM	PPV of 40% (95% CI 12.2–73.8)	—

[a]Lu KH, Skates S, Hernandez MA, et al. A 2-stage ovarian cancer screening strategy using the Risk of Ovarian Cancer Algorithm (ROCA) identified early-stage incident cancers and demonstrates high positive predictive value. *Cancer*. 2013;119(19):3454-3461.

EOC, epithelial ovarian cancer; MMS, multimodal strategy; NROSS, Normal Risk Ovarian Screening Study; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Randomized Controlled Trial; PM, postmenopause; PPV, positive predictive value; RCT, randomized controlled trial; SCSOCS, Shizuoka Cohort Study of Ovarian Cancer Screening; TVS, transvaginal ultrasound; UKCTOCS, UK Collaborative Trial of Ovarian Cancer Screening; USS, ultrasound strategy.

Reproduced with permission from Nebgen DR, Lu KH, Bast RC Jr. Novel Approaches to Ovarian Cancer Screening, *Curr Oncol Rep* 2019 Jul 26;21(8):75.



Table 39–3 Current Concepts Regarding the Origins and Molecular Pathology of Epithelial Ovarian Cancer

Histology	Precursor	Molecular Features
Low-grade serous carcinoma	Cystadenoma–borderline tumor–carcinoma sequence	Mutations in *KRAS* and/or *BRAF*
High-grade serous carcinoma	"De novo" in epithelial inclusion cysts	*p53* mutation and *BRCA1* dysfunction (usually promoter methylation) *PIK3CA*[b] amplification (25%-40%)
Low-grade endometrioid carcinoma	Endometriosis and endometrial-like hyperplasia[a]	Mutations in *CTNNB1* (B-catenin gene) and *PTEN* with microsatellite instability
High-grade endometrioid carcinoma	Epithelial inclusion glands/cysts	*p53* mutation and *BRCA1* dysfunction (usually promoter methylation) *PIK3CA* mutation
Mucinous carcinoma	Cystadenoma–borderline tumor–carcinoma sequence	Mutations in *KRAS*; *p53* mutation associated with transition from borderline tumor to carcinoma.
Clear cell carcinoma	Endometriosis	*PTEN* mutation/loss of heterozygosity *PIK3CA* mutation

[a]Endometriosis and adjacent low-grade endometrioid carcinoma share common genetic events, such as loss of heterozygosity at the same loci involving the same allele (eg, PTEN). In contrast, high-grade and poorly differentiated endometrioid carcinomas are similar to high-grade serous carcinomas.
[b]*PIK3CA* is the gene at chromosome 3q26 that specifically encodes the p110α subunit of the phosphatidylinositol-3-kinase (PI3K) protein.

(AT-rich interactive domain-containing protein 1A) have been documented in tumors associated with endometriosis.[43,44] Common genetic abnormalities identified in endometrioid ovarian carcinomas include somatic mutations of *CTNNB1* and *PTEN*.[45]

Cytokines and Growth Factors

Several cytokines and growth factors have been studied in ovarian carcinogenesis. Although a detailed review of growth factor pathways targeted in ovarian cancer is beyond the scope of this chapter, we will highlight a few of interest.

Levels of interleukin 10 (IL-10) and interleukin 6 (IL-6) are particularly elevated in ovarian cancer ascites. Endogenously produced IL-6 can protect tumor cells from natural killer cell–mediated killing, and IL-6 expression by immunohistochemistry is associated with poor prognosis.[46] Furthermore, IL-6 has been identified as an etiologic paracrine factor in paraneoplastic thrombocytosis and associated poor prognosis in ovarian cancer.[47] When compared with high-grade serous tumors, ovarian clear cell carcinomas are associated with higher circulating levels of IL-6.[48]

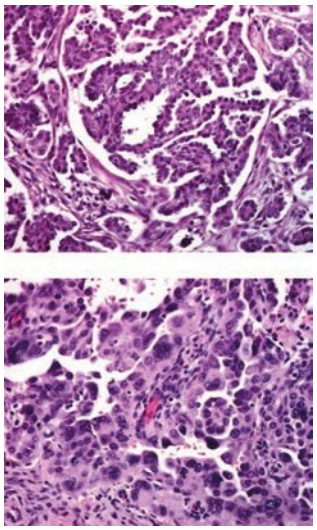
The vascular endothelial growth factor (VEGF) signaling cascade is mediated through a partially redundant set of ligands and receptors, which have emerged as promising targets for antiangiogenic cancer therapy. The VEGF ligand family consists of seven ligands: VEGF A–E, placenta growth factor 1 (PlGF1), and PlGF2. The receptor tyrosine kinases involved in this signaling cascade include VEGF receptor type 1 (VEGFR1), VEGFR2, and VEGFR3. VEGF ligands are overexpressed in EOC cells, although the receptors are present mainly on the tumor endothelial cells.[49] VEGF is a key mediator of angiogenesis, which is stimulated by hypoxia. Bevacizumab, a monoclonal anti–VEGF-A antibody, is the prototypical member of this class and has become a common addition to standard cytotoxic agents in the upfront, platinum-sensitive, and platinum-resistant settings.

Prognostic Factors

Prognostic factors are tumor-related characteristics that determine the biologic behavior and risk of death from the disease; their predictive value may change during the course of treatment and thereafter.

Factors associated with poor prognosis in advanced ovarian cancer (stage III or IV) fall into two subgroups (as determined by multivariate analysis in clinical trials and observational studies):

1. *Variables before systemic treatment predictive of survival:* age, stage at diagnosis, performance status, residual tumor volume after cytoreductive surgery, BRCA status, and tumor histology.
2. *Variables at the time of relapse predictive of time to progression:* less than 6 months from last chemotherapy (platinum-resistant disease), poorer performance status, mucinous histology, larger number of sites of disease, best previous response to chemotherapy, and serum CA 125 levels.



Low-grade serous carcinoma of the ovary is characterized by relative uniformity of the cells and up to 12 mitoses per 10 high-power fields. Courtesy of Anais Malpica, MD.

High-grade serous carcinoma of the ovary is characterized by pleomorphism; there is marked nuclear atypia and >12 mitoses per 10 high-power fields. Courtesy of Anais Malpica, MD.

FIGURE 39–2 **Low-grade and high-grade serous carcinoma. (Used with permission from Anais Malpica, MD.)**

Stage

Stage is a dominant prognostic factor in ovarian cancer. The main prognostic factors in early-stage ovarian cancer (stages I–IIA) are International Federation of Gynecology and Obstetrics (FIGO) stage, histologic grade, histologic type, and patient's age. Early-stage ovarian cancer is discovered in fewer than 30% of patients. In such cases, the 5-year survival is good, ranging from 51% to 98%.[1–3]

Cancer Antigen 125

Cancer antigen 125 is a high-molecular-weight glycoprotein that is elevated in 80% of EOCs.[50] There is no definitive evidence that pretherapeutic CA 125 levels correlate with survival in EOC[51]; however, there has been evidence that the kinetics of an individual's CA 125 level during treatment may be related to the best response to treatment as well as survival.[52]

Residual Disease

It is logical to assume that the extent of postoperative residual tumor volume is affected by both the biology and the history of the disease, as well as the radicality, emphasis, and effort involved in the tumor-reductive surgery. What remains controversial is the relative contribution of these factors to the prognostic significance of residual disease. On one hand, the tumors that are more aggressive and disseminated are more difficult to resect and therefore associated with larger residual disease. Therefore, the preoperative tumor burden may be more predictive of outcome than the amount of residual disease after surgery. Other features—such as the type of chemotherapy, the intrinsic chemosensitivity of the tumor, and the presence of other biological variables—may be as important as, or even more important than, the extent of the surgery. Proponents of the importance of maximal surgical effort point to a wealth of retrospective data and the evolution of "optimal cytoreductive surgery" from less than 2 cm to R0 (no visible residual disease) as evidence for the importance of the surgical result.[53]

Histologic Subtypes

Serous Carcinoma

Serous carcinoma is the most common histologic subtype of EOC, and this subtype can further be divided into HGSCs and LGSCs.[54] In 2004, Malpica and colleagues at MDACC developed a two-tier grading system in serous carcinomas based on nuclear atypia and mitotic rate to distinguish high-grade from low-grade tumors (Fig. 39–2).[55] This system has since been validated and adopted by the gynecologic oncology community to define these two diseases.

High-Grade Serous Carcinoma

HGSCs account for 70% to 80% of all ovarian cancers and are the most common type of EOC. HGSCs may present with varying architectural patterns, but the defining characteristic of these tumors is high mitotic activity (>12 mitoses per 10 high-power fields [HPFs]) and the presence of multinucleated cells.[56]

Low-Grade Serous Carcinoma

Low-grade serous carcinoma accounts for 6% to 10% of serous ovarian cancers and 5% to 8% of all ovarian

cancers. These tumors are now thought to arise from borderline tumors and have distinct molecular aberrations and clinical behavior when compared with their high-grade counterparts. Low-grade serous tumors have low mitotic activity (<12 mitoses per 10 HPFs) and are distinguished from borderline tumors based on destructive invasion of more than 5 mm. Consistent with their distinct pathophysiology and tumor biology, LGSCs are more resistant to chemotherapy and are associated with significantly higher rates of platinum-resistant disease.[57]

Mucinous Carcinoma

In older publications, the proportion of mucinous ovarian cancers is as high as 30%. However, there is now increased recognition that many such tumors, on careful evaluation, are thought to represent metastases from the gastrointestinal tract. A contemporary estimate of the prevalence of primary ovarian mucinous carcinoma is approximately 3%. Primary ovarian origin is favored by unilaterality, size greater than 12 cm (large), smooth external surface, and association with other ovarian pathology. Conversely, metastases tend to be bilateral, measure less than 10 cm in size, exhibit surface involvement, and demonstrate colloid and signet ring morphology. True mucinous ovarian tumors are low-grade malignancies that have a low propensity for metastatic spread and are usually diagnosed as unilateral stage IA tumors even though they may reach a large size (Fig. 39–3).[58] Newer studies have also dispelled the notion that pseudomyxoma peritonei is commonly secondary to an ovarian mucinous carcinoma. It is now recognized that pseudomyxoma peritonei is almost always associated with an appendiceal mucinous lesion.[59]

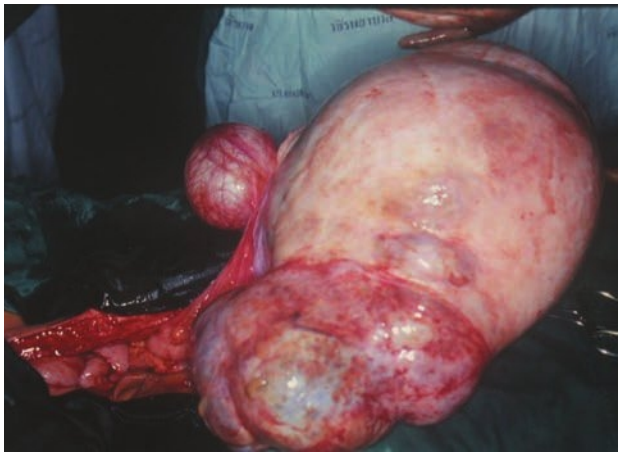


FIGURE 39–3 Operative removal of mucinous ovarian tumor.

Endometrioid Adenocarcinoma

Overall, 10% of epithelial ovarian tumors are of endometrioid histology and resemble endometrial adenocarcinoma. Endometrioid ovarian and endometrial malignancies can occur simultaneously as synchronous primary tumors in as many as 25% of cases in patients younger than 45 years of age.[60] Identification of multifocal disease is important because patients with metastatic disease from the uterus to the ovaries have a 5-year survival rate of 30% to 40%. Those with synchronous multifocal disease have a 5-year survival rate of 70% to 80%. Concurrent endometriosis is present in 10% of cases. The malignant potential of endometriosis is very low, although a transition from benign to malignant epithelium may be seen.

Clear Cell Carcinoma

Clear cell carcinomas comprise 5% to 10% of ovarian cancers and, like endometrioid tumors, may be associated with endometriosis or endometrial cancer. Some studies indicate that clear cell carcinoma may be resistant to standard carboplatin-paclitaxel–based chemotherapy regimens. However, other investigators have shown that when the pathology was carefully reviewed by a gynecologic pathologist, only suboptimal cytoreduction and spread of disease were associated with a significantly increased risk of platinum resistance.[61]

Transitional Cell Carcinoma

Transitional cell carcinomas were previously thought to represent malignant Brenner tumors; however, recent studies have shown that they are molecularly similar to HGSCs. These tumors are now classified as a subtype of HGSC.[62]

Undifferentiated Carcinoma

Undifferentiated carcinomas are thought to represent the most poorly differentiated HGSCs rather than a separate entity.[63]

Histologic Grading

Previously, a three-tier grading system was used in the diagnosis of EOC; however, there was no consensus on the definition of this system. More recently, two-tier grading systems (high grade vs low grade) have been shown to have better prognostic and interobserver variability.[64]

Staging

Accurate staging is critical to the success of surgery and adjuvant therapy. The staging of ovarian cancer

Table 39–4 FIGO Staging for Ovarian Cancer

FIGO		TNM
0	Primary tumor cannot be assessed	TX
	No evidence of primary tumor	T0
I	Tumor confined to ovaries	T1
IA	Tumor limited to one ovary, capsule intact	T1a
	No tumor on ovarian surface	
	No malignant cells in the ascites or peritoneal washings	
IB	Tumor limited to both ovaries, capsules intact	T1b
	No tumor on ovarian surface	
	No malignant cells in the ascites or peritoneal washings	
IC IC1 IC2 IC3	Tumor limited to one or both ovaries Surgical spill Rupture before surgery, tumor on ovarian surface Positive malignant cells in the ascites, or positive peritoneal washings	T1c
II	Tumor involves one or both ovaries with pelvic extension	T2
IIA	Extension and/or implants in uterus and/or tubes	T2a
IIB	Extension to other pelvic organ	T2b
III	Tumor involves peritoneal metastasis outside the pelvis and/or regional lymph node metastasis	T3
IIIA1(i) IIIA1(ii) IIIA2 IIIB	Positive retroperitoneal nodes only ≤10 mm Positive retroperitoneal nodes only >10 mm Microscopic, extrapelvic (above the brim) peritoneal involvement ± positive retroperitoneal lymph nodes Macroscopic, extrapelvic, peritoneal metastasis ≤2 cm ± positive retroperitoneal lymph nodes; includes extension to capsule of liver/spleen	T1, T2, T3aN1 T3a/T3aN1 T3b/T3bN1
IIIC	Macroscopic, extrapelvic, peritoneal metastasis >2 cm ± positive retroperitoneal lymph nodes; includes extension to capsule of liver/spleen	T3c/T3cN1
IVA IVB	Pleural effusion with positive cytology Hepatic and/or splenic parenchymal metastasis, metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity)	M1

Other major recommendations are as follows:
- Histologic type including grading should be designated at staging.
- Primary site (ovary, fallopian tube, or peritoneum) should be designated where possible.
- Tumors that may otherwise qualify for stage I but involved with dense adhesions justify upgrading to stage II if tumor cells are histologically proven to be present in the adhesions.

is based on the gross and pathologic findings of the initial surgical evaluation. The FIGO classification uses the sites and extent of the disease, including capsule rupture and ascites, to categorize ovarian cancer into four stages. This is summarized in Table 39–4.

Diagnosis

Symptoms of ovarian cancer are nonspecific and include early satiety, bloating, constipation, and weight loss. It is not uncommon for patients to have been referred for a gastrointestinal evaluation before the correct diagnosis is reached. Objective signs of ovarian carcinoma are also nonspecific and can include a pelvic mass, ascites, carcinomatosis, possible pleural effusion(s), and occasionally supraclavicular lymphadenopathy.

Management

In general, the initial management and staging of EOC is surgical. In early-stage ovarian cancer, comprehensive staging allows for proper triage to adjuvant therapy. When comprehensive staging is performed, a substantial number of patients initially believed to have disease confined to the pelvis will be staged upward.[65]

In advanced EOC, surgery and chemotherapy are both utilized in initial management; however, there remains debate regarding the sequence of these interventions. Historically, patients have been candidates for neoadjuvant chemotherapy if they have multiple medical comorbidities, poor performance status, or extensive disease on imaging that is not felt to be

amenable to upfront surgery. Despite this, there is no current consensus regarding which patients should have upfront cytoreduction or neoadjuvant chemotherapy (NACT).

The current approach at MDACC is for patients with suspected advanced ovarian cancer who are medically fit for surgery and are without distant metastatic disease (based on computed tomographic [CT] imaging) to undergo a preoperative laparoscopic assessment.

This laparoscopic evaluation provides the following: surgicopathologic diagnosis, assessment of metastatic disease burden and likelihood of complete resection (modified Fagotti score),[66] and research tissue acquisition. Our laparoscopic triage is accomplished by scoring made by two independent and blinded surgeons. Patients scoring less than 10 undergo primary cytoreduction. Those with scores of 10 or more undergo NACT (consisting of 3 or 4 cycles of carboplatin and paclitaxel), followed by consideration of interval cytoreductive surgery and three additional cycles of chemotherapy (with or without maintenance therapy).[67] An outline of our treatment algorithm is shown in Fig. 39–4.

In addition to a preoperative evaluation with lab testing, imaging, and office examination, the NCCN now recommends genetic testing for all newly diagnosed high-grade serous ovarian cancers.

Primary Cytoreductive Surgery

A staging laparotomy involves the following steps:

1. Midline vertical incision
2. Evacuation and cytologic analysis of ascites
3. Inspection and palpation of all peritoneal (intraperitoneal and retroperitoneal) surfaces, including the subdiaphragmatic areas
4. Total abdominal hysterectomy and bilateral salpingo-oophorectomy
5. Omentectomy with debulking to no gross residual disease
6. If disease is limited to the ovaries, staging includes bilateral pelvic and para-aortic lymph node sampling, and multiple biopsies including the paracolonic gutters, cul-de-sac, lateral pelvic walls, vesicouterine reflection, subdiaphragmatic sites, and intra-abdominal areas
7. Appendectomy if a mucinous tumor is found

The goal of primary cytoreductive surgery (PCS) is to remove all visible tumor as the amount of residual disease is inversely correlated with patient survival. Currently, an optimal tumor-reductive surgery is defined as no residual nodules greater than 1 cm in size. More recent studies have tried to refine the definition of *optimal* cytoreductive surgery by distinguishing patients with no visible residual disease. Patients who undergo complete gross resection of all visible disease have improved overall survival (OS), even compared with patients with less than 1 cm of residual disease.

Several retrospective studies have suggested that primary surgery with optimal cytoreduction is more effective than NACT for women with advanced-stage EOC, with improved progression-free survival (PFS) and OS. However, three phase 3 randomized clinical trials found that NACT does not result in inferior OS compared with primary surgery.[68–70] These trials have been criticized because many women who received PCS had more than 1 cm of residual disease after surgery, the survival durations were shorter than expected, and a significant proportion of women received single-agent carboplatin instead of the traditional platinum-based doublet. Despite these concerns, the use of NACT for advanced ovarian cancer has been increasing in the United States in recent years.

Among patients who receive NACT, it may be possible to further reduce morbidity by performing interval cytoreductive surgery using minimally invasive surgical techniques. However, although preliminary data have been promising, it is unknown whether minimally invasive interval cytoreductive surgery delivers oncologic outcomes that are comparable with those achieved in open surgery.

Adjuvant Therapy

Chemotherapy

Early-Stage Disease

Though women with surgically treated early-stage EOC in general have excellent rates of survival, studies have defined a subset of patients with early-stage disease who are at increased risk of relapse ranging from 25% to 45%.[71] These high-risk features include:

1. Stage IC (tumor confined to the ovary with positive peritoneal washings) or II disease
2. Clear cell histology of any stage
3. High-grade tumor

To investigate whether adjuvant therapy after cytoreduction is warranted for early-stage disease, the ACTION (Adjuvant Chemotherapy in Ovarian Neoplasms) trial randomly assigned 448 patients to platinum-based chemotherapy or observation. Overall, adjuvant chemotherapy improved recurrence-free survival (RFS; 70% vs 62%). Although there was no survival advantage in patients who underwent optimal surgical staging, adjuvant chemotherapy after incomplete surgical staging led to a significant improvement in RFS (65% vs 56%) and cancer-specific survival (80% vs 69%).[72] This was also demonstrated in a meta-analysis of five randomized trials.[73] Thus, patients with early-stage disease without high-risk features who undergo complete

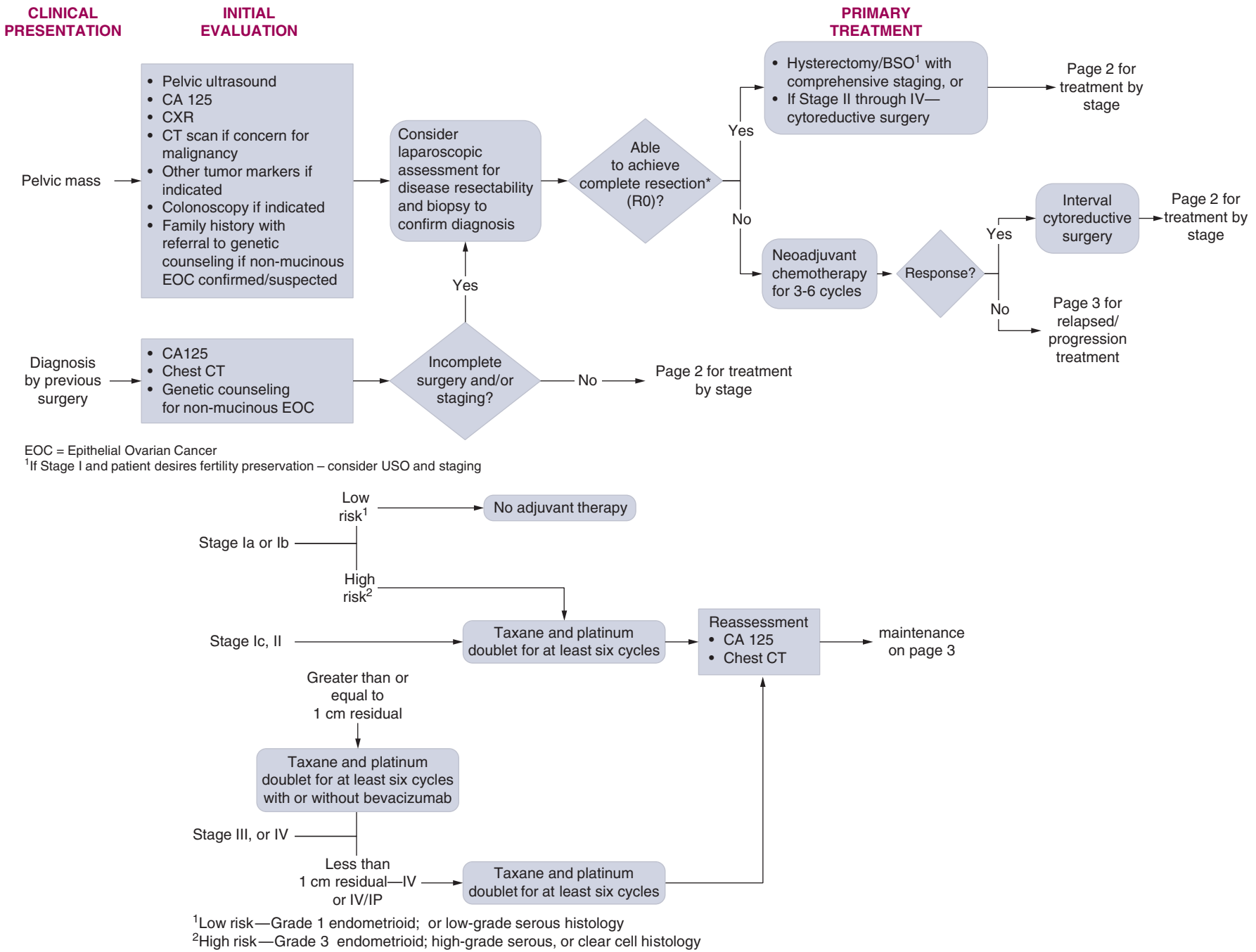
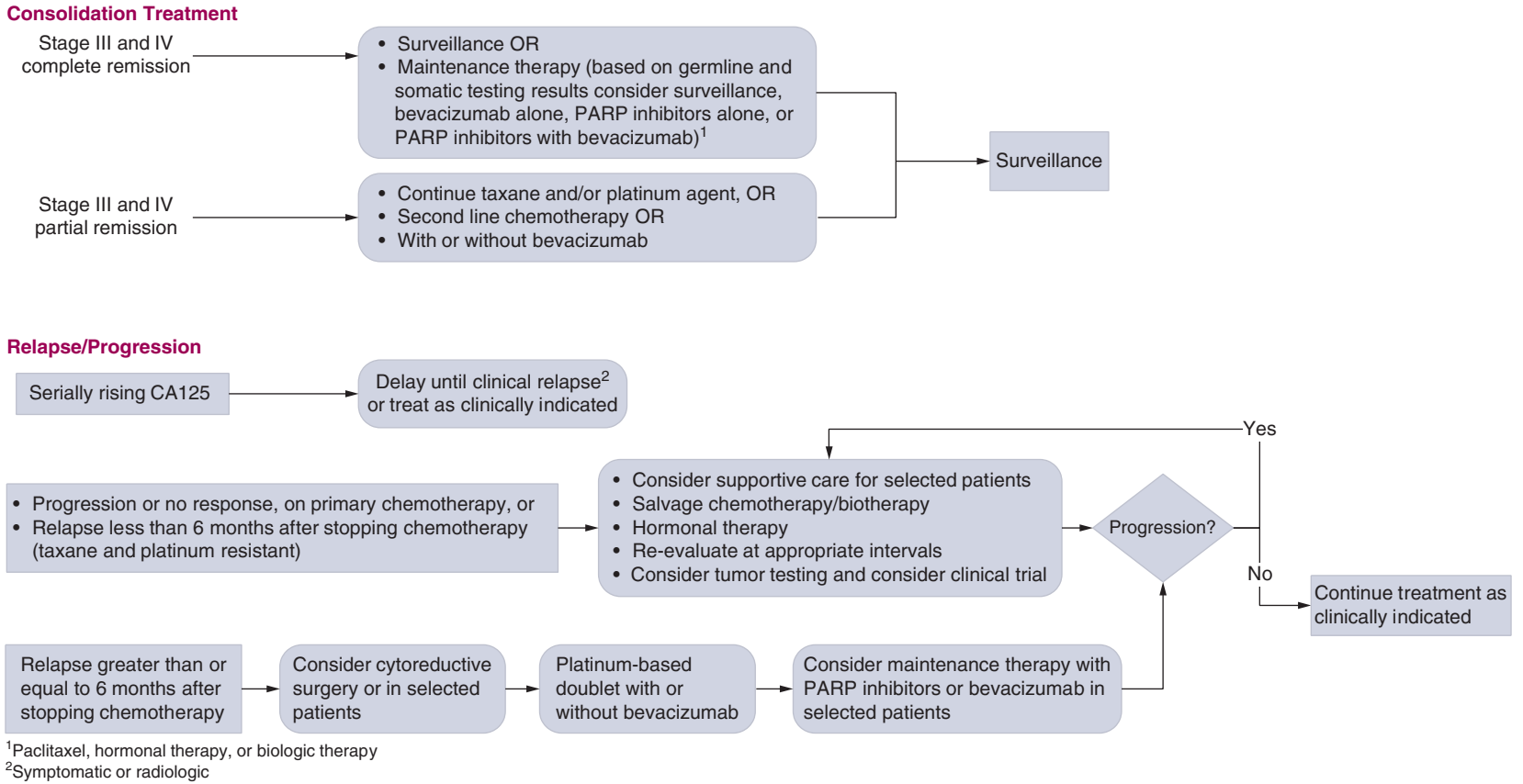


FIGURE 39–4 **Outline of treatment algorithms utilized at MDACC for the treatment of epithelial ovarian cancer. BSO, bilateral salpingo-oophorectomy; CXR, chest x-ray.**



[1]Paclitaxel, hormonal therapy, or biologic therapy
[2]Symptomatic or radiologic

FIGURE 39–4 (*Cont.*)

surgical staging likely do not benefit from postsurgical chemotherapy. Those with high-risk features, however, should be considered for adjuvant therapy. Two meta-analyses have shown that adjuvant chemotherapy improved both RFS and OS in patients with early-stage disease.[73,74] Subgroup analysis demonstrated that adjuvant therapy decreased the risk of death by 52% compared with observation in women with high-risk features (hazard ratio [HR] 0.48, 95% CI 0.32–0.72), but not in women without high-risk features.[73]

For early-stage EOC with high-risk features, treatment strategies are largely extrapolated from regimens with demonstrated efficacy in advanced disease. Thus, these patients often receive a platinum doublet such as carboplatin plus paclitaxel, though retrospective data indicate that single-agent carboplatin may be equally efficacious.[74] In addition, there is no consensus on the optimal number of adjuvant chemotherapy cycles. GOG 157 randomly assigned 457 patients with stage IA grade 3, stage IB grade 3, stage IC, and completely resected stage II ovarian epithelial cancer to six versus three cycles of carboplatin (7.5 area under the curve [AUC] over 30 min) and paclitaxel (175 mg/m^2 over 3 hours) every 21 days.[75] In the standard 3-cycle arm, the estimated probability of cancer recurring within 5 years was 27%, compared with 19% in the 6-cycle arm. The recurrence rate for 6 cycles was 24% lower, though this did not reach statistical significance (HR 0.761; 95% CI 0.51–1.13; $P = .18$). In addition, patients receiving six cycles of chemotherapy had significantly higher rates of grade 3 or 4 neurotoxicity, severe anemia, and neutropenia. It was concluded that the addition of three cycles to the standard three cycles did not significantly alter the rate of recurrence in patients with early-stage EOC.[75] It is notable that this study had 85% power to detect a 50% reduction in recurrence rate, and this optimistic assumption may have left the study underpowered to detect a smaller yet clinically important difference. Moreover, there may be subgroups that benefit from six cycles of chemotherapy. Chan and colleagues conducted an exploratory analysis of GOG 157 and found that the 5-year RFS of patients with serous tumors receiving six cycles was 82.7% compared with 60.4% in those receiving 3 cycles ($P = .007$). This effect was not seen in patients with nonserous cancers. Five-year OS in patients with serous cancer demonstrated a similar trend: 85.6% versus 73.2% in those receiving six versus three cycles, respectively.[76] Thus, it is reasonable to offer six cycles of adjuvant chemotherapy to patients with apparent early-stage HGSC.

Advanced-Stage Disease

Timing of Chemotherapy Initiation

Approximately 75% of women will have stage III or IV disease at diagnosis.[1,2] As mentioned previously, the sequence of chemotherapy and surgery is determined by patient fitness for surgery as well as volume and location of disease. Postoperatively, it is recommended to initiate chemotherapy within a month of surgery, though data are limited. An ad-hoc analysis of GOG 218, a phase 3 randomized placebo-controlled trial investigating the use of bevacizumab in EOC, demonstrated that in patients with stage IV disease who underwent complete surgical resection, chemotherapy initiation beyond 25 days (95% CI 16.6–49.9) was associated with an increased risk of death.[77] Prospective studies have demonstrated similar results in patients with residual disease,[78] and in those receiving postoperative chemotherapy in the neoadjuvant setting.[79] It is important to note that in the absence of randomized data, it is not known whether the detriment in survival is secondary to the delay in chemotherapy or the complications and comorbidities potentially leading to that delay.

Regimens

Carboplatin and paclitaxel remain the gold standard drugs in adjuvant treatment of EOC. Carboplatin is preferred to cisplatin given that multiple phase 3 randomized trials showed comparable efficacy with better tolerability and quality of life.[80,81] The effect of incorporating additional cytotoxic agents (gemcitabine, liposomal doxorubicin, topotecan) in combination with carboplatin and paclitaxel was evaluated in GOG 182. This randomized 4-arm trial showed equivalent PFS and OS in all the arms and a better toxicity profile in the carboplatin-and-paclitaxel-alone arm.[82]

The FDA approved frontline and maintenance bevacizumab for advanced ovarian cancer on June 13, 2018, though only modest benefit has been demonstrated. The addition of bevacizumab to chemotherapy during concurrent treatment and maintenance was tested in GOG 218 and ICON 7.[83,84] Both studies showed that the addition of bevacizumab resulted in a modest improvement in PFS, but without an improvement in OS. In GOG 218, only 19% of patients completed all planned treatments given progressive disease, and a PFS advantage was only seen for patients receiving bevacizumab both concurrently and after chemotherapy (HR 0.72, 95% CI 0.63–0.82). In ICON7, more than 90% of patients completed their treatment and almost two-thirds completed the maintenance phase, but the PFS benefit was 24 versus 22 months without an improvement in OS. Incidence of serious bowel toxicity (perforation or fistulas) and hypertension were about 2% and 23%, respectively.[79] Given the significant costs of bevacizumab and the lack of OS improvement, cost-effectiveness analysis has shown that bevacizumab as part of frontline therapy in ovarian cancer is not cost-effective when administered to all patients.[85] However, there is a

subgroup of patients that likely benefit from the addition of bevacizumab. In a post hoc analysis of GOG 218, Ferriss and colleagues found that patients with ascites who were treated with bevacizumab had significantly improved PFS (10.4 vs 15.2 months, HR 0.71, 95% CI 0.62–0.81; $P < .001$) and OS (39.9 vs 43.3 months, HR 0.82, 95% CI 0.70–0.96; $P = .014$).[86] In the final OS analysis of GOG 218, Tewari and colleagues reported a 10-month survival advantage in stage IV disease with the addition of bevacizumab (HR 0.75, 95% CI 0.59–0.95).[87] This finding was recapitulated in a subgroup analysis of ICON-7, where a predefined poor prognosis group (patients with stage IV, nonoptimally cytoreduced stage III, and inoperable stage III disease) experienced improved OS (34.5 vs 39.3 months) with the addition of bevacizumab to chemotherapy.[88] Thus, in patients with poor prognosis (as defined by ICON7), we recommend considering the addition of bevacizumab to standard chemotherapy.

It is important to note that patients with *BRCA 1* and *2* mutations derive a substantial benefit from the poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor, olaparib, as maintenance therapy as demonstrated by both the phase 3 SOLO-1 trial (olaparib vs placebo maintenance in patients with BRCA mutations) and the phase 3 PAOLA-1 trial (discussed further in the maintenance section). The phase 3 PAOLA-1 trial evaluated maintenance therapy with olaparib versus placebo in patients receiving standard chemotherapy plus bevacizumab (continued as maintenance) and found PFS benefit in patients with a *BRCA* mutation (as well as patients with homologous-recombination deficiency [HRD]).[89] This study did not have an olaparib-only maintenance arm, so the additional benefit of bevacizumab to olaparib maintenance in these patients is unknown.

Recently, PARP inhibitors have been studied in combination with chemotherapy followed by maintenance in patients with newly diagnosed HGSC. A phase 3 trial randomly assigned 1140 patients (receiving adjuvant or neoadjuvant treatment) to receive: (1) chemotherapy plus placebo followed by placebo maintenance, (2) chemotherapy plus the PARP inhibitor veliparib followed by placebo maintenance, or (3) chemotherapy plus veliparib followed by veliparib maintenance. Coleman and colleagues demonstrated a significant PFS advantage in the overall study population (23.5 vs 17.3 months, HR 0.68) in favor of veliparib throughout. This was most pronounced in 200 patients with *BRCA* mutations (34.7 vs 22.0 months, HR 0.44), and 421 patients with HRD (31.9 vs 20.5 months, HR 0.57).[90] It is unclear whether there is benefit from the addition of veliparib to chemotherapy in the absence of veliparib maintenance.

Intraperitoneal Chemotherapy

Given the predilection for ovarian cancer to spread within the peritoneal cavity and the higher concentration of platinum and taxane achieved with intraperitoneal chemotherapy administration, there is a compelling rationale for use of intraperitoneal chemotherapy in patients with advanced-stage disease. Three randomized trials have revealed improved PFS and OS in patients receiving intraperitoneal chemotherapy in the adjuvant setting.[91–93] Although all three trials have been criticized, the results of GOG 172, which revealed a 16-month OS benefit in the intraperitoneal arm (intravenous [IV] paclitaxel/intraperitoneal [IP] cisplatin and IP paclitaxel), led the National Cancer Institute to issue a Clinical Announcement recommending that women with stage III ovarian cancer who undergo optimal surgical cytoreduction be considered for intraperitoneal chemotherapy. However, in the IV/IP arm of this study, fewer than half of the patients were able to complete the six prescribed cycles secondary to excessive toxicity.[91] Furthermore, despite the clear survival benefit, fewer than 50% of patients at NCCN centers received IP/IV chemotherapy between 2003 and 2012,[94] possibly secondary to difficulty with administering the inpatient IV/IP protocol. In hopes of arriving at a more feasible outpatient intraperitoneal regimen, GOG 252 was conducted to compare the GOG 172–derived outpatient regimen (with IP cisplatin) to a dose-dense IV therapy arm; and an IV/IP arm with paclitaxel IV and carboplatin IP; with bevacizumab included in all three arms. After 84.8 month of follow-up in 1560 optimally cytoreduced patients, neither of the IV/IP regimens led to improved PFS but were associated with worse toxicity.[95] The use of dose-dense paclitaxel, the addition of bevacizumab, the decreased dose of cisplatin (from 100 mg/m^2 to 75 mg/m^2), and 28% crossover limit the conclusions from GOG 252. Given that this was the largest study involving IP chemotherapy and it was definitively negative, many have concluded that there is no role for IP chemotherapy in advanced ovarian cancer.[96]

There has been growing interest in hyperthermic intraperitoneal chemotherapy (HIPEC), a treatment strategy initially used in colorectal cancer. Recently, van Driel and colleagues randomly assigned 245 patients with stage III EOC to HIPEC with cisplatin during the time of interval cytoreductive surgery versus surgery alone and found both a PFS (14.2 vs 10.7 months) and an OS (45.7 vs 33.9 months) benefit with the addition of HIPEC.[97] On the other hand, a randomized study by Lim and colleagues[98] showed no benefit from HIPEC. In the setting of multiple limitations of the van Driel study, there has not been a universal change in practice, and HIPEC is not considered standard of care for first-line therapy of ovarian cancer in many centers.

Carboplatin and Dose-Dense (Weekly) Paclitaxel

Weekly dose-dense paclitaxel initially gained popularity in the last decade with preclinical evidence suggesting increased apoptosis of tumor cells, improved drug delivery, and reduction of angiogenesis with this strategy.[99] This was followed by the promising results of the Japanese GOG protocol (JGOG 3016) demonstrating significant survival benefit with this dosing schedule. JGOG 3016 compared the administration of carboplatin (AUC = 6) with paclitaxel (180 mg/m^2) every 3 weeks versus weekly (80 mg/m^2 on days 1, 8, and 15 of a 21-day cycle). This study was the first phase 3 trial to evaluate this regimen and demonstrated significant improvement in both median PFS and OS in the weekly paclitaxel regimen (PFS 18.2 vs 17.5 months; OS 100.5 vs 62.2 months).[100,101] There is question surrounding the generalizability of this trial given that OS in the control arm (62.2 months) was much longer than in any of the platinum-era GOG or European trials, even with the inclusion of patients who underwent suboptimal cytoreductive surgery. Unfortunately, these favorable results have not been replicated in subsequent phase 3 studies.

In a similar design, the GOG group compared carboplatin (AUC = 6) with either weekly paclitaxel (80 mg/m^2) versus paclitaxel every 3 weeks (175 mg/m^2) as adjuvant treatment in patients with stage II–IV EOC after both optimal and suboptimal cytoreductive surgery. However, unlike JGOG 3016, this study allowed the use of bevacizumab (15 mg/kg every 3 weeks), which may have had an impact on the results. Notably, in the intention-to-treat analysis, there was no difference in PFS for either the weekly or every-3-week paclitaxel group. In a subgroup analysis, patients who had not received bevacizumab demonstrated significant improvement in PFS (by 3.9 months) with weekly paclitaxel. This suggests that perhaps dose-dense weekly paclitaxel is only beneficial when anti-angiogenic therapy is not used.[102]

The Multicenter Italian Trials in Ovarian cancer study (MITO-7) compared weekly carboplatin (AUC = 2) and weekly paclitaxel (60 mg/m^2) to conventional therapy with carboplatin (AUC = 6) with paclitaxel (175 mg/m^2) every 3 weeks. Again, there was no significant PFS benefit for either group. Patients treated with the weekly dosing regimen experienced less severe toxicities with less neutropenia, thrombocytopenia, and neuropathy, making this a reasonable option for patients with poor performance status.[103]

In a trial by the International Collaborative Ovarian Neoplasm group (ICON 8 trial), 1566 women in Europe with stage IC–IV EOC after PCS or before neoadjuvant chemotherapy were randomly assigned to one of three groups: (1) carboplatin (AUC 5 or 6) and paclitaxel 175 mg/m^2 every 3 weeks; (2) carboplatin (AUC 5 or 6) every 3 weeks with weekly paclitaxel (80 mg/m^2); or (3) weekly carboplatin (AUC 2) and weekly paclitaxel (80 mg/m^2). There was no improvement in median PFS with either weekly regimen over standard dosing.[104]

GOG 252 also evaluated weekly paclitaxel dosing, but instead used it as the control arm in an attempted evaluation of intraperitoneal chemotherapy. As noted in the previous section, there was no significant PFS benefit observed with intraperitoneal chemotherapy over weekly paclitaxel dosing. In addition, bevacizumab was included in all arms in this trial, again possibly clouding the interpretation of these results.[95,96]

Although four of five phase 3 randomized controlled trials do not demonstrate a benefit of dose-dense paclitaxel, the results of JGOG 3016 are compelling and should not be ignored. It is possible that with the ethnic differences among the populations involved, there could also be genetic differences in processing paclitaxel that are not fully understood. Even so, we do not currently feel there is sufficient evidence to support the standard use of weekly paclitaxel in the adjuvant setting and are not incorporating this into our practice at MDACC.

Alternative Chemotherapeutic Agents

Docetaxel (Taxotere) is a semisynthetic compound structurally related to paclitaxel. Although the toxicity profiles are similar between the two drugs, docetaxel seems to be associated with less neuropathy and more myelosuppression. Prolonged treatment with docetaxel can also increase skin and nail toxicity as well as cause fluid retention and significant edema. In addition, docetaxel is prepared without the cremophor EL diluent used in the preparation of paclitaxel. Cremophor is felt to be responsible for many cases of paclitaxel hypersensitivity. A trial conducted by the Scottish Gynaecological Cancer Trials Group included 1077 patients with FIGO stage IC–IV EOC who were randomly assigned to receive carboplatin in combination with either paclitaxel or docetaxel. The median PFS for both arms was approximately 15 months.[105] The authors concluded that the docetaxel combination appears to be a viable alternative to the paclitaxel combination as first-line chemotherapy in EOC with similar efficacy and different side effect profile.

Maintenance Therapy

High risk of recurrent disease after treatment of advanced-stage EOC has prompted an intensive search for therapeutic strategies that can be implemented after standard-of-care therapy to improve patient outcomes. More than 12 phase 3 trials have been undertaken in this setting, including extension of frontline

agents, administration of short-duration non–cross-resistant chemotherapy, high-dose chemotherapy, whole-abdominal or intraperitoneal radiotherapy, immunotherapy, vaccine therapy, and biologic therapy; however, none have shown an OS advantage against various controls (usually no treatment).[106] The S9701/GOG178 phase 3 trial that administered paclitaxel IV for 12 months (vs 3 months) after an initial response to first-line chemotherapy showed improved PFS. However, the design of the trial (with PFS as the primary end point) led to early closure and lack of data on the effect of this consolidation strategy on OS. This improvement in PFS was associated with significant neurotoxicity, and this strategy has not been widely adopted in routine clinical practice.[107] The chemotherapy regimens utilized at MDACC are outlined in Fig. 39–5.

Conversely, remarkable advancements have been made in the upfront management of patients with germline or somatic *BRCA1* or *2* mutations. The SOLO-1 study demonstrated significant benefit with maintenance olaparib in this patient population. This study was a phase 3 trial evaluating maintenance olaparib in patients with a germline or somatic *BRCA1/2* mutation and newly diagnosed advanced EOC (HGSC or endometrioid) who had a partial or complete response to platinum-based chemotherapy. After 41 months of follow-up, the rate of freedom from disease progression or death was significantly lower with olaparib than with placebo at 3 years (60% vs 27%, HR 0.3, 95% CI 0.23–0.41; $P < .001$).[108] In December of 2018, the FDA expanded approval of olaparib to include this indication and it has become widely adopted in this setting.

Results of three additional clinical trials—PRIMA, PAOLA-1, and VELIA—have been published, also demonstrating benefit of maintenance PARP inhibitor in the upfront setting. PRIMA evaluated 733 patients randomly assigned to niraparib versus placebo after response to platinum-based chemotherapy. In patients with homologous-recombination deficiency, PFS was significantly improved with niraparib maintenance (21.9 vs 10.4 months). Even in the overall population, the PFS was improved with niraparib (13.8 vs 8.2 months).[109] In April 2020, the FDA approved the use of niraparib for maintenance treatment of EOC regardless of biomarker status. In the VELIA trial, a different PARP inhibitor (veliparib) was evaluated. As previously discussed, patients were randomly assigned to one of three arms: (1) first-line chemotherapy with carboplatin, paclitaxel, and veliparib followed by veliparib maintenance therapy; (2) chemotherapy and veliparib followed by placebo maintenance; and (3) chemotherapy and placebo followed by placebo maintenance. Veliparib with chemotherapy followed by maintenance veliparib seemed to derive the greatest survival benefit. Although patients with BRCA mutations seemed to benefit most (PFS 34.7 vs 22.0 months), the HRD cohort and the intention-to-treat population both benefited as well (PFS 31.9 vs 20.5 months and 23.5 vs 17.3 months, respectively).[90] Lastly, PAOLA-1 evaluated maintenance olaparib in the frontline setting in combination with bevacizumab. PFS was significantly improved when olaparib was added to bevacizumab in the maintenance setting with PFS of 22.1 months versus 16.6 months in the overall population.[89]

Follow-up and Treatment of Recurrent Disease

Despite multimodality therapy, 75% to 80% of women with advanced-stage EOC will have disease recurrence. Regular follow-up with CA 125 tumor marker level can detect disease recurrence.[110,111] In women with previously treated EOC that is in clinical remission, the NCCN has recommended assessment of serum CA 125 concentration at every follow-up visit if this concentration was raised at initial diagnosis. After documentation of CA 125 increase in such women, the median time to a clinical relapse of EOC is 2 to 6 months. There is, however, controversy over the benefit of early treatment versus later treatment. The results of a large study showed no survival benefit from early treatment on the basis of rising serum CA 125 concentration alone without clinical evidence of recurrence. With these findings, the authors questioned the value of routine measurement of CA 125 in the follow-up of patients with EOC.[111] It has also been suggested that smaller tumors are more often responsive to treatment, but this does not eliminate the lead-time bias. Others claim that larger tumors have an inferior primary response and grow rapidly. Recurrent ovarian cancer is a mortal disease but—in the absence of data showing that treatment improves quality of life—this does not justify haste in treating patients with recurrence. At MDACC, we follow patients with CA 125 levels in surveillance but in general do not treat patients based solely on a rising value (see Fig. 39–4).

Unfortunately, although chemotherapy can produce meaningful responses in the recurrent setting, it is not curative. The treatment of recurrent EOC is stratified by the amount of time from completion of primary platinum-based chemotherapy. Patients whose disease recurs with a PFS of 6 months or longer are defined as having platinum-sensitive disease. Patients whose disease recurs in less than 6 months from primary chemotherapy are classified as having platinum-resistant disease. Patients whose disease progresses on primary chemotherapy have tumors classified as platinum refractory and have a poor prognosis.[112] A list of treatment regimens utilized at MDACC in platinum-sensitive and platinum-resistant disease can be found in Fig. 39–5.

Systemic Therapy for EOC	
Adjuvant	**IV/IP Paclitaxel cisplatin:** Paclitaxel 135 mg/m2 IV continuous infusion Day 1; Cisplatin 75-100 mg/m2 IP Day 2 after IV paclitaxel; Paclitaxel 60 mg/m2 IP day 8 Repeat every 21 days x 6 cycles **Paclitaxel 175/carboplatin:** Paclitaxel 175 mg/m2 IV followed by carboplatin AUC 5-6 IV Day 1 Repeat every 21 days x 3-6 cycles* **Paclitaxel weekly/carboplatin every 3 weeks:** Dose-dense paclitaxel 80mg/m2 IV Days 1, 8, 15 followed by carboplatin AUC 5-6 Day 1 Repeat every 21 days x 6 cycles **Docetaxel/carboplatin:** Docetaxel 60-75 mg/m2 IV followed by carboplatin AUC 5-6 IV Day 1 Repeat every 21 days x 3-6 cycles* **Carboplatin/PLD:** Carboplatin AUC 5 IV + PLD 30 mg/m2 IV Repeat every 28 days for 3-6 cycles* **Paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab (GOG-218)** Paclitaxel 175 mg/m2 IV followed by carboplatin AUC 6, and bevacizumab 15 mg/kg IV Day 1 Repeat every 21 days x 6 cycles Starting Day 1 of cycle 2, bevacizumab 15 mg/kg every 21 days for up to 22 cycles
Neoadjuvant	Paclitaxel 175/carboplatin (as above) x 3-6 cycles Paclitaxel weekly/carboplatin every 3 weeks (as above) x 3-6 cycles Docetaxel/carboplatin (as above) x 3-6 cycles Carboplatin/PLD (as above) x 3-6 cycles Paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab (GOG-218, or ICON-7), consider holding bevacizumab on the cycle prior to surgery
Maintenance after Frontline	Bevacizumab as above Olaparib (if BRCA 1/2 germline/somatic mutation) Niraparib Bevacizumab/olaparib (if BRCA 1/2 germline/somatic mutation or HRD)
Platinum-Sensitive Recurrence	**Preferred, combination:** Carboplatin/gemcitabine +/- bevacizumab Carboplatin/PLD +/- bevacizumab Carboplatin/paclitaxel +/- bevacizumab Cisplatin/gemcitabine **Preferred, single agents:** Bevacizumab Niraparib (three or more prior chemotherapy lines, BRCA 1/2 germline/somatic mutation or HRD) Olaparib (three or more prior lines of chemotherapy, BRCA 1/2 germline mutation) Rucaparib (two or more prior lines of chemotherapy, BRCA 1/2 germline/somatic mutation)
Maintenance after Platinum-Sensitive Recurrence	Bevacizumab (if prior regimen contained bevacizumab) Niraparib (two or more prior line of platinum-based therapy) Olaparib (two or more prior line of platinum-based therapy) Rucaparib (two or more prior line of platinum-based therapy)
Platinum-Resistant Recurrence**	**Preferred:** Cyclophosphamide/bevacizumab Docetaxel Etoposide Gemcitabine PLD +/- bevacizumab Paclitaxel (weekly) +/- bevacizumab Topotecan +/- bevacizumab Bevacizumab Niraparib (three or more prior chemotherapy lines, BRCA 1/2 germline/somatic mutation or HRD) Olaparib (three or more prior lines of chemotherapy, BRCA 1/2 germline mutation) Rucaparib (two or more prior lines of chemotherapy, BRCA 1/2 germline/somatic mutation)

* For stage I disease: 6 cycles is recommended for high-grade serous; 3-6 cycles for all other ovarian cancer types. For stage II–IV disease: 6 cycles is recommended
IP: Intraperitoneal
AUC: Area under the curve
PLD: Pegylated liposomal doxorubicin
** Encourage clinical trial participation

FIGURE 39–5 **Chemotherapy regimens utilized at MDACC for the treatment of epithelial ovarian cancer. AUC, area under the curve; IP: Intraperitoneal; PLD: Pegylated liposomal doxorubicin; ** Encourage clinical trial participation.**

Treatment of Platinum-Sensitive Disease

As mentioned, patients who have a treatment-free interval of 6 months or greater before recurrence are more likely to respond to repeat platinum treatment. Therefore, as long as patients continue to respond to platinum and have more than a 6-month interval between each treatment, it seems reasonable to continue treatment with platinum, either as a single agent or in a combination regimen (see Fig. 39–5). When selecting single-agent versus combination therapy, it is important to consider the patient's performance status, comorbidities, and toxicities with prior therapies. If combination therapy is elected, then the choice of combination regimen should also take these factors into account to optimize outcome and minimize overlapping toxicities.

Carboplatin and Paclitaxel

Two phase 3 trials have shown the benefit of carboplatin and paclitaxel in the setting of platinum-sensitive recurrence, and the results were published together. The ICON4 and AGO-OVAR-2.2 studies randomly assigned 802 patients to receive conventional single-agent platinum-based chemotherapy or platinum plus paclitaxel. The combination regimen was associated with improved OS (29 vs 24 months, HR 0.82, 95% CI 0.69–0.97; P = .023). There were higher rates of neuropathy and alopecia in the platinum-plus-paclitaxel treatment group but a lower rate of myelosuppression.[113] Although this is only one of two studies to date that has documented an improvement in OS in this setting, one critique of this study is that a large proportion of patients (30%) were not previously treated with taxane therapy, which may have led to an improved response in this patient population.

Carboplatin and Pegylated Liposomal Doxorubicin

The combination of carboplatin and pegylated liposomal doxorubicin was compared with carboplatin and paclitaxel in the Caelyx in Platinum-Sensitive EOC (CALYPSO) trial. Designed as a noninferiority trial with a primary end point of PFS, the experimental arm of carboplatin and pegylated liposomal doxorubicin was determined to be noninferior (P < .001). An analysis of superiority to the carboplatin-and-paclitaxel arm was also significant (median 11.3 vs 9.4 months, HR 0.82, 95% CI 0.72–0.94; P = .005); however, there was no difference in OS (30.7 vs 33 months). The combination of carboplatin plus liposomal doxorubicin led to fewer cases of severe neutropenia, fewer episodes of mild myalgias/arthralgias, and less neuropathy, but it did lead to more cases of severe thrombocytopenia, nausea/vomiting, hand-foot syndrome, and mucositis. Interestingly, this combination also led to fewer episodes of carboplatin hypersensitivity reactions.[114]

Carboplatin and Gemcitabine

A phase 3 trial was performed by the Gynecologic Cancer InterGroup (GCIG) to evaluate carboplatin alone versus carboplatin plus gemcitabine in patients with platinum-sensitive disease. Treatment with the combination regimen showed an improved PFS (8.6 vs 5.8 months), but no improvement in OS. Not surprisingly, there were more toxicities seen in the combination arm, with increased neutropenia and thrombocytopenia.[115]

Targeted Therapies

To date, among targeted therapies, only bevacizumab (OCEANS and GOG-0213) and trebananib (TRINOVA 1, discussed later in treatment of platinum-resistant disease) have been assessed in a phase 3 effort. The OCEANS trial was a randomized phase 3 trial that evaluated carboplatin plus gemcitabine with or without the addition of bevacizumab. Patients received the assigned treatment for 6 to 10 cycles and were then continued on bevacizumab or placebo maintenance until progression. The addition of bevacizumab led to an improved PFS (12.4 vs 8.4 months) with an improved objective response rate (78.5% vs 57.4%; P < .001). However, with a median follow-up of 57 months, OS did not significantly differ between the two arms (33.6 vs 32.9 months; HR 0.96, 95% CI 0.77–1.18; P = .65). As seen with other antiangiogenesis studies, the addition of bevacizumab led to higher rates of hypertension and proteinuria.[116]

GOG-0213 was designed with OS as the primary end point for each of its two primary objectives. The first was to assess the impact of bevacizumab given concomitantly with paclitaxel and carboplatin, as well as in maintenance, among women with one prior line of treatment.[117] The second objective was to evaluate the impact of secondary cytoreduction. In the analysis of the first objective, the experimental arm showed a significant improvement in PFS (13.8 vs 10.4 months, HR 0.63, 95% CI 0.53–0.74; P < .001), as well as a significant improvement in objective response (78% vs 59%, P < .001), including a near doubling of the complete response rate (32% vs 18%). More importantly, bevacizumab given concomitantly with chemotherapy and in maintenance improved OS (42.2 vs 37.3 months, unadjusted HR 0.83, 95% CI 0.68–1.005; P = .056; adjusted HR 0.82, 95% CI 0.68–0.996; P = .045). Adjustment was made based on prespecified stratification variables (platinum-free interval and participation in secondary cytoreduction). Based on the OCEANS

trial and GOG-0213, the FDA approved bevacizumab in combination with chemotherapy for women with platinum-sensitive recurrent EOC in late 2016.

In an effort to compare regimens for platinum-sensitive disease, a randomized phase 3 trial was performed that assigned patients to either (1) carboplatin (AUC 4, day 1) plus gemcitabine (1000 mg/m,^{2} days 1 and 8) plus bevacizumab (15 mg/kg day 1) every 3 weeks; or (2) carboplatin (AUC 5, day 1) plus pegylated liposomal doxorubicin (30 mg/m,^{2} day 1) plus bevacizumab (10 mg/kg, days 1 and 15), both followed by maintenance bevacizumab (15 mg/kg every 3 weeks in both groups) until disease progression or unacceptable toxicity. Median PFS was 13.3 months (95% CI 11.7–14.2) in the experimental group (carboplatin-pegylated liposomal doxorubicin-bevacizumab) versus 11.6 months (95% CI 11.0–12.7) in the standard group (carboplatin-gemcitabine-bevacizumab) (HR 0.81, 95% CI 0.68–0.96; p = .012). This trial demonstrated superior efficacy of the more widely used platinum-based regimen (carboplatin plus pegylated liposomal doxorubicin) plus bevacizumab, suggesting that this is the new standard regimen for patients with recurrent platinum-sensitive ovarian cancer.[118]

Poly-ADP Ribose Inhibitors

The inhibition of DNA repair pathways is another strategy that has led to the development of new active agents in women with EOC. Cells with reduced BRCA protein function are inefficient in the repair of double-stranded DNA breaks by homologous recombination. Consequently, such cells must rely on other pathways to repair DNA damage, in particular the PARP pathway, which detects single-stranded breaks and activates a number of effector proteins to initiate repair. PARP plays an essential part in the repair of single-stranded DNA breaks through the base-excision-repair pathway, and it has been proposed that PARP keeps low-fidelity nonhomologous-end-joining DNA repair machinery in check. Inhibition of PARPs leads to the accumulation of single-stranded breaks, which leads to accumulation of DNA double-strand breaks in those deficient cells. Although germline mutations in the *BRCA1* and *BRCA2* genes are present in only about 15% of high-grade serous EOC, studies have estimated that approximately 50% of high-grade serous EOCs have HR deficiency.[119]

Three of the most commonly used PARP inhibitors (olaparib, niraparib, and rucaparib) have been evaluated in the maintenance setting with platinum-sensitive disease, and as treatment for patients with *BRCA1/2* germline mutations and recurrent disease. (As discussed in a prior section, olaparib and niraparib have also been evaluated in the maintenance setting after upfront adjuvant chemotherapy.)

Olaparib

Treatment

Study 42, a single-arm trial that evaluated olaparib as treatment for patients with recurrent, platinum-resistant EOC and a germline *BRCA1/2* mutation, included patients who received olaparib until disease progression or toxicity. The overall response rate (ORR) was 31.1% and the median PFS and OS were 7 months and 16.6 months, respectively. In a subgroup analysis of 137 patients with three or more prior lines of chemotherapy, olaparib was similarly effective, with an ORR of 34%.[120] On the basis of these data, the FDA granted accelerated approval in 2014 for single-agent olaparib in women with germline BRCA mutations with ovarian cancer for treatment after 3 or more prior therapies.

Maintenance

Study 19, a randomized, double-blind, placebo-controlled, phase 2 study of the use of olaparib as maintenance therapy in the setting of recurrent, platinum-sensitive EOC, enrolled patients regardless of *BRCA* mutation status who had received two or more prior lines of chemotherapy, with a partial response or complete response to the last platinum-based chemotherapy.[121] Those who received olaparib exhibited a significant improvement in PFS (8.4 vs 4.8 months, HR 0.35, 95% CI 0.25–0.49; $P < .001$). A preplanned analysis of this study by retrospective determination of *BRCA* status revealed that PFS was significantly improved in the olaparib group compared with the placebo group among the patients with germline or tumor *BRCA* mutations (HR 0.18, 95% CI 0.10–0.31; $P < .001$).

The subsequent SOLO-2 study, a randomized, double-blind, placebo-controlled phase 3 trial, was developed to assess the efficacy of olaparib maintenance therapy in patients with platinum-sensitive recurrent EOC harboring a *BRCA1/2* mutation who had a complete or partial response to most recent platinum-based therapy and had received at least two previous lines of chemotherapy. Randomization was stratified by response to previous platinum chemotherapy (complete *vs* partial) and length of platinum-free interval (6–12 *vs* ≥12 months). Patients in the experimental arm (olaparib maintenance) had a significantly prolonged median PFS of 19.1 versus 5.5 months in the placebo group (HR 0.30, 95% CI 0.22–0.41; $P < .001$).[122] The FDA granted additional approval for the use of olaparib on August 2017 as maintenance therapy for women with recurrent EOC (with and without *BRCA* mutations) who have achieved a complete or partial response to platinum-based chemotherapy.

Niraparib

Treatment

Niraparib was investigated as monotherapy as a fourth or later line of therapy in the QUADRA trial. This

trial was a multicenter, open-label, single-arm, phase 2 study evaluating niraparib in women with relapsed HGSC who had received three or more previous chemotherapy regimens. The primary objective was ORR in patients with HRD-positive tumors (regardless of BRCA status) and sensitive to their last platinum-based therapy. In this group, there was a 28% response rate. This led to the FDA approval in October 2019 of niraparib for patients with advanced HRD-positive ovarian, fallopian tube, or primary peritoneal cancer who had received three or more prior chemotherapy regimens.

Maintenance

The pivotal phase 3 ENGOT-OV16/NOVA trial of niraparib maintenance therapy enrolled patients with recurrent ovarian cancer with either a partial or complete response to platinum-based chemotherapy and normalization of CA 125. They were categorized by germline *BRCA* mutation status (203 carried a germline *BRCA* mutation [gBRCA] and 350 were not germline *BRCA* carriers [non-gBRCA]). They were then randomly assigned in a 2:1 ratio to receive niraparib (300 mg daily) maintenance versus placebo. Assessment of somatic HRD was made by performing the MyChoice™ assay (Myriad Genetics, Inc.) on submitted tumor samples. Among germline *BRCA* mutation carriers, there was a significant prolongation in PFS in the experimental group relative to placebo (median 21.0 vs 5.5 months, HR 0.27, 95% CI 0.017–0.41; $P < .001$). There was also a benefit in patients without a germline *BRCA* mutation (median 9.3 vs 3.3 months, HR 0.45, 95% CI 0.34–0.61; $P < .001$) and in a prespecified analysis of the HRD-positive subgroup of the non–germline *BRCA* mutation group (median 12.9 vs 3.8 months, HR 0.38, 95% CI 0.24–0.59; $P < .001$). Patients with HRD-negative tumors also had prolonged PFS with niraparib relative to placebo (median 6.9 vs 3.8 months, HR 0.58, 95% CI 0.36–0.92; $P = .02$).[123] In March 2017, the FDA approved niraparib as the first PARP inhibitor for routine administration as a second-line maintenance strategy (after a response to platinum-based treatment) without requiring the use of a molecular biomarker (either *BRCA* mutation or HRD-positive).

Rucaparib

Treatment

ARIEL2 is an international two-part phase 2 trial conducted to assess rucaparib sensitivity in three prospectively defined subgroups and to develop a diagnostic test to identify, through fresh and archival tumor biopsies, a biomarker of HRD. The objective of part 1 was to identify molecular predictors of rucaparib sensitivity in patients with platinum-sensitive recurrent high-grade EOC, including tumors without a germline or somatic *BRCA* mutation.[124] Of the 204 patients who received rucaparib, 192 patients could be classified into one of the three predefined HRD subgroups based on tumor mutational analysis: BRCA mutant (deleterious germline or somatic, $n = 40$); BRCA wild-type and LOH high (LOH high group, $n = 82$); or BRCA wild-type and LOH low (LOH low group, $n = 70$). The median PFS was: *BRCA*-mutant (12.8 months; 95% CI 9.0–14.7), LOH high group (5.7 months; 95% CI 5.3–7.6), and LOH low group (5.2 months; 95% CI 3.6–5.5). PFS was significantly longer in the *BRCA*-mutant subgroup (HR 0.27, 95% CI 0.16–0.44; $P < .001$) and LOH high subgroup (HR 0.62, 95% CI 0.42–0.90; $P = .01$) than in the LOH low subgroup. These results suggest that assessment of tumor LOH can be used to identify patients with *BRCA* wild-type platinum-sensitive EOC who might benefit from rucaparib. In December 2016, the FDA granted accelerated approval to rucaparib for the treatment of patients with deleterious *BRCA*-mutant (germline and/or somatic)–associated advanced EOC who have been treated with two or more chemotherapies.

Maintenance

ARIEL3 is a phase 3 randomized, double-blind, placebo-controlled trial that included patients with platinum-sensitive high-grade serous or endometrioid ovarian carcinoma. All patients received at least two previous platinum-based chemotherapy regimens and achieved complete or partial response to their last platinum-based regimen. Patients were stratified by LOH status, progression-free interval after the penultimate platinum-based regimen, and best response to the most recent platinum-based regimen. Consistent with the SOLO2 and NOVA trials, ARIEL3 revealed a strong effect of rucaparib in the enrolled women. The primary efficacy analysis evaluated three prospectively defined molecular subgroups in a step-down manner: (1) *BRCA*-mutant; (2) HRD-positive; and (3) the intent-to-treat population, or all patients treated in this study. Among patients with a *BRCA*-mutant carcinoma, there was a significant prolongation of PFS in the rucaparib group relative to placebo (16.6 vs 5.4 months, HR 0.23, 95% CI 0.16–0.34; $P < .001$) and in patients with HRD cancers (13.6 vs 5.4 months; $P < .001$). In the intention-to-treat population, PFS was 10.8 months versus 5.4 months (rucaparib vs placebo) ($P < .001$). Unique to ARIEL3, objective response data were collected from patients entering the trial with a partial response in each of the cohorts. In the subgroup of patients with measurable disease at study entry with a *BRCA*-mutant carcinoma, exploratory analysis showed that the rucaparib group achieved higher rates of confirmed RECIST response compared with placebo (38% vs 9%). In HRD-positive patients, the objective response was also higher in the rucaparib group (27% vs 7%).[125] Based on

ARIEL 3, rucaparib was approved by the FDA in April 2018 for maintenance therapy in patients with ovarian cancer that responded to platinum-based chemotherapy. As with olaparib and niraparib, documentation of *BRCA* status or LOH is not needed under this label.

Treatment of Platinum-Resistant Disease

There are several treatment options for the treatment of platinum-resistant recurrent EOC. In general, single-agent treatment regimens are utilized in this patient population to minimize adverse effects, given incurable disease. Although there are several options, no one therapy has been shown to be superior to others as first-line treatment for platinum-resistant disease. A Cochrane review of three of the most commonly used agents (paclitaxel, pegylated liposomal doxorubicin, and topotecan) showed similar efficacy. Thus, choice of first-line therapy is driven by side effect profiles of each of the therapies.

Liposomal Doxorubicin

A pegylated liposomal formulation of doxorubicin was first tested in patients with platinum-refractory disease; the resulting response rate was approximately 26%. Compared with topotecan in a phase 3 setting, liposomal doxorubicin was associated with lower toxicities, including lower rates of grade 3/4 neutropenia and thrombocytopenia, but with equivalent efficacy, with similar response rate (20% vs 17%) and time to progression (22 vs 20 weeks).[126] Based on the data from Gordon et al, the drug was FDA approved for use in ovarian cancer.

Gemcitabine

In a phase 3 study comparing gemcitabine and liposomal doxorubicin, both drugs had similar ORR (6.1% vs 8.3%), PFS (3.6 vs 3.1 months), and OS (12.7 vs 13.5 months).[127] Gemcitabine has been frequently studied in combination with cisplatin. The response rates ranged from 40% to 70%. However, the small number of patients treated as well as their heterogeneity disallows any further conclusion. Furthermore, it is difficult to justify the use of combination chemotherapy in patients without evidence that responses correlated with improvements in quality of life.

Weekly Paclitaxel

Paclitaxel is part of the backbone of treatment for advanced ovarian cancer. Several studies have shown activity of paclitaxel in platinum-resistant patients; however, a proportion of these studies were performed before the incorporation of paclitaxel in primary adjuvant therapy. Most recently, weekly paclitaxel produced a 21% response rate in patients with platinum-resistant disease. Not surprisingly, the main toxicity associated with this regimen is peripheral neuropathy.[128]

Topotecan

Compared with paclitaxel in patients with refractory ovarian cancer, topotecan was found to produce a response rate of 20% versus 13% in patients who received paclitaxel. This resulted in its approval for use by the FDA. In patients with relapsed platinum-resistant ovarian cancer, the ORR to treatment with topotecan ranged from 5% to 18%. The proportion of these patients who achieved stable disease was 17%. In phase 3 studies, topotecan was shown to have an efficacy equal to both paclitaxel and liposomal doxorubicin as second-line therapy in patients with relapsed ovarian cancer.[129]

Etoposide

Etoposide, a topoisomerase II inhibitor, has the advantage of being administered as an oral agent. In patients with platinum-refractory disease who were given 100-mg doses of etoposide orally for 14 days every 21 days, the response rate was about 26%. Lower doses of etoposide, at 50 mg/day, produced similar response rates, ranging from 10% to 27%. The combination of cyclophosphamide and bevacizumab has also been shown to be active in this patient population. A phase 2 trial showed partial response in 24% of patients, with 56% of patients predicted to be alive and progression-free at 6 months.

Bevacizumab

The phase 3 AURELIA study evaluated bevacizumab in addition to single-agent chemotherapy in platinum-resistant ovarian cancer. Patients with disease that progressed less than 6 months after completing adjuvant therapy were eligible, but platinum-refractory patients were excluded. The patients received the treating physician's choice of liposomal doxorubicin, weekly paclitaxel, or topotecan and were then randomly assigned to receive chemotherapy alone or chemotherapy plus bevacizumab. Patients who received bevacizumab had an improved response rate (31% vs 13%) and a reduction in the risk of disease progression (6.7 vs 3.4 months). There was no difference in OS; however, patients were allowed to cross over to receive bevacizumab after disease progression on chemotherapy alone, which may mask the survival advantage.[130] Based on the results of this trial, bevacizumab is now FDA approved for use in combination with chemotherapy for the treatment of platinum-resistant recurrent EOC. Patient-reported outcomes, a secondary end point of AURELIA, showed for the first time in platinum-resistant EOC that treatment can improve symptoms. Bevacizumab improved abdominal/gastrointestinal symptoms, as demonstrated by a significantly higher

proportion of patients achieving the predefined 15% improvement in abdominal/gastrointestinal symptoms using a responder-analysis approach. Effects on a broader range of quality-of-life concerns either favored the bevacizumab group or were no different.

In the TRINOVA 1 study, patients with recurrent EOC who had been treated with three or fewer previous regimens and had a platinum-free interval of 12 months or less (nearly 50% of patients in each arm were considered platinum-resistant), were randomly assigned to receive trebananib (an anti-angiogenic agent acting by neutralizing angiopoietin [Ang] 1 and 2 and preventing interaction with their target tie2 receptors) with paclitaxel versus single-agent paclitaxel. Median follow-up was 18 months, and the primary end point was PFS. The experimental arm had a significant advantage in PFS (7.2 vs 5.4 months, HR 0.66, 95% CI 0.57–0.77; $P < .001$). Although all patients exhibited some improvement in this end point, the subgroup with ascites benefited the most (HR 0.72, 95% CI 0.85–0.93; $P < .01$).[19] Median OS was not significantly improved with trebananib versus placebo (19.3 vs 18.3 months; HR 0.95, 95% CI 0.81–1.11; $P = .52$) in the intent-to-treat population.[131]

Immunotherapy

Over the last 5 years, a number of trials have assessed the efficacy of programmed death protein 1/programmed death ligand 1 (PD-1/PD-L1) immune checkpoint inhibitors in patients with recurrent EOC.[132–138] Although a detailed analysis of these trials is beyond the scope of this chapter, the efficacy results can be summarized as an observed response rate of 10% to 15%, with another 20% to 40% of patients experiencing stable disease. Furthermore, the results in trials that preselected patients based on tumor PD-L1 expression (eg, as with the KEYNOTE-028 study of pembrolizumab) has not been appreciably better, suggesting that PD L1 expression is not a discriminating predictor of response.[134] In the KEYNOTE-100 study, patients with advanced, recurrent ovarian cancer were stratified based on the number of prior lines of systemic therapy and treatment-free interval and were treated with pembrolizumab. However, this study found no significant differences in response or disease control rates based on the aforementioned stratification.[135]

Combination Therapy: Immune-Chemotherapy

Given the strength of the immunosuppressive tumor microenvironment and modest response to single-agent immune checkpoint inhibitor therapies, interest has grown to use combination therapy in ovarian cancer. Wenham and colleagues presented their preliminary findings at the 2018 International Gynecologic Cancer Society Meeting, describing platinum-resistant recurrent ovarian cancer patients having been treated with weekly paclitaxel and pembrolizumab (NCT02440425).[137] In the 37 evaluable patients, the ORR was 51.4% (all partial responses) with disease control rate (DCR) of 86.5%. The 6-month PFS rate was 64.5% and median PFS was 7.6 months with a median OS of 13.4 months.

The JAVELIN trials have investigated the use of avelumab in EOC. In the JAVELIN Ovarian 200 trial, patients with platinum-resistant/refractory ovarian cancer were randomly assigned to receive avelumab alone, pegylated liposomal doxorubicin alone, or both (NCT02580058).[138] Avelumab monotherapy was associated with the worst PFS and OS, and there was no additional benefit with the combination of avelumab to pegylated liposomal doxorubicin.[138]

Combination Therapy: Immune-Targeted therapy

Preclinical studies support a potential synergy between immune checkpoint inhibitors and PARP inhibitors, as well as VEGF targeting drugs. One of the first clinical studies in this area was a phase 1 study by Lee and colleagues, aimed at determining the safety and efficacy of durvalumab (anti–PD-L1) in combination with either olaparib or cediranib (multiple tyrosine kinase inhibitor that targets VEGF receptors 1–3).[139] Although the number of patients with ovarian cancer was small, an ORR in who received durvalumab and olaparib was 20% (two partial responses) with a DCR of 90%. Durable responses in this treatment group were not explained by homologous-recombination DNA repair pathway defects and none of the patients had germline BRCA mutations (two patients with somatic *BRCA* mutations had stable disease). This study included only six evaluable patients who received durvalumab and intermittent cediranib, and three of the six had partial responses. The combination of durvalumab and olaparib in a highly favorable patient population (patients with germline *BRCA* mutations with platinum-sensitive ovarian cancer) was investigated in the MEDIOLA study; (NCT02734004).[140] An ORR of 63% with a DCR of 81% at 12 weeks was observed. In contrast, the TOPACIO/KEYNOTE-162 trial examined the combination of niraparib and pembrolizumab in a population of patients with recurrent, platinum-resistant ovarian cancer who were unselected because of *BRCA* mutations.[141] In the 60 evaluable patients with ovarian cancer, the ORR was 18% with a DCR of 65%.

In another VEGF-PD1–targeting study, the combination of nivolumab and bevacizumab resulted in an ORR of 26.3% in a mixed population of patients with platinum-sensitive and platinum-resistant ovarian cancer.[142]

Combination Therapy: Immune-Immunotherapy

The preliminary results of the phase 2 NRG-GY003 trial (NCT02498600) were reported at the 2018

International Gynecologic Cancer Society Meeting; in that study, 100 patients with recurrent ovarian cancer were randomly assigned to receive either nivolumab alone or nivolumab/ipilimumab followed by maintenance nivolumab. This study revealed a higher ORR in the combination group compared with the nivolumab monotherapy group (31.4% vs 12.2%, respectively; $P = .034$).[143] This came at a cost of higher (but manageable) toxicity in the combination group.

In summary, although there is currently no approved immune checkpoint inhibitor therapy for patients with ovarian cancer, there are a plethora of ongoing studies investigating immune checkpoint inhibitors in combination with other chemotherapy, targeted, and immunologic agents. There is hope that this intense investigation will lead to an approved combination in the coming years.

Secondary Cytoreduction for Recurrent Disease

The two most consistent factors associated with favorable outcome in patients undergoing secondary cytoreductive surgery are time to first recurrence and postoperative residual disease. Therefore, secondary cytoreduction was traditionally reserved for patients with isolated, resectable, and platinum-sensitive disease. The conflicting results of the GOG 213, DESKTOP III, and SOC-1 trials (presented at the virtual American Society of Clinical Oncology [ASCO] meeting in 2020) should be considered to determine the utility of surgery in this setting.

In GOG 213, 485 women with investigator-determined resectable, platinum-sensitive recurrent EOC were randomly assigned 1:1 (stratified by platinum-free interval and chemotherapy) to secondary cytoreduction followed by chemotherapy or chemotherapy alone. Surgical candidacy was predicated on the likelihood to achieve no visible residual tumor (R0). The overall R0 rate in this trial was 67%. OS, the primary end point, was 53.6 months for those in the surgery group versus 65.7 months in the chemotherapy-only group (HR 1.28, 95% CI 0.92–1.79). One patient died of complications from secondary cytoreduction. Given the less than 0.1% chance of meeting superiority with mature survival data (expected at 250 events) the Data and Safety Monitoring Committee recommended releasing the trial results early.[144]

The final analysis of DESKTOP III was reported at the virtual 2020 ASCO Annual Meeting.[145] In this study, patients with EOC and first relapse after six or more months of platinum-free interval were eligible if they presented with a positive AGO score (PS ECOG 0, ascites ≤500 mL, and complete resection at initial surgery) and were randomly assigned to second-line chemotherapy alone versus secondary cytoreductive surgery followed by chemotherapy. Chemotherapy regimens were selected according to the institutional standard. Complete resection was achieved in 74.2% of the patients randomly assigned to surgery. The PFS in women who were randomly assigned to undergo surgery followed by chemotherapy was 18.4 months compared with 14 months in women who were randomly assigned to receive only second-line chemotherapy (HR 0.66, 95% CI 0.55–0.82; $P < .001$). Women randomly assigned to surgery also experienced an improved OS compared with control (53.7 vs 46 months; HR 0.75, 95% CI 0.58–0.96; $P = .02$). In addition, the OS benefit was highest in patients with complete resection (61.9 months; HR 0.57, 95% CI 0.43–0.76).

Finally, the results of SOC-1 were also presented at the virtual ASCO 2020 meeting.[146] In this study, patients with their first relapse after six or more months of platinum-free interval were eligible if they had an iMODEL score of less than or equal to 4.7 and the primary investigators agreed that the tumor could be completely resected based on PET-CT image results. The iMODEL score is comprised of stage, residual disease after primary surgery, length of progression-free interval, performance status, CA 125 level, and ascites at recurrence. This study randomly assigned 182 patients to receive secondary cytoreductive surgery followed by chemotherapy and 175 to receive chemotherapy alone, and had PFS and OS as coprimary end points. In the intention-to-treat population, 72.5% achieved complete cytoreduction to R0. The median PFS in those assigned to surgery was 17.4 months versus 11.9 months in those assigned to control (HR 0.58, 95% CI 0.45–0.74; $P < .001$). Immature OS analysis, however, demonstrated no significant difference between the groups (58.1 vs 53.9 months, HR 0.82, 95% CI 0.57–1.19).

Although the manuscripts for DESKTOP III and SOC-1 have yet to be published, we can summarize that two studies show a PFS benefit (DESKTOP III, SOC-1), one shows an OS benefit (DESKTOPIII), and one shows no benefit (GOG-213) with the addition of secondary cytoreduction to chemotherapy for recurrence. There are important differences in patient characteristics in these studies that should be considered. First, both DESKTOP III and SOC-1 used triage algorithms for patient selection that resulted in higher complete gross resection rates (~75%) than investigator-assessment in GOG 213 (67%). In addition, in GOG 213, 84% of the patients received bevacizumab compared with 23% of participants in DESKTOP III, and 1% in SOC-1. Finally, the control arm in GOG 213 experienced improved OS (65.7 months) compared with DESKTOP III (46 months) and SOC-1 (53.9 months). It is unclear whether the use of bevacizumab mediates the improved survival in the control arm of GOG 213. It is important to note that all the studies caution that suboptimal resection is no better than

chemotherapy alone and may be worse, and future studies are required to clarify patient selection criteria. In addition, the impact of novel agents and maintenance strategies on outcomes after secondary cytoreduction are to be further explored.

Low-Grade Serous Ovarian Carcinoma

Primary Management

Historically, all EOCs have been included together in clinical trials, which has led to a one-size-fits-all strategy for treatment. As with HGSC, the mainstay of treatment for LGSC involves comprehensive surgical staging followed by adjuvant platinum-based chemotherapy. Also like HGSC, maximal cytoreductive effort is important, because decreasing residual disease after PCS is associated with increasing survival. This was demonstrated in an ancillary analysis of a subset of patients with LGSC (n = 189) from GOG protocol 182, a phase 3, randomized, controlled trial of paclitaxel and carboplatin versus triplet or sequential doublet combinations in patients with EOC or primary peritoneal carcinoma. In this analysis, OS was significantly prolonged with cytoreductive surgery to no gross residual disease (96.9 months) versus optimal to less than 1 cm residual disease (44.5 months) and greater than 1 cm residual disease (42.0 months).[147]

Unfortunately, LGSC is relatively chemoresistant when compared with HGSC.[148,149] Despite this, carboplatin and paclitaxel remain first-line adjuvant therapy in advanced disease. However, hormonal therapies have had promising results in the adjuvant and maintenance settings.[150,151] Fader and colleagues performed a retrospective study of 27 patients with LGSC who underwent PCS followed by adjuvant hormonal therapy rather than standard platinum-based chemotherapy.[150] They found that after a median follow-up of 41 months, only 22% of patients had disease recurrence. Gershenson and colleagues have also demonstrated promising results of hormonal therapy in the maintenance setting. In a retrospective analysis of 203 patients with LGSOC, PFS was improved with maintenance hormonal therapy over observation (64.9 vs 26.4 months).[151] The NCCN has now included the use of hormonal therapy as an option for both adjuvant and maintenance treatment in stage 1C–IV disease (category 2B recommendation). A randomized phase 3 trial (NCT04095364) of paclitaxel/carboplatin followed by maintenance letrozole versus letrozole monotherapy as adjuvant treatment after cytoreductive surgery in patients with LGSC has recently started enrolling patients. It is hoped the results of this trial will provide more definitive guidance surrounding management of this disease in the upfront setting.

As noted above, LGSC has also shown relative chemoresistance in the neoadjuvant setting. Schmeler and colleagues retrospectively analyzed 25 women at a single institution who underwent neoadjuvant chemotherapy for advanced low-grade serous ovarian cancer. In this study, only one patient had a complete response, 21 (88%) had stable disease, and two (8%) had progressive disease.[148] Hormonal therapy is under investigation in this space as well. Specifically, a phase 2 trial evaluating fulvestrant and palbociclib as neoadjuvant treatment has recently started enrolling patients at MDACC (NCT03531645).

Management of Recurrent Disease

Recurrent LGSC can be treated with surgery, chemotherapy, hormone therapy, and targeted therapies, including MEK inhibitors. Although GOG 213 did not demonstrate improvement in OS in patients with platinum-sensitive recurrent ovarian cancer who received surgery and chemotherapy versus chemotherapy alone, only 7 (3%) of these patients had LGSC. In a retrospective review of recurrent LGSC, 78% of patients who had secondary cytoreduction had no gross residual disease at the conclusion of surgery, which translated into an improved PFS compared with patients who were left with gross residual disease.[152] Therefore, secondary cytoreductive surgery may be a reasonable approach in this histology.

Similar to the neoadjuvant setting, LGSC is also chemoresistant in the recurrent setting, with a response rate of less than 4%; however, 60% of patients did have stable disease in one study.[149] Numerous hormonal agents have been used in the treatment of recurrent LGSC, with response rates that are only slightly improved compared with chemotherapy. Retrospective series have shown an ORR of 9%; however, similar to chemotherapy, 62% of patients achieved stable disease.[149] In addition, hormonal treatments are usually more tolerable to patients, likely leading to improved quality of life.

Alternatives to chemotherapy and hormonal therapy are under investigation. Given the frequency of *KRAS* and *BRAF* mutations in this histologic subtype, a single-arm phase 2 trial of selumetinib, a MEK 1/2 inhibitor, was performed in recurrent LGSC. The objective response rate was 15%, and 65% of patients had stable disease. Interestingly, there was no correlation between *KRAS* and *BRAF* mutational status and response to the study drug. A different MEK inhibitor, binimetinib (MEK162) was evaluated and compared with physician's choice of liposomal doxorubicin, paclitaxel, or topotecan in the MILO study in women with recurrent or persistent LGSC (NCT01849874). Unfortunately, in the interim analysis, the PFS hazard

ratio crossed the predefined futility boundary, and the study was closed early. More promising results have been reported for a recent phase 2/3 clinical trial (NRG-GOG 0281), which compared treatment using the MEK inhibitor trametinib to the physician's choice of standard-of-care treatment for women with recurrent or progressive LGSC. Results indicated improved PFS (13.0 vs 7.2 months), ORR (26.2 vs 6.2%), and response duration (13.6 vs 5.88 months) favoring trametinib. As of this writing, the results of this trial are not yet published, but they were presented at the European Society for Medical Oncology Congress in September of 2019. This could represent a new standard-of-care treatment option for women with recurrent LGSC.

Future directions will likely continue to steer away from standard cytotoxic chemotherapy regimens and trend toward combination targeted and hormonal therapies. Strategies under development include PARP inhibitors combined with MEK inhibitors as well as cyclin-dependent kinase 4/6 inhibitors with hormonal therapies. For example, GOG 3026 (NCT03673124) is evaluating response to treatment with ribociclib and letrozole in patients with recurrent or progressive LGSC and is currently recruiting.

MALIGNANT GERM CELL TUMORS

Malignant ovarian germ cell tumors (MOGCTs) recapitulate normal embryonic and extraembryonic cells and structures and are derived from the primitive germ cells of the embryonic gonad. The MOGCTs comprise 2% to 3% of all ovarian malignancies, and they usually develop in girls, adolescents, and women of reproductive age. Advances in chemotherapy have yielded cure in the vast majority of patients with these tumors, and modifications in surgical technique have allowed fertility preservation in most patients.[153] These tumors should always be considered in the differential diagnosis in a young woman with a solid ovarian mass, as the median age of diagnosis is 16 to 20 years (range 6–60), and the highest incidence occurs in 15- to 19-year-old girls.

The current classification of ovarian germ cell tumors includes both benign and malignant neoplasms. Most benign ovarian germ cell tumors are mature teratomas. MOGCTs include primitive germ cell tumors, biphasic or triphasic teratomas, and monodermal teratomas (Table 39–5). Immature teratomas should be extensively sampled to determine the amount of immature neural, nonneural, and yolk sac elements and thereby malignant potential. Although we continue to report grading criteria for immature teratomas using a three-tier system, we agree that a biphasic system may allow for greater consistency.

Table 39–5 World Health Organization Classification of Ovarian Germ Cell Tumors

Primitive Germ Cell Tumors	Biphasic or Triphasic Teratoma	Monodermal Teratoma and Somatic-Type Tumors
Dysgerminoma	Immature teratoma (grades 1–3)	Thyroid (struma ovarii)
Endodermal sinus tumor (yolk sac tumor)	Mature teratoma (solid, cystic, or fetiform teratoma)	Carcinoid
Embryonal carcinoma		Neuroectodermal
Polyembryona		Carcinoma
Nongestational choriocarcinoma		Melanocytic
Mixed germ cell tumor		Sarcoma
		Sebaceous
		Pituitary type
		Other

Adapted with permission from Tavassoli FA, Deville P: *World Health Organization Classification of Tumors. Pathology and Genetics of Tumors of the Breast and Female Genital Organs*. Lyon, France: International Agency for Research on Cancer Press; 2003.

Etiology

The etiology of MOGCT is related to gonadal dysgenesis in a minority of patients. Patients with a mosaic variant of Turner syndrome including a Y chromosome may develop gonadoblastoma.[154] Patients with complete gonadal dysgenesis who have a 46, XY genotype and a female phenotype (Swyer syndrome) have up to a 30% risk of developing MOGCT, especially dysgerminomas, and prophylactic removal of both gonads is indicated if the diagnosis is made.[155]

Diagnosis

The diagnosis of MOGCT may be suspected based on the young age of the patient with a solid, palpable ovarian mass, but histologic confirmation is required for the diagnosis. Eighty-five percent of patients present with abdominopelvic pain associated with a palpable mass. Other presenting symptoms and signs include abdominal distention, fever, ascites, and vaginal bleeding. Ten percent of patients present with acute abdominal pain associated with rupture, hemorrhage, or torsion of the mass. Isosexual pseudoprecocity may be caused by β-chorionic gonadotrophin production by the tumor.[156] Evaluation of the pelvic mass in the young patient may be aided by transvaginal ultrasound and magnetic resonance imaging. Supradiaphragmatic disease or pure choriocarcinoma is an indication for magnetic resonance imaging of the brain.[156]

Tumor markers may be especially helpful in MOGCT to suggest individual tumor histology, provide prognostic information, and provide a basis to

Table 39–6 Tumors Markers Helpful in MOGCT

Tumor	AFP	β-HCG	Lactic Dehydrogenase
Pure dysgerminoma	Normal	May be elevated	Elevated
Endodermal sinus tumor	Elevated	Normal	May be elevated
Embryonal carcinoma	Elevated	Elevated	Elevated
Choriocarcinoma	Normal	Elevated	Normal
Immature teratoma	May be elevated	Normal	Normal

follow the response of the disease to therapy (Table 39–6). When MOGCT is suspected, these markers should be measured preoperatively. A karyotype should be performed if gonadal dysgenesis is suspected, because bilateral oophorectomy is indicated if the diagnosis is confirmed. The appropriate minimum diagnostic evaluation for the young woman with a suspicious adnexal mass should include routine blood studies, serum tumor marker analysis, chest radiography, and imaging of the abdomen and pelvis.[156]

Management

Surgery is the mainstay of diagnosis and initial treatment of MOGCT. Laparotomy has been the standard of care, but minimally invasive surgery appears to be feasible when the tumor can be removed intact and complete staging can be performed.[157] Patients who have completed childbearing should undergo total hysterectomy and bilateral salpingo-oophorectomy. However, most patients with MOGCT are of reproductive age, and because outcomes with conservative surgery are comparable to that of hysterectomy with bilateral salpingo-oophorectomy, fertility-sparing surgery should be considered in every patient of reproductive age. Whenever possible, the normal-appearing contralateral adnexa and uterus should be conserved. If both ovaries are grossly involved, bilateral salpingo-oophorectomy may be warranted, but this is the exception rather than the rule. Some discussion has centered on ovarian preservation with postoperative chemotherapy to treat this chemosensitive residual disease, thus allowing fertility preservation even with advanced disease or bilateral ovarian involvement. Even if both ovaries are removed, the uterus may be preserved to allow assisted reproduction with a donor egg.

Several treatment conundrums are encountered not infrequently. If a MOGCT is diagnosed postoperatively after an ovarian cystectomy for disease thought to be benign, subsequent removal of the remaining ovarian tissue may be avoided. Excellent survival has been reported in this setting, although most patients did receive adjuvant chemotherapy.[158] In addition, occasionally patients might present with widespread bulky abdominopelvic disease, and aggressive debulking surgery is followed by rapid tumor regrowth. Although not yet considered standard, neoadjuvant chemotherapy after percutaneous biopsy has been increasingly used to allow for less morbid, more effective fertility-sparing interval cytoreductive surgery.[159]

Staging for MOGCT follows FIGO staging for EOC (see Table 39–4). However, the extent of comprehensive surgical staging is controversial. Comprehensive surgical staging has traditionally been performed in adult patients, including peritoneal cytology, biopsies, omentectomy, bilateral pelvic and para-aortic lymphadenectomy, and removal of any suspicious tissue. In the pediatric setting, staging is typically limited to pelvic washing, tumor removal, and biopsy of suspicious implants. Although proponents of limited staging cite the exquisite sensitivity of MOGCT to chemotherapy, there may be some benefit to complete surgical staging. At our institution, we have performed comprehensive staging to either support the administration of chemotherapy up front in patients with nodal involvement or avoid chemotherapy in fully staged patients without metastatic disease. Regardless, patients with nondysgerminomatous MOGCT should receive chemotherapy unless they have stage 1A disease after comprehensive surgical staging. Surveillance in low-risk patients has been proposed, and studies are ongoing.

Adjuvant Therapy

Although patients with stage I dysgerminoma and stage IA grade 1 immature teratoma may be safely observed after surgery without chemotherapy, combination chemotherapy with three to four courses of bleomycin, etoposide, and cisplatin (BEP) results in the cure of most other patients with MOGCT (Table 39–7). Patients with completely resected disease usually receive three cycles of BEP, although patients with macroscopic residual disease receive four cycles, sometimes omitting bleomycin from cycle 4. Care should be taken to evaluate for bleomycin-related pulmonary toxicity, with periodic lung auscultation, chest radiography, and pulmonary function testing if the patient

Table 39–7 Regimen for Administration of Bleomycin, Etoposide, and Cisplatin (BEP)

After prehydration and premedications:
Cisplatin: 20 mg/m^2 per day in 1 L normal saline with 50 g mannitol IV over 4 hours on days 1–5
Etoposide: 100 mg/m^2 per day in 1 L 5% dextrose in normal saline IV over 2 hours on days 1–5
Bleomycin: 20 U/m^2 in 250 mL normal saline over 24 hours on day 1
OR
Bleomycin: 10 U/d on days 1–3
OR
Bleomycin: 10 U/d on days 1, 8, and 15 (United States)
OR
Bleomycin: 30,000 IU weekly for 12 weeks, with the fourth course consisting of EP alone (Europe/United Kingdom)[a]

[a]Maximum total bleomycin dose not to exceed 270 mg. Regimen repeated every 21 days.

experiences symptoms. Rales, pulmonary consolidation, or a 30% decrease in the diffusion capacity of carbon monoxide prompts deletion of bleomycin from the regimen.[153] Radiation therapy is effective in the treatment of dysgerminoma but is rarely used because of the impact on ovarian function and subsequent fertility.

Although most patients are cured, worse outcomes are related to advanced stage, yolk sac (endodermal sinus) tumor histology, incomplete surgical resection, and advanced age.[160] Patients with high-risk disease or who do not respond to BEP rapidly may be considered for alternate therapies, including paclitaxel combined with BEP (T-BEP) or dose-dense BEP.[153]

Follow-Up

After treatment, patients receive imaging of the chest, abdomen, and pelvis and evaluation of tumor markers. Subsequently, they are monitored every 3 months for the first year, every 4 months for the second year, and every 6 months for years 3 to 5. We do not obtain routine imaging, although in high-risk patients, transvaginal ultrasound may follow and initial abdominopelvic imaging may be obtained.

Treatment of Recurrent Disease

In the small percentage of patients who are thought to have a recurrence, evaluation must include repeat imaging of the chest, abdomen, and pelvis and evaluation of tumor markers, and a biopsy must confirm the diagnosis of recurrent disease because immature teratomas can recur with only mature benign elements (growing teratoma syndrome) or with benign gliosis. Both of these entities are benign and do not automatically require chemotherapy or surgical resection. In the event of true recurrence, surgical resection should be considered, and appropriate salvage chemotherapy should be considered. More than half of patients who have a recurrence after 6 weeks after initial therapy (platinum-sensitive) can achieve cure with VeIP (vinblastine, ifosfamide, and cisplatin) or TIP (paclitaxel, ifosfamide, and cisplatin); high-dose chemotherapy may also be administered.[153] Patients whose disease progresses during treatment or who have a recurrence within 4 to 6 weeks (platinum-resistant) are not curable; standard-dose VeIP may be administered, and in the event of response, high-dose etoposide and carboplatin with stem cell rescue may be given.[153] Other agents with activity include ifosfamide, taxanes, and gemcitabine.

Reproductive Outcomes

Reproductive outcomes after surgical or chemotherapeutic treatment for MOGCT are excellent, with little effect on menstrual cycling, reproductive function, conception, or childbirth. Chemotherapy-induced infertility appears to occur in 18% or less of patients treated with BEP and is unrelated to cisplatin dose. Eighty percent of women resume normal menstrual function. Long-term quality of life and psychosocial outcomes of survivors of MOGCT are also excellent.

SEX CORD STROMAL TUMORS

Sex cord stromal tumors (SCSTs) of the ovary comprise 7% of all ovarian malignancies and have an annual incidence rate of 0.20 per 100,000 women.[161] These tumors can occur in females of all ages, but most occur in peri- and postmenopausal women. Some histologic subtypes, such as juvenile granulosa cell tumors (GCTs) and Sertoli-Leydig cell tumors (SLCTs) have a propensity to develop in adolescents; all histologic subtypes may develop in women of reproductive age. Overall, many of these tumors tend to be indolent, progressing slowly over decades.

Sex cord stromal tumors are a heterogeneous group of tumors classified in Table 39–8.[162] The GCTs are the most common (90% of all malignant ovarian SCSTs) and consist of adult (95% of cases) and juvenile (5% of cases) forms, which differ in their histologic appearance, age of onset, and natural history. Juvenile GCTs usually affect adolescent females, may present with precocious puberty, may be associated with breast cancer, and have high mitotic activity. Adult GCTs tend to occur in older women, produce estrogen, may be associated with endometrial hyperplasia or cancer, and are often quite indolent.[162] SLCTs arise from mesenchyme and sex cords, which

Table 39–8 Classification of Ovarian Sex Cord Stromal Tumors

Ovarian Stromal Tumors with Sex Cord Elements
Adult granulosa cell tumor Juvenile granulosa cell tumor Sertoli-Leydig cell tumor Gynandroblastoma Sex cord tumor with annular tubules
Pure Stromal Tumors
Fibroma and thecomas: typical, cellular, mitotically active malignant tumors (fibrosarcoma)
Other Ovarian Stromal Tumors
Ovarian stromal tumor with minor sex cord elements Sclerosing stromal tumor Signet ring stromal tumor Microcystic stromal tumor Ovarian myxoma Stromal-Leydig cell tumor
Steroid Cell Tumors
Stromal luteoma Leydig cell tumor Steroid cell tumor, not otherwise specified

recapitulate testicular development and may include various proportions of Sertoli and Leydig elements. Pure Sertoli cell tumors and pure Leydig cell tumors are benign, although tumors with Sertoli and Leydig cell components demonstrate degrees of malignant behavior and are classified based on differentiation. The benign differentiated form typically produces androgens; intermediate differentiated forms have immature Sertoli cells; and poorly differentiated forms with sarcomatoid or retiform patterns tend to be more aggressive. Gynandroblastomas are rare, tend to be virilizing, and are usually benign, but large tumors occurring in women aged 30 to 50 years may exhibit malignant behavior. A sex cord tumor with annular tubules (SCTAT) may be associated with Peutz-Jeghers syndrome.

Etiology

The etiology for all SCSTs is unknown. However, a somatic cytosine-to-guanine point mutation in the *FOXL2 403* gene has been identified as pathognomonic for adult GCT formation (but not juvenile GCT).[163] In addition, mutations in *DICER1* appear to be present in some patients with SLCTs and in patients with pleuropulmonary blastoma; children with SLCTs may be screened for *DICER1* mutations and thereby undergo early treatment for pleuropulmonary blastoma, a potentially lifesaving intervention.[164] The SCTATs may be associated with Peutz-Jeghers syndrome and potentially linked to *STK11* mutations in these patients.

Diagnosis

Most patients with SCSTs present with pelvic pain, pelvic pressure, and menstrual irregularities, including precocious puberty, menometrorrhagia, or postmenopausal bleeding.[162] Although these tumors cannot be diagnosed without histologic confirmation of surgical findings, preoperative studies such as pelvic ultrasonography and analysis of certain tumor markers may suggest the diagnosis of SCST. When suspected, preoperative CT of the abdomen and pelvis is warranted. Preoperative laboratory testing should include analysis for serum human chorionic gonadotrophin and routine laboratory testing.

Serum markers may be useful in the preoperative diagnosis of SCST when suspected or in establishing a baseline level with which to follow the tumor status of the patient during treatment and surveillance. Inhibin A, inhibin B, and anti-Müllerian hormone (AMH) are useful markers, and AMH may be highly specific for GCT in postmenopausal women or women whose ovaries have been removed.

Management

Surgery remains the cornerstone of diagnosis and treatment for patients with SCSTs. Although surgery has historically been performed via laparotomy, minimally invasive surgery appears to be safe and feasible for initial limited surgery and staging as well as restaging in many patients with SCSTs, as long as the tumor can be removed intact without contamination of the peritoneal cavity, using a specimen bag for removal.[162] Staging procedures include examination of the entire abdominopelvic cavity; peritoneal washings; infracolic omentectomy; and biopsy of any suspicious lesions of the diaphragmatic peritoneum, paracolic gutters, and pelvic peritoneum. Lymphadenectomy can be omitted in the absence of suspicious lymph nodes given that lymph node metastases are quite uncommon in this histology.[162,165] Although postmenopausal women and women who have completed childbearing should undergo total hysterectomy and bilateral salpingo-oophorectomy, young women and women of reproductive age who have not completed childbearing may undergo conservative surgery to preserve fertility regardless of stage. This is demonstrated by a multiinstitutional study from the United States[166] and a recent population-based study from Sweden where the 5-year OS for patients undergoing fertility-sparing surgery was 100% with a PFS of 98%.[167] In patients with adult GCTs, retrospective studies[168,169] have demonstrated that fertility-sparing surgery does not appreciably affect

survival outcomes, with the notable exception of FIGO stage IC. It is important to note that fertility-sparing surgery refers to removal of the entire involved adnexa as well as surgical staging. There is no role for ovarian cystectomy in definitive surgical treatment.[170] Evaluation of the endometrium should be a part of any surgery for SCSTs because 55% of patients with GCTs have endometrial hyperplasia and 4% to 20% have endometrial adenocarcinoma.[170] The FIGO staging for SCST is the same as that for EOCs (see Table 39–4).[162]

Adjuvant Therapy

Patients with stage IA and IB SCSTs do not require adjuvant therapy after surgery. Therapy for patients with stage IC disease is controversial and may include chemotherapy or hormonal therapy for patients with a high mitotic index. Patients with stage I SLCTs who have poorly differentiated tumors or heterologous elements should be treated with adjuvant chemotherapy. Any patient with advanced-stage (II or above) SCSTs should receive treatment with chemotherapy.[162] The type of chemotherapy administered has historically been 3 to 4 cycles of BEP, but retrospective reports suggest that taxanes, especially when administered with platinum-based chemotherapy, have efficacy and less toxicity than BEP.[170,172] The GOG is currently comparing these two regimens in advanced-stage upfront, and recurrent chemo-naïve SCST patients.

Follow-Up

Most patients with SCST are cured, but 20% have a recurrence; these patients may succumb to their disease.[162] Tumor stage, tumor rupture, age over 50 years, and tumor size are reported prognostic factors.[173] The SCSTs tend to have an indolent nature with a propensity for late recurrence. Therefore, patients require long-term surveillance. Our strategy is to follow patients every 3 months for the first year, every 4 months for the second year, every 6 months for years 3 to 5, and then annually. At each visit, history, physical examination including pelvic examination, and tumor marker values (inhibin A, inhibin B, AMH, and sometimes CA 125) are obtained; imaging is reserved for patients with new symptoms, signs, or elevated marker values.

Treatment of Recurrent Disease

Patients who have a recurrence require a biopsy to confirm the initial recurrence. These patients may benefit from surgical resection in the event of limited resectable recurrent disease. Radiotherapy may also be an option. Treatment with hormonal agents may induce response or long-term stable disease. Chemotherapy using BEP or taxane-platinum combinations may be useful. Most recently, bevacizumab has been shown to be an active agent in the recurrent setting.[174]

MD ANDERSON PRACTICE TIPS

- The current approach at MDACC for patients with suspected advanced ovarian cancer who are medically fit for surgery and are without distant metastatic disease is to undergo a preoperative laparoscopic assessment to assess the likelihood of complete resection (modified Fagotti score). Our laparoscopic triage is accomplished by scoring made by two independent and blinded surgeons. Patients scoring less than 10 undergo primary cytoreduction. Those with scores of 10 or more undergo neoadjuvant chemotherapy followed by consideration of interval cytoreductive surgery and three additional cycles of chemotherapy.
- Based on the results of four of five phase 3 randomized controlled trials, we do not currently feel there is sufficient evidence to support the standard use of weekly paclitaxel in the adjuvant setting and are not incorporating this into our practice.
- In patients with newly diagnosed advanced ovarian cancer and poor prognosis, we recommend considering the addition of bevacizumab to standard chemotherapy.
- We follow patients with CA 125 levels in surveillance but in general do not treat patients based solely on a rising value.
- Identifying women at risk for development of ovarian cancer from a heritable cause is currently the only successful method for ovarian cancer prevention. We recommend genetic testing for patients with a history of ovarian cancer, not only to determine their risk for developing concurrent malignancies and identify treatment options, but also to identify family members who may be at risk and could benefit from preventive measures
- Low-grade serous carcinoma is relatively chemoresistant when compared with high-grade serous carcinoma. Despite this, carboplatin and paclitaxel remain first-line adjuvant therapy in advanced disease. However, hormonal therapies and targeted therapies have had promising results in the adjuvant and maintenance settings.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70:7-30.
2. National Cancer Institute; Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Ovarian Cancer, 2020. Accessed March 9, 2020. https://seer.cancer.gov/statfacts/html/ovary.html
3. Peres LC, Sinha S, Townsend MK, et al. Predictors of survival trajectories among women with epithelial ovarian cancer. *Gynecol Oncol.* 2020;156(2):459-466.
4. Stanzel AE, Buas MF, Moysich KB. Survival disparities among racial/ethnic groups of women with ovarian cancer: an update on data from the Surveillance, Epidemiology and End Results (SEER) registry. *Cancer Epidemiol*. 2019;62:101580.
5. Bristow RE, Powell MA, Al-Hammandi N, et al. Disparities in ovarian cancer care quality and survival according to race and socioeconomic status. *J Natl Cancer Inst.* 2013;105:823-832.
6. Howell EA, Egorova N, Wisnivesky J, et al. Racial disparities in the treatment of advanced epithelial ovarian cancer. *Obstet Gynecol.* 2013;122(5):1025-1032.
7. Rauh-Hain JA, Melamed A, Schaps, D et al. Racial and ethnic disparities over time in the treatment and mortality of women with gynecological malignancies. *Gynecol Oncol.* 2018;149:4-11.
8. Crum CP. Intercepting pelvic cancer in the distal fallopian tube: theories and realities. *Mol Oncol.* 2009;3(2):165-170.
9. Auersperg N. The origin of ovarian cancers--hypotheses and controversies. *Front Biosci (Schol Ed).* 2013;5:709.
10. Wong AS, Auersperg N. Ovarian surface epithelium: family history and early events in ovarian cancer. *Reprod Biol Endocrinol.* 2003;1:70.
11. Jarboe E, Folkins A, Nucci MR, et al. Serous carcinogenesis in the fallopian tube: a descriptive classification. *Int J Gynecol Pathol.* 2008;27:1-9.
12. Carlson JW, Jarboe EA, Kindelberger D, et al. Serous tubal intraepithelial carcinoma: diagnostic reproducibility and its implications. *Int J Gynecol Pathol.* 2010;29:310-314.
13. Lee Y, Miron A, Drapkin R, et al. A candidate precursor to serous carcinoma that.
14. Hirst JE, Gard GB, McIllroy K, et al. High rates of occult fallopian tube cancer diagnosed at prophylactic bilateral salpingo-oophorectomy. *Int J Gynecol Cancer.* 19:826-829.
15. Domchek S, Friebel T, Garber J, et al. Occult ovarian cancers identified at risk-reducing salpingo-oophorectomy in a prospective cohort of BRCA1/2 mutation carriers. *Breast Cancer Res Treat.* 2010;124:195-203.
16. Yates MS, Meyer LA, Deavers MT, et al. Microscopic and early-stage ovarian cancers in BRCA1/2 mutation carriers: building a model for early BRCA-associated tumorigenesis. *Cancer Prev Res (Phila)*. 2011;4(3):463-470.
17. Piedimonte S, Cairina F, Laprise C, et al. Occult tubal carcinoma after risk-reducing salpingo-oophorectomy: a systematic review. *Obstet Gynecol.* 2020;135(3):498-508.
18. Soong TR, Howitt BE, Horowitz N, et al. The fallopian tube, "precursor escape" and narrowing the knowledge gap to the origins of high-grade serous carcinoma. *Gynecol Oncol.* 2019;152(2):426.
19. Savalanien L, Lassus H, But A, et al. Risk of gynecologic cancer according to the type of endometriosis. *Obstet Gynecol.* 2018;131(6):1095.
20. Grandi G, Toss A, Cortesi L, et al. The association between endometriomas and ovarian cancer: preventive effect of inhibiting ovulation and menstruation during reproductive life. *Biomed Res Int.* 2015:751-571.
21. Van Gorp T, Amant F, Never P, et al. Endometriosis and the development of malignant tumours of the pelvis. A review of literature. *Best Pract Res Clin Obstet Gynaecol.* 2004;18(2):349.
22. Ledermann JA, Luvero D, Shafer A, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for mucinous ovarian carcinoma. *Int J Gynecol Cancer.* 2014;24(9 suppl 3):S14-S19.
23. Cheasley D, Wakefield MJ, Ryland GL, et al. The molecular origin and taxonomy of mucinous ovarian carcinoma. *Nat Commun.* 2019;10(1):3935.
24. Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. *JAMA.* 2017;317(23):2402.
25. Norquist BM, Harrell MI, Brady MF, et al. Inherited mutations in women with ovarian carcinoma. *JAMA Oncol.* 2016;2(4):482-490.
26. Barriw E, Robinson L, Alduaij W, et al. Cumulative lifetime incidence of extracolonic cancers in Lynch syndrome: a report of 121 families with proven mutations. *Clin Genet.* 2009;75(2):141.
27. Dowty JG, Win AK, Buchanan DD, Cancer risks for MLH1 and MSH2 mutation carriers. *Hum Mutat.* 2013;34(3):490.
28. Bonadona V, Bonaïti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *JAMA.* 2011;305:2304-2310.
29. Møller P, Seppälä TT, Bernstein I, et al. Cancer risk and survival in *path_MMR* carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. *Gut.* 2018;67:1306-1316.
30. Engel C, Loeffler M, Steinke V, et al. Risks of less common cancers in proven mutation carriers with lynch syndrome. *J Clin Oncol.* 2012;30:4409-4415.
31. Gates MA, Rosner BA, Hecht JL, et al. Risk factors for epithelial ovarian cancer by histologic subtype. *Am J Epidemiol.* 2010;171:45-53.
32. Tsilidis KK, Allen NE, Key TJ, et al. Oral contraceptive use and reproductive factors and risk of ovarian cancer in the European Prospective Investigation into Cancer and Nutrition. *Br J Cancer.* 2011;105:1436-1442.
33. Olsen CM, Green AC, Whiteman DC, et al. Obesity and the risk of epithelial ovarian cancer: a systematic review and meta-analysis. *Eur J Cancer.* 2007;43:690-709.
34. Collaborative Group on Epidemiological Studies of Ovarian C. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. *Lancet*. 2008;371:303-314.
35. Menon U, Griffin M, Gentry-Maharaj A. Ovarian cancer screening—current status, future directions. *Gynecol Oncol*. 2014;132:490-495.
36. Skates SJ, Xu FJ, Yu YH, et al. Toward an optimal algorithm for ovarian cancer screening with longitudinal tumor markers. *Cancer*. 76:2004-2010.
37. Buys SS, Partridge E, Black A, et al. Effect of screening on ovarian cancer mortality: the prostate, lung, colorectal and ovarian (plco) cancer screening randomized controlled trial. *JAMA*. 2011;305:2295-2303.
38. Kobayashi H, Yamada Y, Sado T, et al. A randomized study of screening for ovarian cancer: a multicenter study in Japan. *Int J Gynecol Cancer*. 2008;18:414-420.
39. Van Nagell JR Jr, Miller RW, Desimone CP, et al. Long-term survival of women with epithelial ovarian cancer detected by ultrasonographic screening. *Obstet Gynecol*. 2011;118:1212-1221.
40. Jacobs IJ, Menon U, Ryan A, et al. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. *Lancet.* 2016;387(10022):945-956.
41. Cope L, Wu R-C, Shih I-M, et al. High level of chromosomal aberration in ovarian cancer genome correlates with poor clinical outcome. *Gynecol Oncol*. 2013;128:500-505.
42. Wong K-K, Tsang YTM, Deavers MT, et al. BRAF mutation is rare in advanced-stage low-grade ovarian serous carcinomas. *Am J Pathol*. 2010;177:1611-1617.

43. Kuo K-T, Mao T-L, Jones S, et al. Frequent activating mutations of PIK3CA in ovarian clear cell carcinoma. *Am J Pathol*. 2009;174:1597-1601.
44. Jones S, Wang T-L, Shih I-M, et al. Frequent mutations of chromatin remodeling gene ARID1A in ovarian clear cell carcinoma. *Science*. 2010;330:228-231.
45. Catasús L, Bussaglia E, Rodríguez I, et al. Molecular genetic alterations in endometrioid carcinomas of the ovary: similar frequency of beta-catenin abnormalities but lower rate of microsatellite instability and PTEN alterations than in uterine endometrioid carcinomas. *Hum Pathol*. 2004;35:1360-1368.
46. Coward J, Kulbe H, Chakravarty P, et al. Interleukin-6 as a therapeutic target in human ovarian cancer. *Clin Cancer Res*. 2011;17:6083-6096.
47. Stone RL, Nick AM, McNeish IA, et al. Paraneoplastic thrombocytosis in ovarian cancer. *N Engl J Med*. 2012;366:610-618.
48. Anglesio MS, George J, Kulbe H, et al. IL6-STAT3-HIF signaling and therapeutic response to the angiogenesis inhibitor sunitinib in ovarian clear cell cancer. *Clin Cancer Res*. 2011;17:2538-2548.
49. Smith NR, Baker D, James NH, et al. Vascular endothelial growth factor receptors VEGFR-2 and VEGFR-3 are localized primarily to the vasculature in human primary solid cancers. *Clin Cancer Res*. 2010;16:3548-3561.
50. Bast RCJ, Badgwell D, Lu Z, et al. New tumor markers: CA125 and beyond. *Int J Gynecol Cancer*. 2005;15:274-281.
51. Steffensen KD, Waldstrøm M, Brandslund I, et al. Prognostic impact of prechemotherapy serum levels of HER2, CA125, and HE4 in ovarian cancer patients. *Int J Gynecol Cancer*. 2011;21:1040-1047.
52. Gadducci A, Cosio S, Tana R, et al. Serum and tissue biomarkers as predictive and prognostic variables in epithelial ovarian cancer. *Crit Rev Oncol Hematol*. 2009;69:12-27.
53. Chang S-J, Bristow RE. Evolution of surgical treatment paradigms for advanced-stage ovarian cancer: redefining "optimal" residual disease. *Gynecol Oncol*. 2012;125:483-492.
54. Bodurka DC, Deavers MT, Tian C, et al. Reclassification of serous ovarian carcinoma by a 2-tier system. *Cancer*. 2012;118:3087-3094.
55. Malpica A, Deavers MT, Lu K, et al. Grading ovarian serous carcinoma using a two-tier system. *Am J Surg Pathol*. 2004;28(4):496-504.
56. Gourley C, Farley J, Provencher DM, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for ovarian and primary peritoneal low-grade serous carcinomas. *Int J Gynecol Cancer*. 2014;24:S9-S13.
57. Gershenson DM, Sun CC, Lu KH, et al. Clinical behavior of stage II-IV low-grade serous carcinoma of the ovary. *Obstet Gynecol*. 2006;108:361-368.
58. Leen SLS, Singh N. Pathology of primary and metastatic mucinous ovarian neoplasms. *J Clin Pathol*. 2012;65:591-595.
59. Rouzbahman M, Chetty R. Mucinous tumours of appendix and ovary: an overview and evaluation of current practice. *J Clin Pathol*. 2014;67:193-197.
60. Soliman PT, Slomovitz BM, Broaddus RR, et al. Synchronous primary cancers of the endometrium and ovary: a single institution review of 84 cases. *Gynecol Oncol*. 2004;94:456-462.
61. Rauh-Hain JA, Winograd D, Growdon WB, et al. Prognostic determinants in patients with uterine and ovarian clear carcinoma. *Gynecol Oncol*. 2012;125:376-380.
62. Ali RH, Seidman JD, Luk M, Kalloger S, Gilks CB. Transitional cell carcinoma of the ovary is related to high-grade serous carcinoma and is distinct from malignant brenner tumor. *Int J Gynecol Pathol*. 2012;31:499-506.
63. Shih I-M, Kurman RJ. Ovarian tumorigenesis: a proposed model based on morphological and molecular genetic analysis. *Am J Pathol*. 2004;164:1511-1518.
64. Malpica A, Deavers MT, Tornos C, et al. Interobserver and intraobserver variability of a two-tier system for grading ovarian serous carcinoma. *Am J Surg Pathol*. 2007;31:1168-1174.
65. Young RC, Decker DG, Wharton J, et al. Staging laparotomy in early ovarian cancer. *JAMA*. 1983;250:3072-3076.
66. Fagotti A, Ferrandina G, Fanfani F, et al. A laparoscopy-based score to predict surgical outcome in patients with advanced ovarian carcinoma: a pilot study. *Ann Surg Oncol*. 2006;13:1156-1161.
67. Nick AM, Coleman RL, Ramirez PT, et al. A framework for a personalized surgical approach to ovarian cancer. *Nat Rev Clin Oncol*. 2015;12(4):239-245.
68. Vergote I, Tropé CG, Amant F, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N Engl J Med*. 2010;363(10): 943-953.
69. Kehoe S, Hook J, Nankivell, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomized, controlled, non-inferiority trial. *Lancet*. 2015;386:249-257.
70. Fagotti A, Ferrandina MG, Vizzielli G, Pasciuto T, Fanfani F, et al. Randomized trial of primary debulking surgery versus neoadjuvant chemotherapy for advanced epithelial ovarian cancer (SCORPION-NCT01461850). Int J Gynecol Cancer. 2020; 30(11):1657-1664.
71. Trimbos B, Timmers P, Pecorelli S, et al. Surgical staging and treatment of early ovarian cancer: long-term analysis from a randomized trial. *J Natl Cancer Inst*. 2010;102:982-987.
72. Winter-Roach BA, Kitchener H, Lawrie TA. Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer. *Cochrane Database Syst Rev*. 2012:CD004706.
73. Elit L, Chambers A, Fyles A, et al. Systematic review of adjuvant care for women with stage I ovarian carcinoma. *Cancer*. 2004;101(9):1926.
74. Adams G, Zekri J, Wong H, et al. Platinum-based adjuvant chemotherapy for early-stage epithelial ovarian cancer: single or combination chemotherapy? *BJOG*. 2010;117(12):1459.
75. Bell J, Brady MF, Young RC, et al. Randomized phase III trial of three versus six cycles of adjuvant carboplatin and paclitaxel in early stage epithelial ovarian carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2006;102:432-439.
76. Chan JK, Tian Chunqiao, Fleming GF, et al. The potential benefit of 6 vs. 3 cycles of chemotherapy in subsets of women with early-stage high-risk epithelial ovarian cancer: an exploratory analysis of a Gynecologic Oncology Group study, *Gynecol Oncol*. 2010;116(3):301-306.
77. Tewari KS, Java JJ, Eskander RN, et al. Early initiation of chemotherapy following complete resection of advanced ovarian cancer associated with improved survival: NRG Oncology/Gynecologic Oncology Group study. *Ann Oncol*. 2016;27(1):114.
78. Hofstetter G, Concin N, Braicu I, et al. The time interval from surgery to start of chemotherapy significantly impacts prognosis in patients with advanced serous ovarian carcinoma - analysis of patient data in the prospective OVCAD study. *Gynecol Oncol*. 2013;131(1):15.
79. Timmermans M, van der Aa MA, Lalisang Rim et al. Interval between debulking surgery and adjuvant chemotherapy is associated with overall survival in patients with advanced ovarian cancer. *Gynecol Oncol*. 2018;150(3):446.
80. du Bois A, Lück HJ, Meier W, et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. *J Natl Cancer Inst*. 2003;95(17):1320.
81. Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol*. 2003;21(17):3194.

82. Bookman MA, Brady MF, McGuire WP, et al. Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: a phase III trial of the Gynecologic Cancer InterGroup. *J Clin Oncol*. 2009;27:1419-1425.
83. Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med*. 2011;365:2473-2483.
84. Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med*. 2011;365:2484-2496.
85. Cohn DE, Kim KH, Resnick KE, et al. At what cost does a potential survival advantage of bevacizumab make sense for the primary treatment of ovarian cancer? A cost-effectiveness analysis. *J Clin Oncol*. 2011;29:1247-1251.
86. Ferriss JS, Java JJ, Bookman MA, et al. Ascites predicts treatment benefit of bevacizumab in front-line therapy of advanced epithelial ovarian, fallopian tube and peritoneal cancers: an NRG Oncology/GOG study. *Gynecol Oncol.* 2015;139(1):17.
87. Tewari KS, Burger RA, Enserro D, et al. Final overall survival of a randomized trial of bevacizumab for primary treatment of ovarian cancer. *J Clin Oncol.* 2019;37(26):2317.
88. Oza AM, Cook AD, Pfisterer J, et al. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. *Lancet Oncol.* 2015;16(8):928-936.
89. Ray-Coquard I, Pautier O, Pignata S, et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. *N Engl J Med.* 2019;381:2416-2428.
90. Coleman RL, Fleming GF, Brady MF, et al. Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer. *N Engl J Med.* 2019 Dec 19; 381(25):2403–2415.
91. Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med*. 2006;354:34-43.
92. Alberts DS, Liu PY, Hannigan EV, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *N Engl J Med*. 1996;335:1950-1955.
93. Markman M, Bundy BN, Alberts DS, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. *J Clin Oncol*. 2001;19:1001-1007.
94. Wright AA, Cronin A, Milne DE, et al. Use and effectiveness of intraperitoneal chemotherapy for treatment of ovarian cancer. *J Clin Oncol.* 2015 Sep 10; 33(26):2841–2847.
95. Walker JL, Brady MF, Wenzel L, et al. Randomized trial of intravenous versus intraperitoneal chemotherapy plus bevacizumab in advanced ovarian carcinoma: an NRG Oncology/Gynecologic Oncology Group study. *J Clin Oncol.* 2019;37(16):1380.
96. Vergote I, Harter P, Chiva L. Is there a role for intraperitoneal chemotherapy, including HIPEC, in the management of ovarian cancer? *J Clin Oncol.* 2019;37(27):2420-2423.
97. Van Driel WJ, Koole SN, Sikorska K, et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. *N Engl J Med.* 2018;378(3):230-240.
98. Lim MC, Chang SJ, Yoo HJ, et al. Randomized trial of hyperthermic intraperitoneal chemotherapy (HIPEC) in women with primary advanced peritoneal, ovarian, and tubal cancer. *J Clin Oncol.* 2017;35(suppl);abstract 5520.
99. Marchetti P, Urien S, Capellini GA, et al. Weekly administration of paclitaxel: theoretical and clinical basis. *Crit Rev Oncol Hematol.* 2002;44(suppl):S3-S13.
100. Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. *Lancet*. 2009;374:1331-1338.
101. Katsumata N, Yasuda M, Isonishi S, et al. Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016): a randomised, controlled, open-label trial. *Lancet Oncol*. 2013;14:1020-1026.
102. Chan J, Brady M, Penson R, et al. Phase III trial of every-3-weeks paclitaxel versus dose dense weekly paclitaxel wth carboplatin +/ bevacizumab in epithelial ovarian, peritoneal, fallopian tube cancer. Presented at GOG 262, European Society of Gynecologic Oncology Annual Meeting; October 19-22, 2013; Liverpool, UK.
103. Pignata S, Scambia G, Katsaros D, et al. Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol*. 2014;15:396-405.
104. Clamp AR, James EC, McNeish IA, et al. Weekly dose-dense chemotherapy in first-line epithelial ovarian, fallopian tube, or primary peritoneal carcinoma treatment (ICON8): primary progression free survival analysis results from a GCIG phase 3 randomised controlled trial. *Lancet.* 2019;394(10214):2084-2095.
105. Vasey PA, Jayson GC, Gordon A, et al. Phase III randomized trial of docetaxel–carboplatin versus paclitaxel–carboplatin as first-line chemotherapy for ovarian carcinoma. *J Natl Cancer Inst*. 2004;96:1682-1691.
106. Markman M. Maintenance chemotherapy in the management of epithelial ovarian cancer. *Cancer Metastasis Rev*. 2015;34:11-17.
107. Markman M, Liu PY, Moon J, et al. Impact on survival of 12 versus 3 monthly cycles of paclitaxel (175 mg/m2) administered to patients with advanced ovarian cancer who attained a complete response to primary platinum-paclitaxel: follow-up of a Southwest Oncology Group and Gynecologic Oncology Group phase 3 trial. *Gynecol Oncol*. 2009;114:195-198.
108. Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med.* 2018;379(26):2495-2505.
109. Gonzalez-Martin A, Pothuri B, Vergote I, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med.* 2019;381(25):2391-2402.
110. van der Burg MEL, Lammes FB, Verweij J. The role of CA 125 in the early diagnosis of progressive disease in ovarian cancer. *Ann Oncol*. 1990;1:301-302.
111. Rustin GJS, van der Burg MEL, Griffin CL, et al. Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial. *Lancet*. 2010;376:1155-1163.
112. Friedlander M, Trimble E, Tinker A, et al. Clinical trials in recurrent ovarian cancer. *Int J Gynecol Cancer*. 2011;21:771-775.
113. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. *Lancet*. 2003;361:2099-2106.
114. Wagner U, Marth C, Largillier R, et al. Final overall survival results of phase III GCIG CALYPSO trial of pegylated liposomal doxorubicin and carboplatin vs paclitaxel and carboplatin in platinum-sensitive ovarian cancer patients. *Br J Cancer*. 2012;107:588-591.
115. Pfisterer et al. "Combination therapy with gemcitabine and carboplatin in recurrent ovarian cancer." *Int J Gynecol Cancer*. 2005;15(suppl 1):36-41.
116. Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol*. 2012;30:2039-2045.
117. Coleman RL, Brady MF, Herzog TJ, et al. Bevacizumab and paclitaxel–carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG

Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 2017;18(6):779-791.
118. Pfisterer J, Shannon CM, Baumann K, et al. Bevacizumab and platinum-based combinations for recurrent ovarian cancer: a randomized, open-label, phase 3 trial. *Lancet Oncol.* 2020;21(5):699-709.
119. Armbruster S, Coleman RL, Rauh-Hain JA. Management and treatment of recurrent epithelial ovarian cancer. *Hematol Oncol Clin North Am.* 2018;32(6):965-982.
120. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med*. 2012;366:1382-1392.
121. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. *Lancet Oncol*. 2014;15:852-861.
122. Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2017;18(9):1274-1284.
123. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *N Engl J Med.* 2016;375(22):2154-2164.
124. Swisher EM, Lin KK, Oza AM, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. *Lancet Oncol.* 2017;18(1):75-87.
125. Coleman RL, Oza AM, Lorusso D, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2017;390(10106):1949–1961.
126. Gordon AN, Fleagle JT, Guthrie D, et al. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. *J Clin Oncol*. 2001;19:3312-3322.
127. Mutch DG, Orlando M, Goss T, et al. Randomized phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer. *J Clin Oncol*. 2007;25:2811-2818.
128. Markman M, Blessing J, Rubin SC, et al. Phase II trial of weekly paclitaxel (80 mg/m2) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: a *Gynecologic Oncol*ogy Group study. *Gynecol Oncol*. 2006;101:436-440.
129. Lorusso D, Pietragalla A, Mainenti S, Masciullo V, Di Vagno G, Scambia G. Review role of topotecan in gynaecological cancers: current indications and perspectives. *Crit Rev Oncol Hematol.* 2010;74(3):163-174.
130. Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. *J Clin Oncol*. 2014;32:1302-1308.
131. Monk BJ, Poveda A, Vergote I, et al. Anti-angiopoietin therapy with trebananib for recurrent ovarian cancer (TRINOVA-1): a randomised, multicentre, double-blind, placebo-controlled phase 3 trial. *Lancet Oncol.* 2014;15(8):799-808.
132. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med.* 2012;366(26):2455-2465.
133. Hamanishi J, Mandai M, Ikeda T, et al. Safety and antitumor activity of anti-PD-1 antibody, nivolumab, in patients with platinum-resistant ovarian cancer. *J Clin Oncol.* 2015;33(34):4015-4022.
134. Varga A, Piha-Paul S, Ott PA, et al. Pembrolizumab in patients with programmed death ligand 1-positive advanced ovarian cancer: analysis of KEYNOTE-028. *Gynecol Oncol.* 2019;152(2):243-250.
135. Matulonis UA, Shapira-Frommer R, Santin AD, et al. Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: results from the phase II KEYNOTE-100 study. *Ann Oncol.* 2019;30(7):1080-1087.
136. Disis ML, Taylor MH, Kelly K, et al. Efficacy and safety of avelumab for patients with recurrent or refractory ovarian cancer: phase 1b results from the JAVELIN solid tumor trial. *JAMA Oncol.* 2019;5(3):393-401.
137. Wenham RM, Apte SM, Mian M, et al. Phase II trial of dose dense (weekly) paclitaxel with pembrolizumab (MK-3475) in platinum-resistant recurrent ovarian cancer. *J Clin Oncol.* 2016;34(suppl 15):TPS5612.
138. Pujade-Lauraine E, Fujiwara K, Ledermann JA, et al. Avelumab alone or in combination with pegylated liposomal doxorubicin versus pegylated liposomal doxorubicin alone in platinum-resistant or refractory epithelial ovarian cancer: primary and biomarker analysis of the phase III JAVELIN Ovarian 200 trial. *Gynecol Oncol.* 2019;154(suppl 1):21-22.
139. Lee JM, Cimino-Mathews A, Peer CJ, et al. Safety and clinical activity of the programmed death-ligand 1 inhibitor durvalumab in combination with poly (ADP-Ribose) polymerase inhibitor olaparib or vascular endothelial growth factor receptor 1-3 inhibitor cediranib in women's cancers: a dose-escalation, phase I Study. *J Clin Oncol.* 2017;35(19):2193-2202.
140. Drew Y, de Jonge M, Hong SH, et al. An open-label, phase II basket study of olaparib and durvalumab (MEDIOLA): results in germline BRCA-mutated (gBRCAm) platinum-sensitive relapsed (PSR) ovarian cancer (OC). *Gynecol Oncol.* 2018;149(suppl 1):246-247.
141. Konstantinopoulos PA, Waggoner S, Vidal GA, et al. Single-arm phases 1 and 2 trial of niraparib in combination with pembrolizumab in patients with recurrent platinum-resistant Ovarian carcinoma. *JAMA Oncol.* 2019;5(8):1141-1149.
142. Liu JF, Herold C, Gray KP, et al. Assessment of combined nivolumab and bevacizumab in relapsed ovarian cancer. *JAMA Oncol.* 2019;5(12):1731-1738.
143. Burger R, Sill M, Zamarin D, et al. NRG Oncology phase II randomized trial of nivolumab with or without ipilimumab in patients with persistent or recurrent ovarian cancer. Presented at the 17th Biennial Meeting of the International Gynecologic Cancer Society; September 14-16, 2018; Kyoto, Japan.
144. Coleman RL, Spirtos NM, Enserro D, et al. Secondary surgical cytoreduction for recurrent ovarian cancer. *N Engl J Med.* 2019;381(20):1929-1939.
145. Du Bois A, Sehouli J, Vergot I, et al. Randomized controlled phase III study evaluating the impact of secondary cytoreductive surgery in recurrent ovarian cancer: final analysis of AGO DESKTOP III/ENGOT-ov20. *J Clin Oncol.* 2020;38(suppl 15):abstract 6000.
146. Zang R, Zhu J, Shi T, et al. A randomized phase III trial of secondary cytoreductive surgery in later recurrent ovarian cancer: SOC1/SGOG-OV2. *J Clin Oncol*. 2020;38(supple 15):abstract 6001.
147. Fader AN, Java J, Ueda S, et al. Survival in women with grade 1 serous ovarian carcinoma. *Obstet Gynecol.* 2013;122(2 pt 1):225-232.
148. Schmeler KM, Sun CC, Bodurka DC, et al. Neoadjuvant chemotherapy for low-grade serous carcinoma of the ovary or peritoneum. *Gynecol Oncol*. 2008;108:510-514.
149. Gershenson DM, Sun CC, Bodurka D, et al. Recurrent low-grade serous ovarian carcinoma is relatively chemoresistant. *Gynecol Oncol*. 2009;114:48-52.
150. Fader AN, Bergstrom J, Jernigan A, et al. Primary cytoreductive surgery and adjuvant hormonal monotherapy in women with advanced low-grade serous ovarian carcinoma: Reducing

overtreatment without compromising survival? *Gynecol Oncol.* 2017;147(1):85-91.
151. Gershenson DM, Bodurka DC, Coleman RL, et al. Hormonal maintenance therapy for women with low-grade serous cancer of the ovary or peritoneum. *J Clin Oncol.* 2017;35(10):1103-1111.
152. Crane EK, Sun CC, Ramirez PT, et al. The role of secondary cytoreduction in low-grade serous ovarian cancer or peritoneal cancer. *Gynecol Oncol*. 2015;136:25-29.
153. Brown J, Friedlander M, Backes FJ, et al. Gynecologic Cancer Intergroup (GCIG) consensus review for ovarian germ cell tumors. *Int J Gynecol Cancer*. 2014;24:S48-S54.
154. Brant WO, Rajimwale A, Lovell MA, et al. Gonadoblastoma and Turner syndrome. *J Urol*. 2006;175:1858-1860.
155. Jonson AL, Geller MA, Dickson EL. Gonadal dysgenesis and gynecologic cancer. *Obstet Gynecol*. 2010;116:550-552.
156. Gershenson DM. Management of ovarian germ cell tumors. *J Clin Oncol*. 2007;25:2938-2943.
157. Shim S-H, Kim D-Y, Lee S-W, et al. Laparoscopic management of early-stage malignant nonepithelial ovarian tumors: surgical and survival outcomes. *Int J Gynecol Cancer*. 2013;23:249-255.
158. Beiner ME, Gotlieb WH, Korach Y, et al. Cystectomy for immature teratoma of the ovary. *Gynecol Oncol*. 2004;93:381-384.
159. Nakamura H, Makino K, Kochi M, et al. Evaluation of neoadjuvant therapy in patients with nongerminomatous malignant germ cell tumors. *J Neurosurg Pediatr*. 2011;7:431-438.
160. Solheim O, Kærn J, Tropé CG, et al. Malignant ovarian germ cell tumors: presentation, survival and second cancer in a population based Norwegian cohort (1953–2009). *Gynecol Oncol*. 2013;131:330-335.
161. Quirk JT, Natarajan N. Ovarian cancer incidence in the United States, 1992-1999. *Gynecol Oncol. 2005;97(2):519-523.*
162. Ray-Coquard I, Brown J, Harter P, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for ovarian sex cord stromal tumors. *Int J Gynecol Cancer*. 2014;24:S42-S47.
163. Shah SP, Köbel M, Senz J, et al. Mutation of FOXL2 in granulosa-cell tumors of the ovary. *N Engl J Med*. 2009;360:2719-2729.
164. Schultz KAP, Pacheco MC, Yang J, et al. Ovarian sex cord-stromal tumors, pleuropulmonary blastoma and DICER1 mutations: a report from the International Pleuropulmonary Blastoma Registry. *Gynecol Oncol*. 2011;122:246-250.
165. Brown J, Sood AK, Deavers MT, et al. Patterns of metastasis in sex cord-stromal tumors of the ovary: can routine staging lymphadenectomy be omitted? *Gynecol Oncol*. 2009;113:86-90.
166. Nasioudis D, Frey MK, Chapman-Davis E, Caputo TA, Holcomb K. Fertility-preserving surgery for advanced stage ovarian germ cell tumors. *Gynecol Oncol.* 2017;147(3):493-496.
167. Johansen G, Dahm-Kähler P, Staf C, et al. Fertility-sparing surgery for treatment of non-epithelial ovarian cancer: oncological and reproductive outcomes in a prospective nationwide population-based cohort study. *Gynecol Oncol.* 2019;155(2):287-293.
168. Bergamini A, Cormio G, Ferrandina G, et al. Conservative surgery in stage I adult type granulosa cells tumors of the ovary: results from the MITO-9 study. *Gynecol Oncol.* 2019;154(2):323-327.
169. Wang D, Cao D, Jia C, et al. Analysis of oncologic and reproductive outcomes after fertility-sparing surgery in apparent stage I adult ovarian granulosa cell tumors. *Gynecol Oncol.* 2018;151(2):275.
170. Gershenson DM. Current advances in the management of malignant germ cell and sex cord-stromal tumors of the ovary. *Gynecol Oncol*. 2012;125:515-517.
171. Evans AT 3rd, Gaffney TA, Malkasian GD Jr, Annegers JF. Clinicopathologic review of 118 granulosa and 82 theca cell tumors. *Obstet Gynecol*. 1980;55:231-238.
172. Brown J, Shvartsman HS, Deavers MT, et al. The activity of taxanes in the treatment of sex cord-stromal ovarian tumors. *J Clin Oncol*. 2004;22:3517-3523.
173. Zhang M, Cheung MK, Shin JY, et al. Prognostic factors responsible for survival in sex cord stromal tumors of the ovary—an analysis of 376 women. *Gynecol Oncol*. 2007;104:396-400.
174. Brown J, Brady WE, Schink J, et al. Efficacy and safety of bevacizumab in recurrent sex cord-stromal ovarian tumors: results of a phase 2 trial of the Gynecologic Oncology Group. *Cancer.* 2014;120:344-351.

40 Tumors of the Uterine Corpus

Michaela A. Onstad
Shannon N. Westin
Karen H. Lu

KEY CONCEPTS

- For women with early-stage, intermediate-risk endometrial cancer, there is no evidence that adjuvant therapy improves overall survival. For women with *low-intermediate-risk disease*, observation is favored. For women with *high-intermediate-risk disease*, vaginal cuff brachytherapy is favored.
- Women with high-risk disease have either serous or clear cell adenocarcinoma (any stage) or have pathologic stage III disease with extrauterine involvement. Adjuvant treatment may involve radiation, chemotherapy, or a combination of the two modalities, based on histology, stage, and other factors
- Recurrent or metastatic endometrial cancer is associated with a poor prognosis. Clinical trial GOG 209 supports the use of carboplatin and paclitaxel in this setting.
- Immunotherapy may be considered as second-line treatment for recurrent/metastatic endometrial cancer. Pembrolizumab has a response rate (RR) of 53% for women with mismatch repair–deficient tumors. The combination of pembrolizumab with the tyrosine kinase inhibitor lenvatinib has a RR of 38% among women with microsatellite stable tumors.
- Targeted therapies with demonstrated efficacy in second-line treatment include single-agent bevacizumab (GOG229E), and the combination of the mTOR inhibitor everolimus with letrozole.
- Endocrine therapy may also be used to treat metastatic/recurrent endometrial cancer. It tends to be well tolerated with relatively minor side effects, and has modest RRs, ranging from 11% to 24%. Characteristics that improve the likelihood that a patient will have a favorable response to hormone therapy include having a low tumor grade (1 or 2), endometrioid histology, the presence of estrogen and progesterone receptors, having a longer disease-free interval, and being asymptomatic or minimally symptomatic.

EPITHELIAL UTERINE TUMORS

Epidemiology

Endometrial cancer is the most common gynecologic malignancy, and the fourth most common cancer among women in the United States, affecting 1% to 2% of US women.[1] Approximately 75% of women diagnosed with endometrial cancer are diagnosed at an early stage and have a 5-year overall survival (OS) of 74% to 91%.2 For women with stage III or IV disease, 5-year OS rates are 57% to 66% and 20% to 26%, respectively.[2] This disease primarily affects women in their postmenopausal and perimenopausal years, with an average age at diagnosis of 61 years,[2] although 5% to 30% of women are under the age of 50 years.[3]

Risk Factors

The main risk factors for endometrial cancer are age, obesity, diabetes, and exposure to excess estrogen without adequate opposition by progesterone. This includes the use of exogenous unopposed estrogen therapy, the use of estrogen agonists (such as tamoxifen), and physiologic states that lead to excess endogenous estrogen. Excess endogenous estrogen can be found in women with obesity, chronic anovulation, early age at menarche, nulliparity, late age of menopause, and in the setting of rare estrogen-secreting tumors.

Obesity is a well-established risk factor for the development of endometrial cancer. A meta-analysis of 19 prospective studies showed that for every 5 kg/m^2

increase in body mass index (BMI), a women's risk of developing endometrial cancer significantly increases.[4] One explanation for these findings is that women who are obese have higher levels of endogenous estrogen because of the conversion of androstenedione into estrone and the aromatization of androgens to estradiol, which occurs in the peripheral adipose tissue. There are additional proposed mechanisms for this association, including alterations in insulin signaling and insulin resistance, alterations in expression of circulating adipokines, as well as alterations in pathways involving inflammation.[5–7] Obesity increases the risk of endometrial cancer in both post- and premenopausal women. In fact, the majority of young, premenopausal women diagnosed with endometrial cancer have a BMI greater than 30.[2]

Lynch syndrome is an autosomal dominant hereditary cancer syndrome characterized by an increased risk in endometrial cancer, colon cancer, and several other malignancies. It is associated with a germline defect in a DNA mismatch repair gene (MutL homolog 1 [*MLH1*], MutS homolog 2 [*MSH2*], MutS homolog 6 [*MSH6*], postmeiotic segregation 2 [*PMS2*]). Women who have Lynch syndrome have a 15% to 66% lifetime risk of developing endometrial cancer, a 15% to 68% lifetime risk of developing colon cancer, and a 1% to 20% lifetime risk of developing ovarian cancer, depending on the specific mutation involved.[8,9]

Diagnosis and Screening

Screening

Except for patients who have been diagnosed with Lynch syndrome, there is insufficient evidence to support routine screening for endometrial cancer in asymptomatic women in the general population, even in those with risk factors such as tamoxifen use, history of unopposed estrogen, obesity, or diabetes. The American Cancer Society currently recommends that all women be informed about the risks and symptoms of endometrial cancer at menopause. Women should alert their physicians of any unexpected bleeding or spotting in the postmenopausal years and abnormal uterine bleeding in the pre- or perimenopausal years.

The American Cancer Society recommends yearly screening with endometrial biopsy beginning at age 35 for women who are known to carry Lynch syndrome–associated mutations, those who have a family member known to carry this mutation, or women from families with an autosomal dominant predisposition to colon cancer in the absence of genetic testing for Lynch syndrome.[10] Prophylactic hysterectomy and salpingo-oophorectomy have been shown to be effective in decreasing the risk of endometrial and ovarian cancers and should be offered to women with Lynch syndrome after childbearing is complete.[11]

Diagnosis

The primary symptom of endometrial cancer is postmenopausal bleeding or abnormal uterine bleeding in pre- or perimenopausal women. A histologic diagnosis is typically obtained by office endometrial sampling or dilation and curettage.

Histopathology

Endometrial Hyperplasia

Women with histologic diagnoses of endometrial hyperplasia often present with postmenopausal bleeding or menometrorrhagia. The risk factors associated with the development of endometrial hyperplasia, including obesity and unopposed estrogen, are similar to those associated with endometrial cancer.[12] The World Health Organization defined endometrial hyperplasia based on two characteristics: (1) simple or complex glandular/stromal architectural pattern, and (2) the presence or absence of nuclear atypia. The presence of nuclear atypia correlates highest with the risk of developing malignancy. In this spectrum, those with simple hyperplasia without atypia are least likely to develop endometrial carcinoma, whereas women with complex hyperplasia with atypia are most likely to develop carcinoma. In a long-term follow-up study conducted by Kurman et al, endometrial carcinoma occurred in simple, complex, simple atypical, and complex atypical hyperplasia in 1%, 3%, 8%, and 29% of cases, respectively.[13] A report from one meta-analysis showing a wider range of risk of cancer progression based on four prospective follow-up studies is summarized in Table 40–1.[14]

Endometrioid Carcinoma

Endometrioid adenocarcinoma is the most common subtype of endometrial cancer, accounting for 75% to 80% of endometrial cancer. Endometrioid adenocarcinomas are graded 1 through 3, based on degrees of differentiation. Grade 1 tumors are well differentiated, composed of glands resembling normal endometrial tissue (Fig. 40–1A). In less-differentiated tumors, glandular formations are less evident or are replaced with solid areas (Fig. 40–1B). The percentage of tumor consisting of these nonsquamous or nonmorular solid areas is the criterion for grading, with grade 1 having a 5% or less solid component, grade 2 having more than 5% but less than or equal to 50%, and grade 3 having greater than 50%. Notably, the presence of nuclear atypia that does not correlate with the architectural features should lead to a one-step upgrade of the tumor.

Table 40–1 Risk of Progression from Endometrial Hyperplasia to Endometrial Cancer

Hyperplastic Type	No. of Cases	Risk of Progression (%)	Mean Risk (%)
Simple hyperplasia	164	0–10	4.3
Complex hyperplasia	193	3–22	16.1[a]
Simple hyperplasia with atypia	27	7.8	7.4[a]
Complex hyperplasia with atypia	151	29–100	47.0

[a]Complex hyperplasia architecture carries a higher risk of progressing to carcinoma than does atypical simple hyperplasia.

Uterine Serous Carcinoma

Uterine serous carcinomas (USCs) are highly aggressive tumors that should be distinguished from other types of uterine carcinoma. Serous carcinomas tend to occur in older women, are usually present in advanced stages, and represent 1% to 5% of cases. Deep myometrial invasion, extensive lymphovascular space invasion (LVSI), and extrauterine spread are common. Intraperitoneal involvement is often observed even when the primary lesion is localized. The histologic features of serous carcinoma resemble those of ovarian or tubal carcinoma. Cytologic atypia is so prominent that serous carcinomas are always graded as poorly differentiated tumors.

Clear Cell Carcinoma

Another aggressive form of uterine carcinoma, clear cell carcinoma, represents 5% to 10% of endometrial cancer cases and is also considered a high-grade tumor. Clear cell carcinoma tends to occur in older women. Morphologically, it resembles clear cell carcinoma arising from other sites (eg, vagina, cervix, ovary), but clear cell carcinoma of the uterine corpus, unlike that of the vagina or cervix, is not associated with intrauterine exposure to diethylstilbestrol. The microscopic appearance varies and can include solid clear cell features; prominent glycogen content; and a glandular, tubulocystic, or papillary pattern. The cells have abundant clear or eosinophilic cytoplasm, sometimes

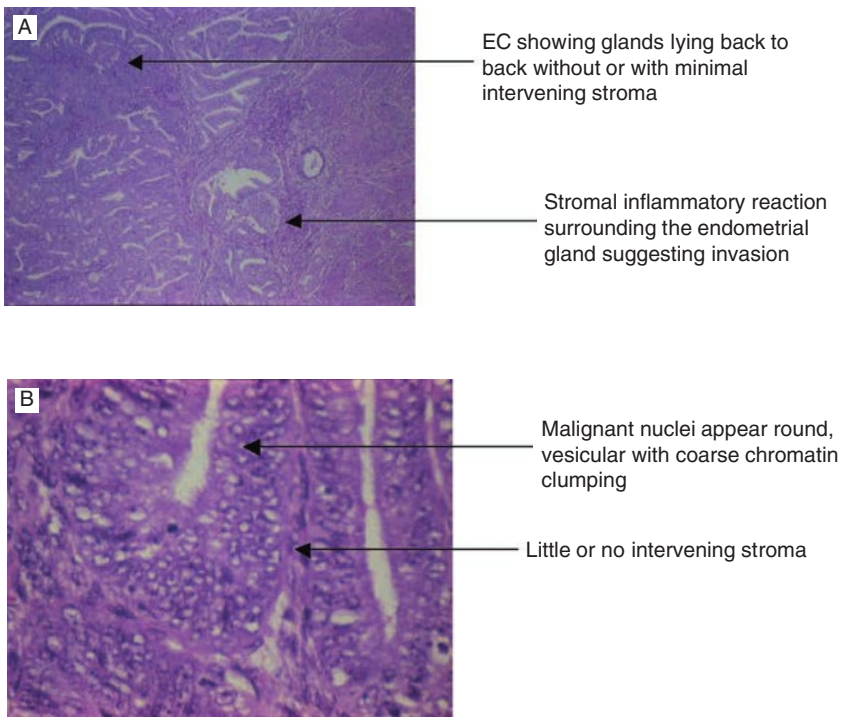


FIGURE 40–1 Endometrioid adenocarcinoma. A. Endometrial cancer with superficial myometrial invasion. The stromal inflammatory reaction surrounding the endometrial gland can aid in the diagnosis in some equivocal cases. B. High-power magnification shows malignant nuclei in the endometrial glands.

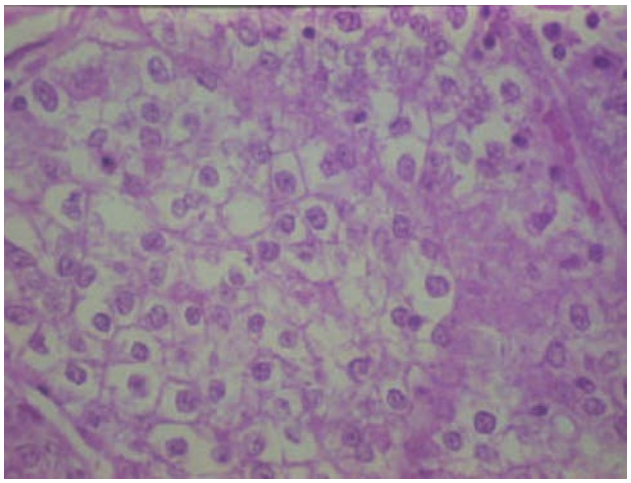


FIGURE 40–2 Clear cell carcinoma: a more aggressive type of endometrial cancer than the usual endometrioid carcinoma. The clear cytoplasmic content is glycogen rather than mucin.

containing periodic acid–Schiff–positive hyaline globules (Fig. 40–2). The nuclei show marked atypia with frequent mitotic figures. The characteristic "hobnail" appearance is seen as cells with scanty cytoplasm and nuclei protruding into the lumen of the gland. At least half of the clear cell carcinomas are admixed with USC; this has contributed to ideas that the poor prognosis associated with clear cell carcinoma is caused by the presence of serous histology.

Mixed-Cell Type

As the name implies, mixed-cell endometrial cancers contain more than one type of tumor. The proportion of the minor component should exceed 10% for a tumor to be designated a mixed-cell type.

Carcinosarcomas

Carcinosarcomas (also called malignant mixed Müllerian tumors [MMMTs]) consist of two components: malignant epithelial and mesenchymal tissue. In homologous carcinosarcomas, the sarcomatous component can be tissue that is normally found in the uterus; endometrial stromal sarcoma (ESS) or leiomyosarcoma are common. The so-called "heterologous" type of carcinosarcoma consists of tissue that does not normally appear in the uterus; rhabdomyosarcoma and chondrosarcoma are two common types.[15–17] Carcinosarcomas are believed to be aggressive carcinomas, rather than true sarcomas.

Staging

In 1988, the International Federation of Gynecology and Obstetrics (FIGO) committee established a surgical staging system for endometrial cancer (FIGO 1988) (Table 40–2). In 2009, this staging system was updated to better stratify patients based on clinically relevant prognostic factors (FIGO 2009, Table 40–3).

Table 40–2 The 1988 FIGO Staging System

Stages	Characteristics
I	Tumor limited to uterus
IA	Confined to endometrium
IB	Invades ≤1/2 the myometrial depth[a]
IC	Invades >1/2 the myometrial depth[a]
II	Cervical extension
IIA	Involves endocervical gland only
IIB	Invades cervical stroma
III	Pelvic structures or intra-abdominal lymph node involvement
IIIA	Invades serosa or adnexa or is peritoneal cytology positive
IIIB	Vaginal metastasis
IIIC	Pelvic or para-aortic lymph node metastasis
IV	Other organ involvement
IVA	Invades bladder or rectal mucosa
IVB	Distant metastasis, including inguinal lymph node involvement

[a]Ideally, width (depth) of myometrial invasion should be measured and recorded with the depth (thickness) of the entire myometrium.

Prognostic Factors

There are clinical and pathologic factors that can be used to predict the behavior of endometrial cancer. Clinical factors include age, ethnicity, and stage of disease. Pathologic factors include histologic type, grade, depth of myometrial invasion, lymphovascular space invasion (LVSI), and spread of tumor outside the uterine cavity, including the retroperitoneal lymph nodes.

Clinical Factors

Studies have shown that outcomes for women with endometrial cancer are more favorable among younger patients. A retrospective study showed that patients younger than 45 years old were statistically more likely to have endometrioid histology, grade I tumors, and stage IA disease, whereas women over age 65 were significantly more likely to have serous histology and grade 3 tumors. A subset analysis of patients older than 75 years old showed an increase in the percentage of patients with aggressive serous histology, higher-grade (grade 3) disease, and advanced-stage disease compared with those younger than 45 years old. Evaluation of patients with endometrioid tumors

Table 40–3 The 2009 FIGO Surgical Staging for Endometrial Carcinoma

Stages	Characteristics
I[a]	Tumor confined to the corpus uteri
IA[a]	No or less than half myometrial invasion
IB[a]	Invasion equal to or more than one-half the myometrium
II[a]	Tumor invades cervical stroma but does not extend beyond the uterusb
III[a]	Local and/or parametrial involvementc
IIIA[a]	Tumor invades serosa and/or adnexaec
IIIB[a]	Vaginal and/or parametrial involvementc
IIIC[a]	Metastases to pelvic and/or para-aortic lymph nodesc
IIIC1[a]	Positive pelvic nodes
IIIC2	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
IV[a]	Tumor invasion of bladder and/or bowel mucosa and/or distant metastases
IVA[a]	Tumor invasion of bladder and/or bowel mucosa
IVB[a]	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

[a]Either G1, G2, or G3.
[b]Endocervical glandular involvement only should be considered as stage I and no longer as stage II.
[c]Positive cytology has to be reported separately without changing stage.
FIGO, International Federation of Gynecology and Obstetrics.
Reproduced with permission from Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet*. 2009;105(2):103-104.

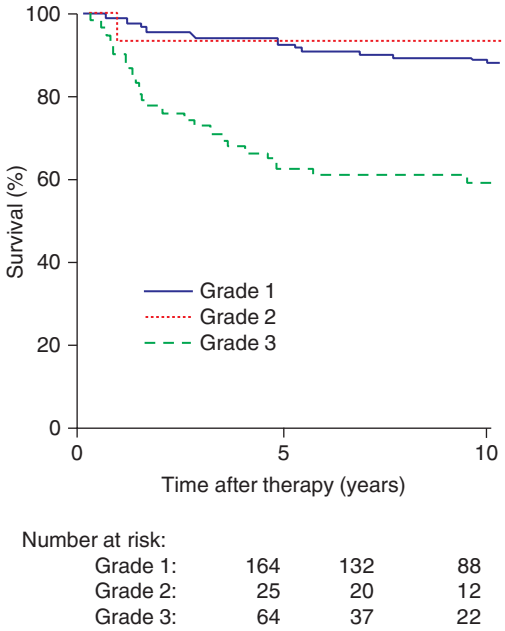


FIGURE 40–3 Tumor grade and survival in endometrial cancer. Use of the two-tier grading system is favored because of less interobserver variability and similar outcome for patients with grade 1 or 2 tumors ($n = 243$). (Reproduced with permission from Scholten AN, Creutzberg CL, Noordijk EM, et al: Longterm outcome in endometrial carcinoma favors a two instead of a three-tiered grading system, *Int J Radiat Oncol Biol Phys* 2002 Mar 15;52(4):1067-1074.)

revealed a similar pattern of deeper myometrial invasion and higher tumor grade as age increased.[18] Other studies have shown that the risks of locoregional relapse and death among patients older than 60 years were twice as high as the risks among those aged 60 years or younger.[19]

Studies in the United States have demonstrated that White women are more likely to be diagnosed with endometrial cancer than Black women. Unfortunately, however, Black women diagnosed with endometrial cancer have a 55% higher mortality risk compared with White women.[20] They tend to be diagnosed at a later stage, with higher-grade tumors, and are more likely to have serous histology. However, after controlling for these factors as well as other comorbid factors, a higher disease-specific mortality rate among Black women still exists.[21]

Pathologic Factors

With regard to histologic subtype, serous carcinoma and clear cell carcinoma are associated with worse prognosis than endometrioid carcinoma. Increasing tumor grade is associated with increased myometrial

Table 40–4 Pathologic Features of Endometrial Carcinoma Grades and Their Association with Depth of Myometrial Invasion

Grade	Pathologic Features	Percentage of Patients with Each Depth of Myometrium Invasion			
		Endometrial Only	Superficial	Middle	Deep
1	5% or less of nonsquamous solid area	24	53	12	10
2	6%–50% of nonsquamous solid area	11	45	24	20
3	>50% of nonsquamous solid area	7	35	16	42

invasion, pelvic and para-aortic node involvement, recurrence, and a poorer OS (Table 40–4, Fig. 40–3).[22]

Lymphovascular space invasion, an independent risk factor for recurrence, is present in about 15% of endometrial cancer cases. Multivariate analyses have shown LVSI to be associated with survival in endometrial cancer regardless of disease stage. Independent of tumor grade or depth of myometrial invasion, LVSI is also associated with risk of pelvic and para-aortic node involvement and thus should lead to consideration of surgical nodal assessment or radiotherapy in patients with unstaged disease.[22]

The depth of myometrial invasion is associated with degree of tumor differentiation, LVSI, lymph node involvement, extrauterine spread, recurrence, and OS (Fig. 40–4, Table 40–5). Adnexal metastasis correlates strongly with metastatic involvement of pelvic and para-aortic nodes; in one study, 32% of patients with adnexal involvement had positive pelvic nodes, as compared with 8% of those without adnexal disease.[22] However, the alternate possibility of simultaneous ovarian and endometrial primaries must be ruled out because the surgical management and prognosis are vastly different. Up to 11% of patients with clinical early-stage disease have lymph node involvement.[22] The risk of para-aortic node involvement increases if the pelvic nodes are positive for tumor.

The current FIGO staging system does not incorporate peritoneal washings because the evidence for their prognostic value is limited. Positive findings on peritoneal cytology are often associated with other unfavorable prognostic factors, such as deep myometrial invasion, cervical extension, and extrauterine spread.

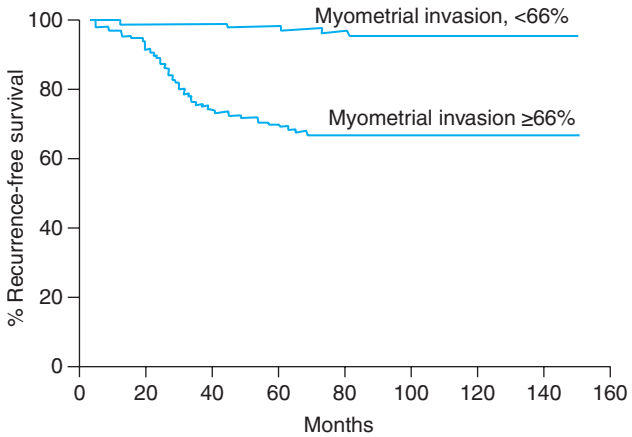


FIGURE 40–4 **Recurrence-free survival rates for 282 patients with stage I endometrial cancer were significantly reduced when the depth of myometrial invasion exceeded two-thirds of the total thickness of the myometrium (P < .001). (Reproduced with permission from Mariani A, Webb MJ, Keeney GL, et al. Surgical stage I endometrial cancer: predictors of distant failure and death, *Gynecol Oncol* 2002 Dec;87(3):274-280.)**

Table 40–5 Association of Lymph Node Metastasis with Other Prognostic Factors in Endometrial Carcinoma

Risk Factors	Percentage of Patients with Positive Pelvic Nodes	Percentage of Patients with Positive Para-aortic Nodes
Histology		
Endometrioid carcinoma	9	5
Others	9	18
Tumor grade		
Grade 1	3	2
Grade 2	9	5
Grade 3	18	11
Depth of myometrial invasion		
None	1	1
Superficial	5	3
Middle	6	1
Deep	25	17
Tumor site		
Fundus	8	4
Isthmus or cervix	16	14
Lymphovascular space invasion		
Absent	7	9
Present	27	19
Peritoneal cytologic findings		
Negative	7	4
Positive	25	19
Extrauterine metastasis		
Absent	7	4
Present	51	23

In particular, USC demonstrates a high rate of positive washings. Even in clinical stage I disease that is confined to the uterus, cytologic findings have been positive in as many as 16% to 17% of cases.[23] However, in at least two studies, the 5-year survival rates for patients with cytologically positive disease but no other risk factors have been higher than 90% (Fig. 40–5).[23]

In conclusion, these prognostic factors correlate with clinical course of disease, recurrence, and risk of death. However, the relative importance of each factor is not always clear because of interrelations and interdependence among them. Results of a multivariate analysis by Zaino and colleagues of factors affecting survival in stages I and II endometrial cancer are summarized in Table 40–6.[24]

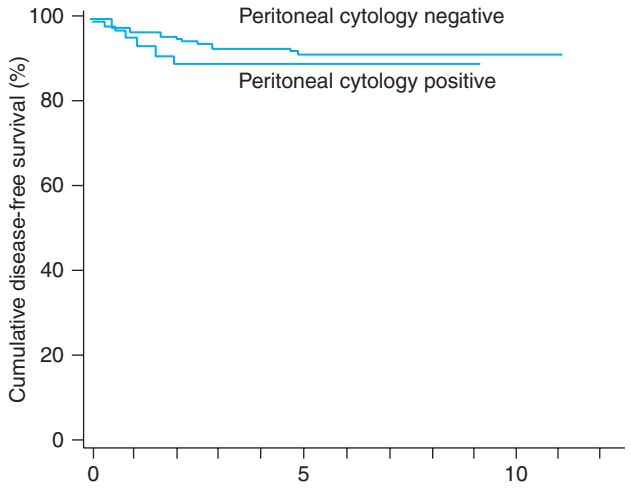


FIGURE 40–5 Five-year survival rates for patients with endometrial cancer confined to the uterus with positive findings on peritoneal cytology (91%) were not different from those with cytonegative findings (95%) (*n* = 280). (Reproduced with permission from Kasamatsu T, Onda T, Katsumata N, et al. Prognostic significance of positive peritoneal cytology in endometrial carcinoma confined to the uterus, *Br J Cancer* 2003 Jan 27;88(2):245-250.)

Evaluation

When evaluating a patient diagnosed with endometrial cancer, in addition to a history and physical examination, chest radiography should be performed, and imaging of the abdomen and pelvis may be considered based on other histologic factors. The measurement of cancer antigen 125 (CA 125) may occasionally be useful (Fig. 40–6).

At MDACC, for patients with disease confined to the uterus, we recommend primary surgery with total hysterectomy and bilateral salpingo-oophorectomy, except in cases with significant medical comorbidities or in patients desiring future fertility (see Fig. 40–6). Lymph node evaluation can be performed using sentinel lymph node mapping techniques or full pelvic and para-aortic lymphadenectomy based on intraoperative evaluation of grade and depth of invasion. Patients with gross cervical involvement may either undergo radical hysterectomy, bilateral salpingo-oophorectomy, with full staging, including pelvic and para-aortic lymph node sampling, or they may undergo primary radiation therapy (see Fig. 40–6). For disease that is not confined to the uterus, surgical debulking is considered (see Fig. 40–6).

Surgery

The standard staging procedure for endometrial cancer includes total hysterectomy, bilateral salpingo-oophorectomy, and assessment of the lymph nodes. In the past, full pelvic and para-aortic lymphadenectomy were performed for all women with presumed stage 1 disease. This was, in part, because of findings of improved survival in several retrospective studies. However, two large randomized, controlled trials of lymphadenectomy in endometrial cancer did not reveal a survival benefit for this surgical procedure. Although no survival benefit was demonstrated, nodal status can inform stage and prognosis, and may direct adjuvant therapy. Thus, indications for performing lymphadenectomy for staging remain controversial.

In the interest of obtaining information on nodal status, while reducing complications and operating room time, sentinel lymph node mapping has been explored as an alternative to full lymphadenectomy in clinical stage I endometrial cancer. Several studies have been reported indicating that this practice has a low false-negative rate when compared with full pelvic and para-aortic lymphadenectomy, in both low-risk and high-risk tumors.[25,26]

In the absence of sentinel lymph node mapping, some surgeons continue to practice routine pelvic or pelvic and para-aortic lymphadenectomy for all patients with endometrial cancer, whereas others perform these procedures only for patients with an increased risk of lymph node metastases based on preoperative and intraoperative assessments. There is a low rate of lymph node metastases in patients with early disease, specifically those with low-grade endometrioid adenocarcinoma with less than 50% invasion of the myometrium. The absence of LVSI and a tumor size of 2 cm or less in diameter also add reassurance that the lymph nodes are not involved.[27] Based on this, intraoperative gross inspection and frozen section of the uterus may be performed to evaluate the extent of uterine disease (see Fig. 40–6) and guide the decision of whether a lymph node dissection will be performed. The preoperative histologic findings and intraoperative pathologic findings that correlate with an increased risk of nodal involvement include grade 3 endometrioid histology; other aggressive histologies, including clear cell, serous or squamous carcinoma; tumor invasion of more than half of the myometrium; tumor size greater than 2 cm; and the presence of extrauterine disease. When these findings are present, there may be a benefit for surgical resection of the pelvic and para-aortic lymph nodes.[22]

Minimally Invasive Approaches

In two reports by the Gynecologic Oncology Group (GOG), laparoscopic surgical methods were compared with conventional laparotomy. The GOG LAP-2 study is the largest randomized trial ever performed in endometrial cancer. In this phase 3 prospective, multi-institutional, randomized study, 2616 patients

Table 40–6 Associations Between Pathologic Prognostic Factors and Relative Risk and Survival Rates

Prognostic Factors	5-Year Survival Rate (%)	Relative Risk of Surgical Stage I–II Tumors[a]		
		Grade 1	Grade 2	Grade 3
Histologic Cell Type				
Clear cell	67.7	5.1	3.5	2.5
Mucinous	100	—	—	—
Serous	55	2.2	3.1	4.4
Endometrioid	82.1	1.0	1.3	1.8
Endometrioid with squamous differentiation	89.4	1.2	1.0	0.8
Villoglandular	91.2	0.01	0.5b	41.9[b]
Myometrial Invasion				
Endometrial only	92.9		1	
Superficial	87.6		0.5	
Middle	84.5		3.3	
Deep	62.6		4.6	
Lymphovascular Space				
Invasion				
No	85.8		—	
Yes	60.9		1.4	
Grade				
1	91.1		—	
2	82		—	
3	66.4		—	
Peritoneal Washings				
Negative	85.3		—	
Positive	56		—	

[a]Typical endometrioid grade 1 as the reference for all cell types.
[b]$P < .05$.

with stage I–IIA uterine cancer were assigned to laparoscopy ($n = 1696$) or laparotomy ($n = 920$). Study end points were morbidity and mortality at 6 weeks, length of hospitalization, failure to complete laparoscopy, site of recurrence, and recurrence-free survival. Consistent with previous studies, laparoscopy required longer operative time but led to fewer postoperative adverse events and shorter hospitalization. The rate of intraoperative complications was similar. One unexpected outcome was that as many as 26% of patients in the laparoscopy arm were converted to laparotomy. Laparoscopic failure was associated with increasing age and BMI.[28]

In a companion report, patients undergoing surgical staging via laparoscopy versus laparotomy were assessed with quality-of-life (QOL) measures. The study's objective was to compare the QOL of patients with endometrial cancer undergoing surgical staging via laparoscopy versus laparotomy. Although patients in the laparoscopy arm had overall better QOL measures at 6 weeks post-surgery, except for better body image in the laparoscopy arm, no difference was detected between the two arms at 6 months.[29]

Robot-assisted surgery, an alternative minimally invasive technique, was evaluated in a systematic review including 36 studies, encompassing 8075 patients undergoing surgery for endometrial cancer. When robot-assisted surgery was compared with laparotomy, it was associated with lower estimated blood loss at time of surgery, lower rates of postoperative complications, and lower rates of conversion to laparotomy. There was no difference in duration of surgery; however, there was a significantly shorter mean length of stay after robot-assisted surgery compared

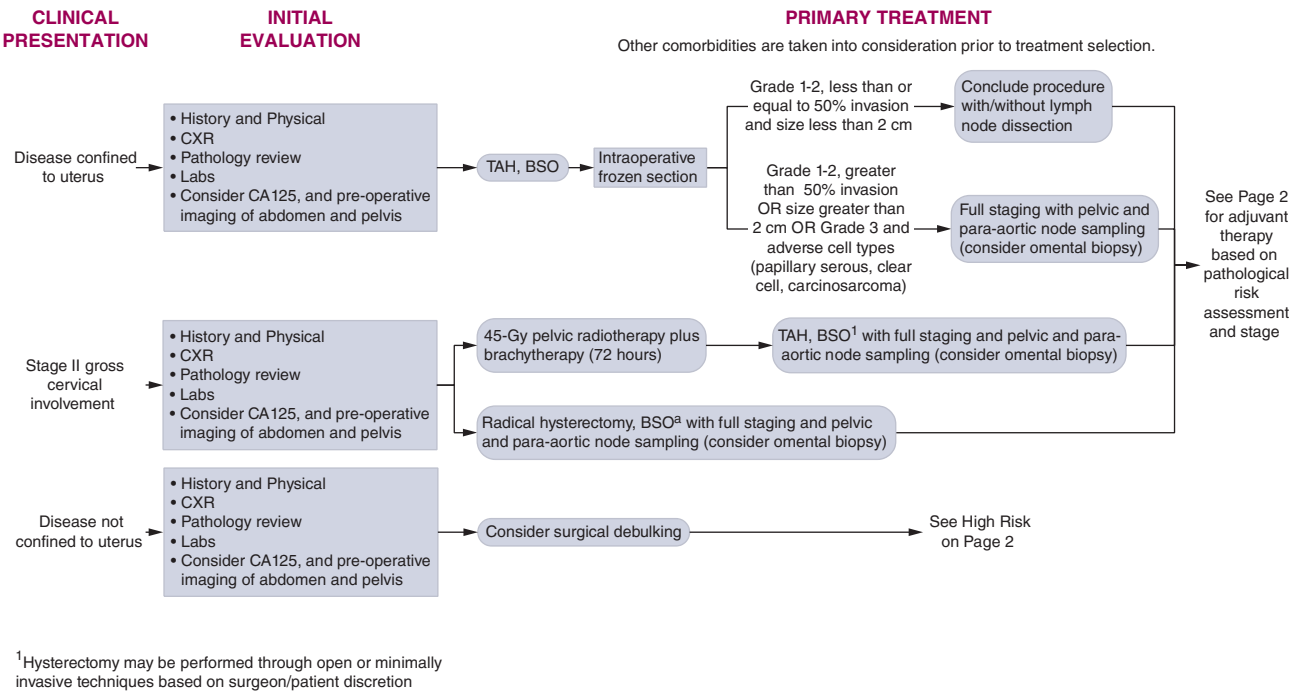


FIGURE 40–6 **MDACC schema for initial evaluation and treatment of patients with endometrial cancer. TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy.**

with laparotomy. Cost was noted to be higher with the robotic approach.[30]

The decision to perform open or minimally invasive surgery depends on patient preference, the skill and experience of the surgeon, the availability of the equipment, the size of the uterus, the parity of the patient, and the patient's medical condition. At MDACC, minimally invasive approaches, both laparoscopic and robotic, are the standard of care for the majority of women with endometrial cancer.

Adjuvant Therapy

To determine who is likely to benefit from adjuvant therapy, we stratify patients according to features of the disease and various prognostic factors. Women with grade 1 or 2 endometrioid tumors with no myometrial invasion or LVSI are considered to have *low-risk* disease. Low-risk disease is associated with an excellent prognosis, with 5-year survival approaching 90% and a low risk for recurrence after surgery. Therefore, in general, we do not recommend adjuvant therapy for this group of patients (see Fig. 40–7). Women with stage III–IV disease, regardless of histology or grade, and women with serous carcinoma or clear cell carcinoma at any stage are considered to have *high-risk* disease and typically undergo adjuvant therapy. *Intermediate-risk* disease, therefore, includes women with grade 1–2 endometrioid endometrial cancer confined to the uterus that invades the myometrium or the cervix. The intermediate-risk group can be further stratified based on the presence of specific prognostic factors, including deep myometrial invasion, grade 2 or 3 disease, and the presence of LVSI. Women are considered to have *high-intermediate-risk* disease if they are (1) any age with all three factors, (2) age 50 to 69 with two factors, and (3) age 70 or more years old with one factor. They are otherwise considered to have *low-intermediate-risk* disease.

Low-Risk Disease

As mentioned, most patients with low-risk disease are unlikely to benefit from adjuvant therapy. Therefore, it is not generally recommended for this group.

Intermediate-Risk Disease

As of this writing, there is no evidence that adjuvant therapy improves OS for women with intermediate-risk disease. For women with low-intermediate-risk disease, observation is favored. For women with high-intermediate-risk disease, vaginal cuff brachytherapy is favored.

Women with low-intermediate-risk disease have a good overall prognosis, and there is little benefit to be gained from radiation therapy (Fig. 40–8). In GOG-99, women with early-stage uterine cancer who underwent surgical staging were randomly assigned to undergo adjuvant radiation therapy versus observation. In the

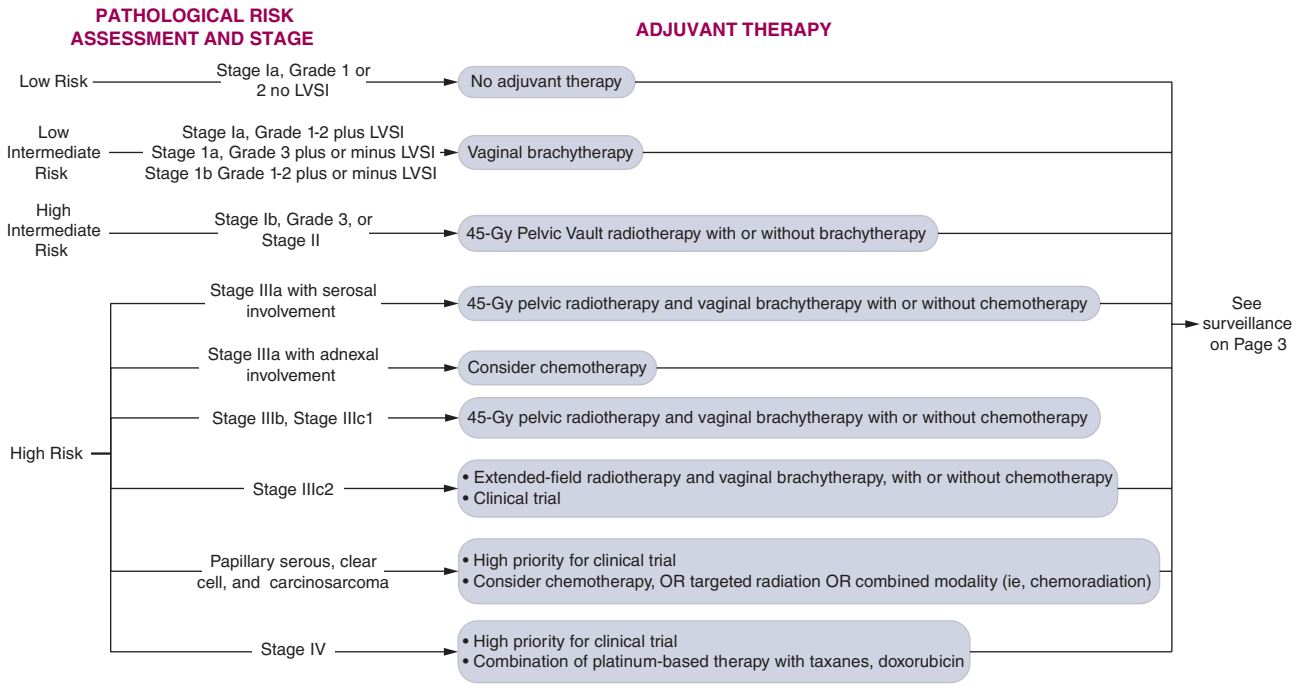


FIGURE 40–7 **MDACC algorithm for adjuvant therapy in endometrial cancer based on postoperative pathologic risk assessment and stage. LVSI, lymphovascular space invasion.**

subgroup analysis of patients who met criteria for low-intermediate-risk disease, those who underwent adjuvant radiation had a lower incidence of recurrence than women who underwent observation, but this was not statistically significant (hazard ratio [HR] 0.46, 95% CI 0.19–1.11). There was no difference in the rate of distant recurrence.[31]

For high-intermediate-risk patients, adjuvant radiation therapy reduces the incidence of pelvic recurrence but does not prolong OS.[32] In GOG 99, women with high-intermediate-risk disease who underwent adjuvant radiation had a reduction in risk of local recurrence compared with those who underwent surveillance (2-year cumulative incidence rate 6% vs 26% in radiation vs no radiation arms; relative HR 0.42). In fact, it was this study that defined the high-intermediate-risk subgroup described previously. The authors concluded that adjunctive radiation in early-stage intermediate-risk endometrial carcinoma decreases the risk of recurrence but should be limited to patients whose risk factors fit a high-intermediate-risk definition. Similarly, the PORTEC-1 (Post-Operative Radiation Therapy in Endometrial Carcinoma) study randomly assigned 714 women with intermediate-risk endometrial cancer after surgical staging to either external beam radiotherapy (46 Gy) or no adjuvant treatment.[32] At 5 years, local recurrence was significantly lower for patients in the experimental arm (4%) versus the control arm (14%).[32] At 10-year follow-up, the local recurrence rates were similar: 5% in the radiotherapy arm versus 14% in the control arm.[33] There was no significant difference in distant recurrence rates at either 5 or 10 years and no OS benefit seen at either time point.

We prefer vaginal cuff brachytherapy alone for most patients with high-intermediate-risk disease because outcomes are equivalent to pelvic radiation. This is based on results from PORTEC-2, which randomly assigned 427 women with high-intermediate-risk disease to vaginal brachytherapy or pelvic radiation. At 45 months, there were no statistically significant differences between the two treatment modalities in terms of locoregional recurrence, distant metastases, or 5-year disease-free survival. Vaginal brachytherapy was associated with a significantly lower rate of side effects, including treatment-related diarrhea and other bowel symptoms.[34,35]

High-Risk Disease

Women with high-risk disease have either serous or clear cell adenocarcinoma (any stage) or have pathologic stage III disease with extrauterine involvement. Treatment may involve radiation, chemotherapy, or a combination of the two modalities, based on histology, stage, and other factors (see Fig. 40–7). A meta-analysis evaluated the use of chemotherapy alone versus radiation alone versus chemoradiation in women with stage III or IV endometrial cancer. Compared with radiation, the use of a combination

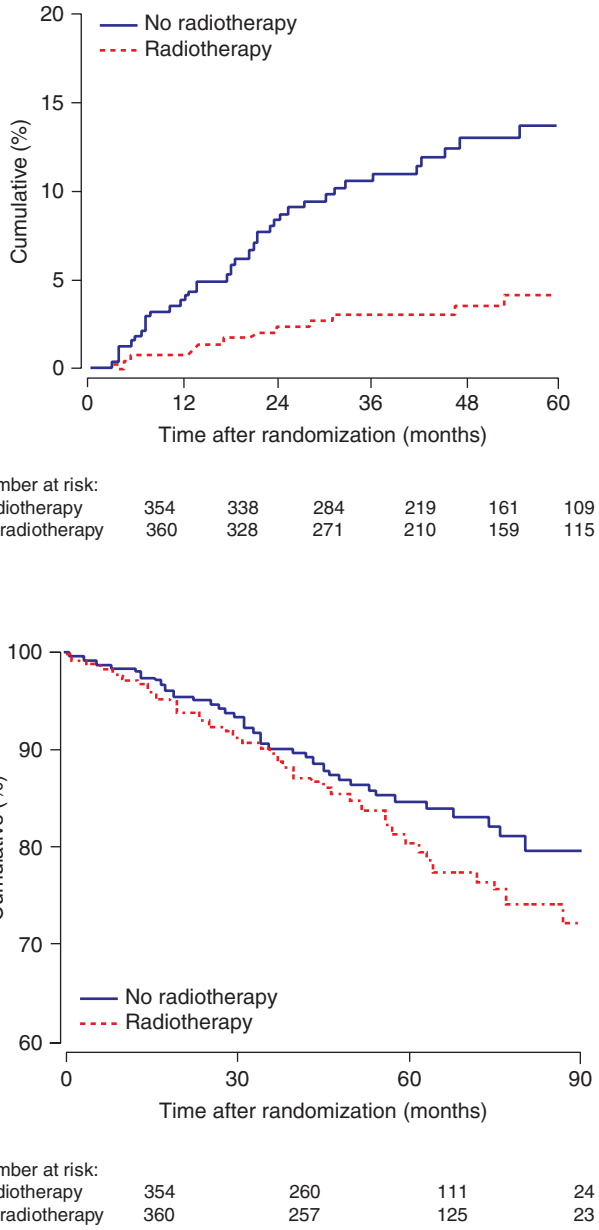


FIGURE 40–8 Pelvic radiotherapy in stage I endometrial cancer. The PORTEC Study Group multicenter randomized trial of 715 patients with stage I endometrial cancer of any type (excluding grade 3 tumors or those with >50% myometrial invasion) showed that pelvic radiotherapy reduced locoregional relapse rates (4% vs 14%, *top panel*) but did not affect 5-year overall survival rates (81% radiotherapy vs 85% observation, *bottom panel*). (Reproduced with permission from Creutzberg CL, van Putten WL, Koper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomized trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma, *Lancet* 2000 Apr 22;355(9213):1404-1411.)

platinum-based chemotherapy regimen resulted in a statistically significant improvement in OS (HR 0.75, 95% CI 0.57–0.99) and progression-free survival (PFS) (HR 0.74, 95% CI 0.59–0.92).[36] Two randomized controlled trials recently addressed the role of chemotherapy and radiation for the treatment of high-risk endometrial cancer. GOG258 assessed whether treatment with chemoradiation followed by four cycles of chemotherapy reduced the rate of recurrence or death compared with chemotherapy for six cycles in women with stage III/IVA or stage I/II serous or clear cell cancers.[37] PORTEC3 explored the impact of chemoradiation followed by chemotherapy to radiation therapy alone on OS and failure-free survival in a similar high-risk population (stage I grade 3 with deep myometrial invasion and/or LVSI); stage II/III; or serous/clear cell histology.[38] In GOG258, chemoradiation therapy reduced the rate of local recurrence (vaginal, nodal) compared with chemotherapy alone, whereas distant recurrences were more common in the chemoradiation arm. The addition of radiation to chemotherapy did not significantly improve recurrence-free survival compared with chemotherapy alone (HR 0.9, 95% CI 0.74–1.10).[37] Conversely, PORTEC3 demonstrated improved 5-year failure-free survival in patients treated with chemoradiation therapy compared with radiation alone (75.5% vs 68.9%, HR 0.71, 95% CI 0.53–0.95). However, OS was not significantly improved in the chemoradiation group (HR 0.79, 95% CI 0.57–1.12). Interestingly, among patients with stage III disease, 5-year failure-free survival, HR, and OS were significantly improved in the women treated with chemoradiation.[38] For patients with nodal disease, at MDACC, we typically treat with chemoradiation followed by chemotherapy with four cycles of carboplatin and paclitaxel. The MDACC algorithm further delineates our practice pattern for these patients (see Fig. 40–7).

Recurrent or Metastatic Disease

Women with disease outside the pelvis, either at their initial diagnosis or at the time of recurrence, are considered to have metastatic endometrial cancer. In general, these patients carry a poor prognosis and may benefit from systemic chemotherapy.

The GOG 209 study compared carboplatin plus paclitaxel with the combination of paclitaxel, doxorubicin, and cisplatin (TAP) in 1300 women with chemotherapy-naïve stage III, IV, or recurrent metastatic endometrial cancer. Both regimens were administered every 3 weeks for a total of seven cycles. The data are not yet mature; however, initial findings were presented at the 2012 Society of Gynecologic Oncology Annual Meeting. Compared with TAP, carboplatin plus paclitaxel had a similar overall response rate (RR) (51% in each arm), similar PFS (median of 13 months in

each arm), and similar OS (37 months for carboplatin and paclitaxel vs 40 months for TAP). Importantly, the toxicity in the carboplatin-and-paclitaxel arm was significantly lower than in the TAP arm. Peripheral neurotoxicity was 19% in the carboplatin/paclitaxel arm compared with 26% in patients assigned to receive TAP. Based on this study, carboplatin plus paclitaxel is preferred.[39]

In general, response to second-line chemotherapy in advanced and metastatic disease is low.[40] Thus, research regarding the use of immunotherapy and targeted therapies in this setting has been extensive. Mismatch repair deficiency (MMRd) is found in approximately 30% of all endometrial cancer, representing a key therapeutic opportunity in endometrial cancer.[41] A study of the programmed death-1 inhibitor, pembrolizumab, in MMRd solid tumors (including endometrial cancer) demonstrated impressive activity (RR 53%), which yielded a tissue-agnostic FDA approval.[42] Further study of this agent, in addition to other checkpoint inhibitors such as avelumab, durvalumab, and dostarlimab, have confirmed the activity of these agents in MMRd endometrial cancer.[43–46] Activity of single-agent immunotherapy in microsatellite stable (MSS) tumors has been limited with the exception of dostarlimab, which demonstrated a RR of 21% in this subtype.[44] In 2019, the combination of pembrolizumab with the tyrosine kinase inhibitor, lenvatinib, was granted accelerated approval by the FDA based on a 38% RR in MSS endometrial cancer.[47,48]

Multiple other relevant targeted agents have been explored in endometrial cancer. Single-agent bevacizumab demonstrated clinical activity and was well tolerated in GOG 229E.[49] However, the combination of bevacizumab with cytotoxic chemotherapeutic regimens did not offer survival benefit in two randomized phase 2 studies in advanced and recurrent endometrial cancer.[50,51] Because of the large number of aberrations in the PI3K pathway in endometrial cancer, the use of agents to target this pathway have also been under investigation. A phase 2 trial of the mTOR (mechanistic target of rapamycin) inhibitor everolimus plus letrozole demonstrated a high clinical benefit rate and RR,[52] which led to a subsequent trial comparing everolimus and letrozole with the hormonal regimen of alternating medroxyprogesterone acetate and tamoxifen. Everolimus and letrozole yielded similar RR; however, PFS was improved when compared with the hormonal regimen.[53]

Endocrine Therapy

Progestins have been used to treat advanced endometrial cancer for more than 50 years. These medications tend to be well tolerated with relatively minor side effects, including weight gain, thrombophlebitis, headache, and occasional hypertension. RRs tend to be modest, ranging from 11% to 24%.[54,55] In GOG 121, women with no previous chemotherapy or hormonal treatment were given megestrol acetate (800 mg/d). The overall RR was 24%, with PFS of 2.5 months and OS of 7.6 months.[54] Unlike in breast cancer, there does not appear to be a dose-response effect for progestins in endometrial cancer. In a randomized trial of oral medroxyprogesterone acetate (GOG 81), women who received a low-dose regimen (200 mg/d) actually had a higher RR compared with women who received the high-dose regimen (1000 mg/d).[55]

Certain characteristics improve the likelihood that a patient will have a favorable response to hormone therapy. These include having a low tumor grade (1 or 2), endometrioid histology, the presence of estrogen and progesterone receptors, having a longer disease-free interval, and being asymptomatic or minimally symptomatic.

Tamoxifen has been shown to have some efficacy in this population, with improved rates among women with hormone receptor–positive disease. Interestingly, it has been shown that short-term use of tamoxifen may lead to an increase in progesterone receptors. In GOG 153, women were given a regimen of tamoxifen for 3 weeks, alternating with megestrol acetate for 3 weeks. The overall RR was 27%, with a median PFS of 2.7 months and OS of 14 months.[56] Letrozole and anastrozole are both aromatase inhibitors that have been evaluated in advanced or recurrent endometrial cancer in phase 2 trials. Both agents have shown a RR of less than 10%.[57,58]

Surgery for Relapsed Disease

At MDACC, we evaluate all patients who have experienced an isolated central pelvic recurrence after radiotherapy for radical pelvic surgery or pelvic exenteration; these procedures remain the only potentially curative options that offer the possibility of long-term survival. However, given the high incidence of major postoperative complications, such as urinary/intestinal tract fistulas, pelvic abscesses, septicemia, pulmonary emboli, and cerebrovascular accidents, we consider only selected patients with isolated central recurrences for this treatment.

Postoperative Surveillance

There are no prospective studies to guide frequency of postoperative follow-up. At MDACC, for patients with stage IA, grade 1–2 disease, we schedule office visits every 6 months for the first year and annually during years 2 to 5. For all other patients in surveillance, we schedule office visits every 3 months for year 1, every 4 months for year 2, and every 6 months for years 3 to 5 (Fig. 40–9). At each visit, patients undergo a physical

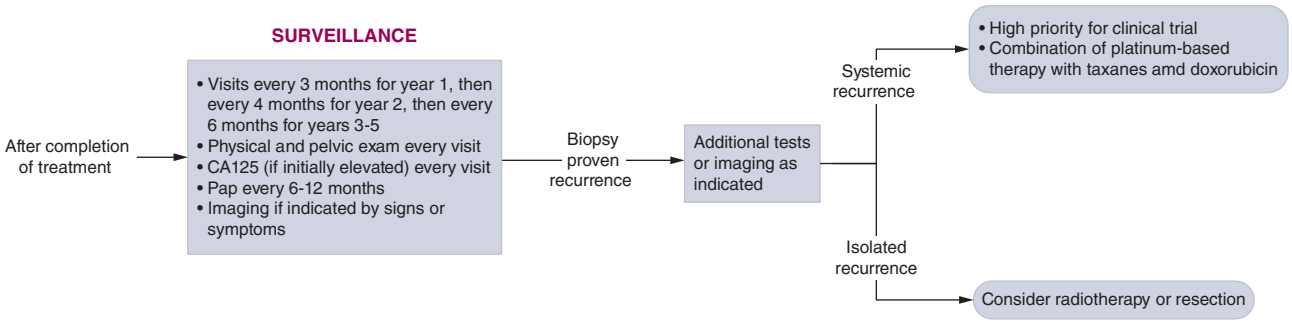


FIGURE 40–9 **Sample surveillance protocol for patients with intermediate- and high-risk disease.**

and pelvic examination. Performing routine vaginal cytology in endometrial cancer survivors is not recommended by the Society of Gynecologic Oncology. This is because multiple studies have suggested that Papanicolaou tests are not as effective in detecting endometrial cancer recurrences compared with physical examination alone[59,60] and are costly and inefficient.[61] In one of these studies, abnormal vaginal cytology had a sensitivity of 40% and specificity of 88% for detecting a vaginal recurrence. The positive predictive value was 7.3% and negative predictive value was 98.4%.[60]

Serum CA 125 level measurements may be helpful for certain patients. In patients with elevated serum CA 125 levels at diagnosis, they can be used as a marker for recurrent disease. In one study, among patients with advanced endometrial cancer who initially had high CA 125 levels, 26% to 58% showed elevated CA 125 at recurrence.[62] The use of serial CA 125 assays is most beneficial in diagnosing recurrence in a high-risk population, although there have been no studies to show that their use improves survival. False elevations may occur after radiation therapy.

Hormone Replacement Therapy After Treatment

The use of estrogen replacement therapy in premenopausal women who have been treated for endometrial cancer is controversial. For young women experiencing vasomotor symptoms, nonhormonal treatment options are considered safe and include selective serotonin reuptake inhibitors, gabapentin, and clonidine. There is also evidence that interventions such as yoga, acupuncture, and cognitive behavioral therapy may be helpful.

For women with low-risk disease who have undergone oophorectomy at the time of surgical staging, estrogen replacement therapy may be considered. In GOG 137, a double-blind, randomized, phase 3 trial, 1236 women with a history of stage I or occult stage II endometrial cancer were enrolled. All enrolled patients had an indication for treatment with estrogen replacement therapy, including hot flashes, vaginal atrophy, increased risk of cardiovascular disease, or an increased risk of osteoporosis, and were randomly assigned to receive estrogen replacement or placebo for 3 years after surgery. This study closed early when the results of the Women's Health Initiative study showed increased overall risks in the estrogen and progestin arm.[63] Based on the results of the Women's Health Initiative study, GOG 137 closed prematurely, and the study was left with insufficient power to detect a difference in patients with intermediate- or high-risk early endometrial cancers. The results of this study are inconclusive. However, the authors noted that in the low-risk population, the absolute recurrence rate was low (2.1%). The relative risk of recurrence/death in the estrogen replacement therapy group was 1.27 compared with the placebo group (80% CI 0.916–1.77).

At MDACC, we approach the use of estrogen replacement therapy on an individual basis. Overall risk of disease recurrence in low-risk patients is low, even in the setting of exogenous estrogen replacement. Therefore, estrogen replacement therapy may be considered for this population on a case-by-case basis. If adjuvant therapy is given after surgery, we recommend a 6- to 12-month waiting period before initiation of hormone replacement therapy.

Carcinosarcomas

Uterine carcinosarcomas account for less than 5% of malignant neoplasms of the uterus.[64] Histologically, they are comprised of both malignant epithelial and mesenchymal elements. These tend to be aggressive tumors and carry a poor overall prognosis. Even when diagnosed at an early stage, 5-year survival rates are dismal, with reports as low as 30% (Fig 40–10).[65]

Epidemiologically, carcinosarcomas usually appear in women aged 60 or older.[64,66] Risk factors are similar to endometrial carcinomas and include obesity, nulliparity, use of exogenous estrogens in the absence of progestin, and tamoxifen. Black women have a twofold higher

incidence of uterine carcinosarcoma compared with non-Hispanic White women. A history of prior pelvic radiation also increases the risk of uterine carcinosarcoma.

Treatment

Surgery

Surgical management of carcinosarcoma, when feasible, includes total abdominal hysterectomy with bilateral salpingo-oophorectomy (BSO) and pelvic and para-aortic lymph node dissection.[67–70] Peritoneal cytology, omentectomy, and peritoneal biopsies are also recommended.[67,71–74] Approximately 20% to 60% of patients will have more advanced disease during surgical staging.[75–77] Among women with stage I–III uterine carcinosarcoma, 5-year OS, disease-free survival, and median survival are significantly improved for patients who undergo lymph node dissection compared with those who do not.[78] With regard to the role of cytoreductive surgery in carcinosarcoma, a series of 44 patients demonstrated increased OS in patients who had a complete cytoreductive surgery versus those that had residual disease (52.3 vs 8.6 months, respectively).[79] Complete cytoreductive surgery should be attempted, when possible, in patients with carcinosarcoma.

Adjuvant Therapy

For stage IA tumors, at MDACC we recommend adjuvant therapy with platinum-based chemotherapy and vaginal cuff brachytherapy (the preferred regimen listed in the National Comprehensive Cancer Network guidelines); however, the ideal treatment strategy remains unclear. A retrospective multi-institutional study of early-stage disease demonstrated improved PFS with adjuvant chemotherapy compared with observation

Because of the overall poor prognosis of these cancers, adjuvant chemotherapy with or without pelvic radiation and/or vaginal cuff brachytherapy is recommended. In early-stage disease, a multi-institutional retrospective cohort study demonstrated improved PFS among women who received chemotherapy compared with those who underwent radiation alone or observation. Unfortunately, there was no impact on OS.[80] Adjuvant radiation therapy decreases local recurrence but does not impact PFS or OS.[78] In advanced-stage disease, a meta-analysis showed improved OS (HR 0.75; 95% CI 0.60–0.94) and reduced disease progression (HR 0.72; 95% CI, 0.58–0.90) with combination chemotherapy versus single-agent ifosfamide.[81–83] More recently, the results of GOG 261 were presented in abstract form. This is a randomized, phase 3 trial comparing carboplatin and paclitaxel versus ifosfamide and paclitaxel among women with stage I–IV persistent or recurrent carcinosarcoma. Median OS was longer for women who underwent carboplatin and paclitaxel (37 vs 29 months) and this combination was found to be noninferior to ifosfamide and paclitaxel and represents the new standard regimen.



FIGURE 40–10 **Gross appearance of a fleshy hemorrhagic polypoid MMMT protruding into the endometrial cavity in a hemiuterus specimen. Such tumors, which typically present with vaginal bleeding, must be distinguished from submucous myoma. Several endometrial tissue biopsies are sometimes needed for diagnosis because of the necrotic and hemorrhagic nature of this tumor.**

NONEPITHELIAL UTERINE TUMORS

Uterine sarcoma is uncommon, accounting for only 3% to 9% of all tumors arising from the uterine corpus.[75,76,84] Most uterine sarcomas originate from mesodermal tissue, although some are derived from specialized Müllerian mesenchyme, such as endometrial stroma, and a few originate from nonspecific or non-Müllerian mesenchyme (eg, smooth or skeletal muscle, vessels, or lymphoid tissue). The three most common types of uterine sarcoma are leiomyosarcoma, ESS, and adenosarcomas. Overall, uterine sarcomas are aggressive tumors with a 5-year OS rate of 17.5% to 54.7%.[84]

Epidemiology

Leiomyosarcoma and ESS usually affect women in their early 50s. Adenosarcomas have been reported in women 14 to 84 years old; the median age at appearance is in the late 50s.[85–87] Although uterine sarcoma differs somewhat from endometrial cancer in its clinical and pathologic characteristics, some risk factors—such as hypertension, diabetes mellitus, and obesity—are common to both. Previous history of pelvic irradiation has been associated with carcinosarcomas and undifferentiated sarcomas, occurring in 2% to

29% of patients so exposed at an interval ranging from 1 to almost 40 years.[88,89] Prior exposure to pelvic radiation, however, is not felt to be associated with leiomyosarcomas.[89] Although the link between estrogen and endometrial cancer is well established, no such clear relationship is evident for estrogen and uterine sarcoma. An association between tamoxifen use and uterine sarcoma was confirmed in a study by Bergman et al, showing increased numbers of uterine sarcomas among women taking tamoxifen and sarcomas constituting about 10% of total malignancies in these cases.[90]

Leiomyosarcoma

Histology

Leiomyosarcomas represent only 1% to 2% of uterine malignancies; however, they are the most common among uterine sarcomas.[75,91,92] Gross features of leiomyosarcoma (Fig. 40-11) are typified by variegation at the cut surface (unlike the whorl-like surface typical of a benign leiomyoma).

Cells are spindle shaped and arranged in fascicles with eosinophilic cytoplasm. The nuclei are usually elongated with rounded ends, appearing hyperchromatic with coarse chromatin and prominent nucleoli. The most important criterion for the diagnosis of leiomyosarcoma is a high mitotic rate, generally exceeding 15 mitotic figures per 10 high-power fields. Other features, such as extrauterine extension, large size, infiltrating border, necrosis, and atypical mitotic figures can also aid in the diagnosis.[84]

Smooth Muscle Tumor of Uncertain Malignant Potential

Uterine smooth muscle tumors with histologic features of necrosis, nuclear atypia, or mitoses that do not meet all diagnostic criteria for leiomyosarcoma fall into the category of smooth muscle tumor of uncertain malignant potential (STUMP).[93] The STUMPs are a group of smooth muscle tumors for which a diagnosis of sarcoma cannot be made because of their uncertain malignant characteristics. Most of these tumors are associated with favorable prognosis, and only follow-up of the patients is recommended.[94] In a study conducted at MDACC of 41 cases of STUMP, the recurrence rate was 7%. One of the three recurrences was a leiomyosarcoma; the others were STUMPs.[95]

Clinical Presentation

Vaginal bleeding is the most common presenting symptom of uterine leiomyosarcomas. Other symptoms, such as back pain, urinary retention or hematuria, gastrointestinal symptoms, or weight loss may indicate an invading or metastasizing tumor.[96–98]

Diagnosis

The definitive diagnosis of leiomyosarcomas is usually made after myomectomy or hysterectomy performed for presumed benign leiomyomas, with the diagnosis based on histologic examination. Methods using pulsed Doppler ultrasonography to preoperatively distinguish between a benign leiomyoma and leiomyosarcoma are reported but not clinically useful.[99] Although useful for detecting extrauterine disease, imaging studies such as computed tomography and magnetic resonance imaging are not specific for diagnosing leiomyosarcomas.[100]

Prognosis and Clinical Course

Leiomyosarcomas are aggressive tumors with high recurrence rates of 50% to 70%, even when diagnosed at early stages.[76] The 5-year OS rate ranges from 15% to 25%, and the 5-year survival rate for patients with stages I and II disease is 40% to 70%.[101,102] Previous

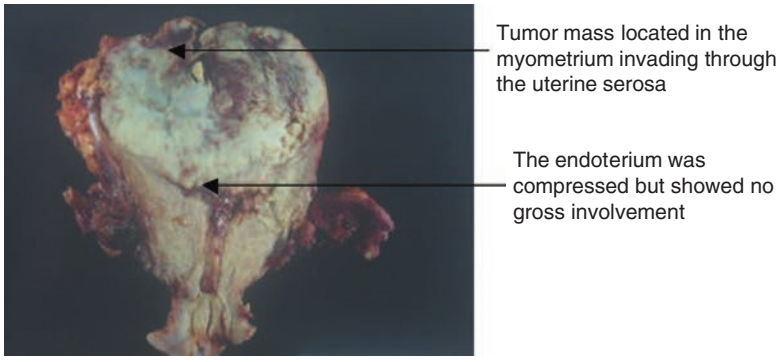


FIGURE 40–11 **Gross appearance of a leiomyosarcoma in the upper uterus. The cut surface shows a grayish-tan tumor with hemorrhage and necrosis, without the whorl-like appearance typical of benign leiomyoma. The mass clearly involves most of the myometrium but not the endometrium.**

studies have reported mitotic index, cellular atypia, vascular invasion, and tumor size to correlate with survival.

Treatment

Surgery

Surgery remains the mainstay of treatment for uterine leiomyosarcoma. For disease confined to the uterus, hysterectomy is recommended. Uterine morcellation should be avoided when there is a preoperative diagnosis of uterine sarcoma or an elevated suspicion for sarcoma. It is not clear if bilateral oophorectomy at the time of surgery affects outcomes in premenopausal women with leiomyosarcoma; therefore, the decision to remove bilateral ovaries should be made on an individual basis. The rate of adnexal masses is low (~3%),[77] and two large retrospective database studies demonstrated no difference in OS between women who underwent oophorectomy and those who did not.[103,104]

The need for lymph node dissection is also controversial. Leiomyosarcoma has a substantially lower risk of nodal involvement than clinical stage I or stage II endometrial cancer with other risk factors. A GOG study of early-stage sarcoma found that nodal metastases were present in only 3.5% of leiomyosarcoma cases, and the pelvic nodes were twice as likely to be involved as the para-aortic nodes.[96] However, the patients in this series underwent lymph node sampling rather than intended dissection, so the reported incidence may be falsely low. Goff et al found lymph node involvement in about 27% of leiomyosarcoma cases, but only in those cases that involved recurrent or disseminated intraperitoneal disease.[96] Two more recent studies identified lymph node metastases in 7% to 11% of patients who underwent lymph node dissection.[103,104] In the series by Kapp et al, the 5-year disease-specific survival rate was 26% in patients who had positive lymph nodes compared with 64% in those who had negative nodes.[104]

Adjuvant Therapy

For early-stage leiomyosarcomas, there has been no clear benefit shown for adjuvant chemotherapy.[105–107] In these patients, surveillance versus referral to a clinical trial are reasonable treatment options. Advanced-stage leiomyosarcomas, on the other hand, have a high risk of recurrence, and individuals so affected are typically offered adjuvant therapy. We work closely with our sarcoma medical oncology colleagues for treatment recommendations. Combination chemotherapy improves RRs over single-agent therapy; however, the impact on PFS and OS has been limited. Various combinations have been investigated, with RRs ranging from 18% to 53%.[106,108–111] The two most common combination regimens used at MDACC are doxorubicin plus ifosfamide or gemcitabine plus docetaxel. Of note, the combination of olaratumab, a platelet-derived growth factor receptor inhibitor, and doxorubicin demonstrated OS benefit in initial investigations compared with doxorubicin alone; however, this was not confirmed in the subsequent confirmatory phase 3 randomized trial.[112,113] Examples of these combination chemotherapies are shown in Table 40–7. Unfortunately, it is not uncommon for these patients to have disease progression after primary chemotherapy. Among single-agent options, the chemotherapy agent trabectedin and the small-molecule inhibitor, pazopanib, are FDA approved for metastatic soft-tissue sarcomas based on favorable impact on PFS.[114,115]

Endometrial Stromal Sarcoma

Histology

Endometrial stromal sarcoma accounts for about 23% of all uterine sarcomas.[64,65] The ESSs originate from endometrial stromal cells that invade the myometrium. Low- and high-grade variants differ in their clinical behavior. Gross features of a low-grade ESS presenting as multiple, small, lobulated tumor masses in the myometrium are shown in Fig. 40–12A.

In fresh specimens, tumor invading the lymphovascular spaces can sometimes be compressed out of the vascular lumen, giving a vermiform appearance. Tumor cells resemble endometrial stromal cells during the proliferative phase of the menstrual cycle and

Table 40–7 Drug Combinations Used to Treat Leiomyosarcomas

Type of Tumor	Drug Regimen	First Author and Year of Study (Reference)	No. of Patients	Intent	Results
Leiomyosarcoma	Dox vs dox + dacarbazine	Omura, 1983[111]	48	Pall	ORR 25% vs 30%
	Dox + ifosfamide	Sutton, 1996[113]	33	Pall	ORR 30.3%
	Eto + hydroxyurea + dacarbazine	Currie, 1996[112]	39	Pall	ORR 18.4%
	Mitomycin C + dox + cisplatin	Edmonson, 2002[114]	23	Pall	ORR 23%
	Gemcitabine + docetaxel	Hensley, 2009[109]	25	Adj	2-year PFS 45%

Adj, adjuvant; dox, doxorubicin; eto, etoposide; ORR, overall response rate; Pall, palliative; PFS, progression-free survival.

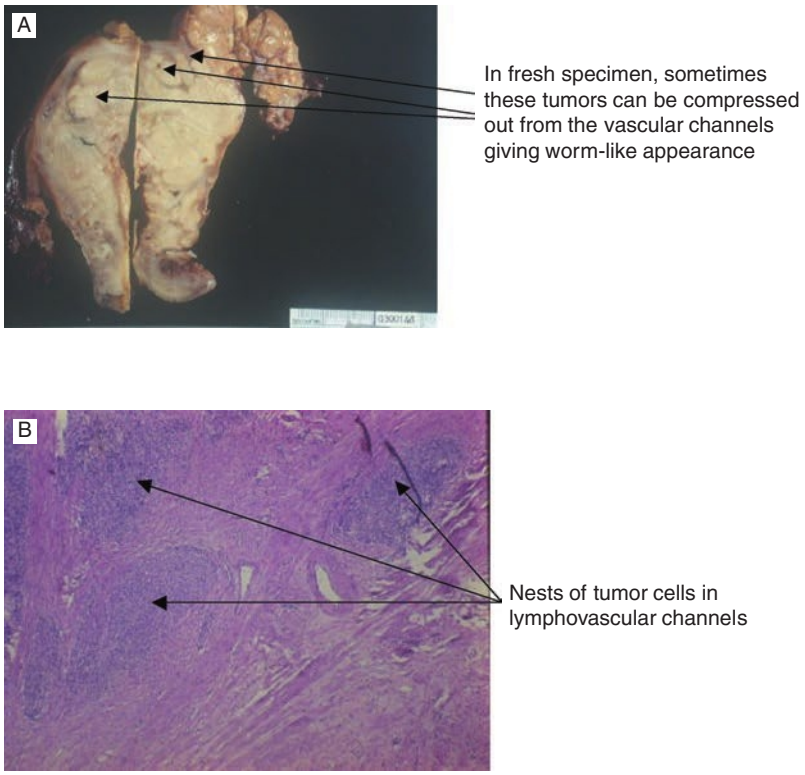


FIGURE 40–12 **A. Gross appearance of an endometrial stromal sarcoma infiltrating most of the myometrium. The lobulated appearance corresponds with the presence of tumor in the lymphovascular spaces, as verified on microscopy in panel B. B. Endometrial stromal sarcoma cells with invasion of the intralymphatic spaces.**

are monotonous and of uniform shape and size.[95] The presence of spiral arteriole-like vessels is a characteristic finding of ESS, as is the propensity of the tumor cells to invade the lymphovascular spaces (Fig. 40-12B).

ESS tumors contain both estrogen and progesterone receptors.[84] In addition, these tumors are generally positive for CD10 and frequently have a t(1;17) chromosomal translocation that expresses a fusion protein composed of JAZF1 and JJAZ1.[84]

Clinical Presentation

Like leiomyosarcomas, vaginal bleeding is the most common presenting symptom. Another common presenting symptom in ESS and adenosarcoma is the appearance of a prolapsed polypoid mass through the cervical os.[96–98]

Prognosis and Clinical Course

Low-grade ESSs are indolent tumors.[116] Generally, patients with ESS have favorable prognoses; however, recurrence can appear late after primary diagnosis and treatment, even in stage I disease.[117,118] The FIGO stage, depth of myometrial invasion, tumor grade, positive margins, and patient characteristics such as age, race, and menopausal status have been reported to be prognostic factors.[64,119–121] Mitotic activity and cytologic atypia were found to be important by some[64,101,122] but not by others.[117,123] Extrauterine and nodal disease is prevalent in ESS.

Treatment

Surgery

Initial treatment for ESS is largely surgical, and hysterectomy with BSO is recommended. ESS is often sensitive to hormones, and patients with intact ovaries may be at a higher risk for recurrence.[124–127] However, there is no consensus on the absolute need for oophorectomy in early-stage ESS. In a study by Li et al, BSO did not appear to affect time to recurrence or OS in patients with stage I ESS.[125] In a recent report of 384 women with low-grade ESS, lymph node metastasis and ovarian preservation were not significant prognostic factors for survival in this study. Lymph node metastasis was found in 7% of patients.[126] In two smaller series, only two of the nine patients with ESS who had undergone lymph node sampling were found to have lymph node metastases.[96,122] The choice of lymph node dissection for ESS should be made on an individual basis.

Adjuvant Therapy

Observation is generally recommended for stage I ESS. Patients with more advanced stages of ESS are typically offered additional therapy after surgical resection, although the data are limited given this rare tumor type. Because these tumors typically express estrogen and progesterone receptors, hormone therapy is considered first-line treatment. Limited retrospective data have reported response of metastatic and recurrent ESS to hormonal agents such as medroxyprogesterone acetate or letrozole.[118,122,124,128,129] A small retrospective study found longer recurrence-free survival and less toxicity among patients treated with aromatase inhibition compared with progestin therapy.[130] Tamoxifen is contraindicated in the treatment of ESS because of its stimulatory effect on the endometrial stromal cells.[128]

Because of its rarity and because low-grade ESS usually responds well to hormonal therapy, ESS has not been well studied in chemotherapeutic trials. A cisplatin-based chemotherapy regimen was tested in a study of uterine sarcoma in which about 10% of the cases were ESS.[131] Despite a relatively high RR of 54%, the regimen was too toxic to be clinically useful. Radiotherapy may help to improve local control, but its role as adjuvant therapy in ESS is unclear.[132]

Undifferentiated Endometrial Sarcoma

Histology

In undifferentiated endometrial sarcomas, previously considered high-grade ESS, the tumor cells tend to be larger, with more vesicular nuclei, coarse clumps of chromatin, and more prominent nucleoli.[133] Mitotic counts are usually low in low-grade ESS, and this is the principal criterion for distinguishing between the low- and high-grade forms.[133] However, numerous mitotic figures can be present in otherwise typical low-grade tumors, and high-grade tumors can have only a few mitotic figures.[117,134] Flow cytometry with DNA ploidy seems to be associated more with the behavior of the tumor than with mitotic count.[135] In the 2002 classification of ESS by the World Health Organization, high-grade tumors were considered as pleomorphic or undifferentiated sarcoma rather than as a type of ESS because of their distinctive and aggressive clinical behavior. Undifferentiated sarcomas generally stain for Ki67, p16, and p53 and not for estrogen and progesterone receptors. These tumors also do not have any known chromosomal abnormalities.[84]

Prognosis and Clinical Course

In contrast to individuals with low-grade ESS, those with undifferentiated sarcomas have poor OS regardless of stage. The median PFS in one series was 7.3 months, and OS was only 11.8 months.[136] Patients are also likely to have disease that progresses quickly despite an initial response to treatment.[136]

Treatment

Surgery

Undifferentiated endometrial sarcomas are treated with up-front surgical management, including hysterectomy and oophorectomy with or without lymphadenectomy. Because of the aggressive nature of this disease, these patients require adjuvant therapy.

Adjuvant Therapy

Unlike ESS, undifferentiated endometrial sarcomas are not responsive to hormone therapy. Adjuvant chemotherapy is similar to that for leiomyosarcoma, as discussed previously.

Adenosarcoma

Histology

Adenosarcomas have two tissue components: the mesenchymal tissue is malignant, and the epithelial part is benign. The epithelial component commonly resembles a proliferative or inactive endometrial gland, often appearing as cleftlike spaces dispersed throughout the proliferative stroma in a phyllode pattern. Slight atypia may be present.[86] The mesenchymal stromal component is usually homologous tissue, such as stromal sarcoma, fibrosarcoma, or leiomyosarcoma.[86,137] The pattern of stromal cell hypercellularity surrounding the glands is characteristic, and the stromal cells show variable atypia and mitosis.[85] Adenosarcomas with extensive stromal sarcoma proliferation are called *adenosarcoma with sarcoma overgrowth* if the sarcomatous component constitutes more than 25% of the tumor.[85,86] This subtype should be recognized because its prognosis is worse than that of a typical adenosarcoma and more similar to that of carcinosarcoma.[138]

Prognosis and Clinical Course

Adenosarcoma is considered a low-grade malignant tumor with an excellent prognosis.[85–87] Most cases are confined to the uterus at the time of diagnosis and require no adjuvant therapy. Distant metastases have been reported in 5% of cases, and the recurrence rate is approximately 23%, with about one-third of recurrences occurring more than 5 years after initial treatment.[85,86,139] Extrauterine spread at diagnosis, deep infiltrating tumors, sarcomatous overgrowth, LVSI, and tumor cell necrosis have all been associated with increased risk of recurrence but are rare.[85,101,121,140]

Treatment

Surgery

Management of adenosarcomas consists of hysterectomy, and as discussed previously, additional therapy is generally not required given the excellent prognosis.

Adjuvant Therapy

Only a few reports have described cases in which adenosarcoma was successfully treated with chemotherapeutic drugs such as liposomal doxorubicin.[87] Krivak and colleagues reported adjuvant chemotherapeutic treatment of nine patients with residual or recurrent adenosarcoma with sarcomatous overgrowth. The drugs used were cisplatin and ifosfamide; doxorubicin; and cisplatin and doxorubicin. The progression-free interval for four patients ranged from 7 to 22 months; all patients had died of recurrent or progressive disease by 39 months.[141] A study from MDACC including 100 patients with uterine adenosarcoma found no optimal treatment strategy for this disease; however, adjuvant therapy was associated with increased PFS.

MD ANDERSON PRACTICE TIPS

- Women with Lynch syndrome should undergo yearly screening with endometrial biopsy beginning at age 35 years. Prophylactic hysterectomy and salpingo-oophorectomy have been shown to be effective in decreasing the risk of endometrial and ovarian cancers and should be offered to women with Lynch syndrome after childbearing is complete.
- The surgical staging procedure for endometrial cancer includes total hysterectomy, bilateral salpingo-oophorectomy, and assessment of the lymph nodes. Sentinel lymph node mapping is standardly used at MDACC as an alternative to full lymphadenectomy in clinical stage I endometrial cancer. Several studies indicate that this practice has a low false-negative rate when compared with full pelvic and para-aortic lymphadenectomy, in both low-risk and high-risk tumors.
- At MDACC, minimally invasive approaches to surgical staging, both laparoscopic and robotic, are the standard of care for the majority of women with endometrial cancer.
- We approach the use of estrogen replacement therapy after treatment for endometrial cancer on an individual basis. Overall risk of disease recurrence in low-risk patients is low, even in the setting of exogenous estrogen replacement. Therefore, estrogen replacement therapy may be considered for this population on a case-by-case basis. If adjuvant therapy is given after surgery, we recommend a 6- to 12-month waiting period before initiation of hormone replacement therapy.
- At MDACC, we evaluate all patients who have experienced an isolated central pelvic recurrence after radiotherapy for radical pelvic surgery or pelvic exenteration; these procedures remain the only potentially curative options that offer the possibility of long-term survival. However, given the high incidence of major postoperative complications, such as urinary/intestinal tract fistulas, pelvic abscesses, septicemia, pulmonary emboli, and cerebrovascular accidents, we consider only selected patients with isolated central recurrences for this treatment.
- When selecting second-line therapy for metastatic/recurrent endometrial cancer, MSS testing can inform treatment decisions. Pembrolizumab has a RR of 53% for women with microsatellite instable tumors. The combination of pembrolizumab with lenvatinib has a RR of 38% among women with MSS tumors.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin.* 2020;70(1):7-30.
2. Creasman WT, Odicino F, Maisonneuve P, et al. Carcinoma of the corpus uteri. *J Epidemiol Biostat/* 2001;6:47-86.
3. Soliman PT, Oh JC, Schmeler KM, et al. Risk factors for young premenopausal women with endometrial cancer. *Obstet Gynecol.* 2005;105(3):575-580.
4. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet.* 2008;371(9612):569.
5. Mu N, Zhu Y, Wang Y, Zhang H, Xue F. Insulin resistance: a significant risk factor of endometrial cancer. *Gynecol Oncol.* 2012;125(3):751-757.
6. Wang T, Rohan TE, Gunter MJ, et al. A prospective study of inflammation markers and endometrial cancer risk in postmenopausal hormone nonusers. *Cancer Epidemiol Biomarkers Prev*. 2011;20(5):971-977.
7. Luhn P, Dallal CM, Weiss JM, et al. Circulating adipokine levels and endometrial cancer risk in the prostate, lung, colorectal, and ovarian cancer screening trial. *Cancer Epidemiol Biomarkers Prev*. 2013;22(7):1304-1312.
8. Hampel H, Stephens J, Pukkala E, et al. Cancer risk in hereditary nonpolyposis colorectal cancer syndrome: later age of onset. *Gastroenterology*. 2005;129:415.
9. Watson P, Vasen HFA, Mecklin JP, et al. The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. *Int J Cancer*. 2008;123:444.
10. Smith RA, Cokkinides V, Brawley OW. Cancer screening in the United States, 2009: a review of current American Cancer Society guidelines and issues in cancer screening. *CA Cancer J Clin*. 2009;59:27-41.
11. Schmeler KM, Lynch HT, Chen LM, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. *N Engl J Med*. 2006;354(3):261-269.
12. Epplein M, Reed SD, Voigt LF, et al. Risk of complex and atypical endometrial hyperplasia in relation to anthropometric measures and reproductive history. *Am J Epidemiol*. 2008;168:563-570; discussion 71-76.
13. Kurman RJ, Kaminski PF, Norris HJ. The behavior of endometrial hyperplasia. A long-term study of "untreated" hyperplasia in 170 patients. *Cancer*. 1985;56:403-412.
14. Silverberg SG. Problems in the differential diagnosis of endometrial hyperplasia and carcinoma. *Mod Pathol*. 2000;13:309-327.
15. Larson B, Silfversward C, Nilsson B, et al. Prognostic factors in uterine leiomyosarcoma. A clinical and histopathological study of 143 cases. The Radiumhemmet series 1936-1981. *Acta Oncol*. 1990;29:185-191.
16. Nielsen SN, Podratz KC, Scheithauer BW, et al. Clinicopathologic analysis of uterine malignant mixed mullerian tumors. *Gynecol Oncol*. 1989;34:372-378.
17. Silverberg SG, Major FJ, Blessing JA, et al. Carcinosarcoma (malignant mixed mesodermal tumor) of the uterus. A Gynecologic Oncology Group pathologic study of 203 cases. *Int J Gynecol Pathol*. 1990;9:1-19.
18. Lachance JA, Everett EN, Greer B, et al. The effect of age on clinical/pathologic features, surgical morbidity, and outcome in patients with endometrial cancer. *Gynecol Oncol*. 2006;101:470-475.
19. Alektiar KM, Venkatraman E, Abu-Rustum N, et al. Is endometrial carcinoma intrinsically more aggressive in elderly patients? *Cancer*. 2003;98:2368-2377.
20. Doll KM, Snyder CR, Ford CL. Endometrial cancer disparities: a race-conscious critique of the literature. *Am J Obstet Gynecol.* 2018;474-482.32. .
21. Ruterbusch JJ, Ali-Fehmi R, Olson SH, et al. The influence of comorbid conditions on racial disparities in endometrial cancer survival. *Am J Obstet Gynecol*. 2014;211(6):612.
22. Creasman WT, Morrow CP, Bundy BN, et al. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group study. *Cancer*. 1987;60:2035-2041.
23. Kasamatsu T, Onda T, Katsumata N, et al. Prognostic significance of positive peritoneal cytology in endometrial carcinoma confined to the uterus. *Br J Cancer*. 2003;88:245-250.
24. Zaino RJ, Kurman RJ, Diana KL, et al. Pathologic models to predict outcome for women with endometrial adenocarcinoma: the importance of the distinction between surgical stage and clinical stage—a Gynecologic Oncology Group study. *Cancer*. 1996;77:1115-1121.
25. Darai E, Dubernard G, Bats AS, Heitz D, Mathevet P, Marret H, et al. Sentinel node biopsy for the management of early stage endometrial cancer: long-term results of the SENTI-ENDO study. *Gynecol Oncol.* 2015;136:54-59.
26. Soliman P, Westin S, Dioun S, Sun C, Euscher E, Munsell M, et al. Sentinel lymph node mapping accurately identifies positive nodes in women with high risk endometrial cancer; a prospective validation trial. *Int J Gynecol Cancer.* 2016;26.
27. Rossi EC, Kowalski LD, Scalici J, Cantrell L, Schuler K, Hanna RK, Method M, Ade M, Ivanova A, Boggess JF. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. *Lancet Oncol.* 2017;18(3):384-392.
28. Walker JL, Piedmonte MR, Spirtos NM, et al. Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group study LAP2. *J Clin Oncol*. 2009;27:5331-5336.
29. Kornblith AB, Huang HQ, Walker JL, et al. Quality of life of patients with endometrial cancer undergoing laparoscopic International Federation of Gynecology and Obstetrics staging compared with laparotomy: a Gynecologic Oncology Group study. *J Clin Oncol*. 2009;27:5337-5342.
30. Ind T, et al. A comparison of operative outcomes between standard and robotic laparoscopic surgery for endometrial cancer: A systematic review and meta-analysis. *Int J Med Robot.* 2017.
31. Keys HM, Roberts JA, Brunetto VL, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2004;92:744-751.
32. Creutzberg CL, van Putten WL, Koper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Postoperative radiation therapy in endometrial carcinoma. *Lancet*. 2000;355:1404-1411.
33. Scholten AN, van Putten WL, Beerman H, et al. Postoperative radiotherapy for stage 1 endometrial carcinoma: Long-term outcome of the randomized PORTEC trial with central pathology review. *Int J Radiat Oncol Biol Phys*. 2005;63:834-838.
34. Nout RA, Smit VT, Putter H, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomized trial. *Lancet.* 2010:375(9717):816.
35. Nout RA, Putter, H., Jürgenliemk-Schulz IM, et al. Vaginal brachytherapy versus external beam pelvic radiotherapy for high-intermediate risk endometrial cancer: results of the randomized PORTEC-2 trial [abstract]. *J Clin Oncol*. 2008;26:LBA5503.
36. Galaal K, Al Moundhri M, Bryant A, Lopes AD, Lawrie TA. Adjuvant chemotherapy for advanced endometrial cancer. *Cochrane Database Syst Rev*. 2014;5:CD010681.
37. Matei D, Filiaci V, Randall ME, Mutch D, Steinhoff MM, Disilvestro, et al. Adjuvant chemotherapy plus radiation for locally

advanced endometrial cancer. *N Engl J Med.* 2019;380(24):2317-2326.
38. de Boer SM, Powell ME, Mileshkin L, Katsaros D, et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicenter, randomised, phase 3 trial. *Lancet Oncol.* 2018;19(3):295-309.
39. Miller D, Filiaci V, Fleming G, et al. Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial cancer: a Gynecologic Oncology Group study [SGO abstract LBA-1]. *Gynecol Oncol.* 2012;125(3):771-773.
40. Bregar A, Robison K, Dizon DS. Update on the chemotherapeutic management of endometrial cancer. *Clin Adv Hematol Oncol.* 2014;12(10):659-665.
41. Kandoth C, Schultz N, Cherniack AD, et al; Cancer Genome Atlas Research Network. Integrated genomic characterization of endometrial carcinoma. *Nature.* 2013;497:67-73.
42. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science.* 2017;357:409-413.
43. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. *J Clin Oncol.* 2020;38:1-10.
44. Oaknin A, Ellard SL, Leath C, et al. Preliminary safety, efficacy, and PK/PD characterization from GARNET, a phase 1 clinical trial of the anti-PD-1 monoclonal antibody, TSR-042, in patients with recurrent or advanced MSI-H endometrial cancer. *Ann Oncol.* 2018;29(suppl 8):viii334.
45. Konstantinopoulos PA, Luo W, Liu JF, et al. Phase II study of avelumab in patients with mismatch repair deficient and mismatch repair proficient recurrent/ persistent endometrial cancer. *J Clin Oncol.* 2019;37:2786-2794. .
46. Antill YC, Kok PS, Robledo K, et al. Activity of durvalumab in advanced endometrial cancer (AEC) according to mismatch repair (MMR) status: the phase II PHAEDRA trial (ANZGOG1601). *J Clin Oncol.* 2019;37(suppl 15):abstract 5501.
47. Makker V, Rasco D, Vogelzang NJ, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: an interim analysis of a multicentre, openlabel, single-arm, phase 2 trial. *Lancet Oncol.* 2019;20:711-718.
48. Makker V, Taylor MH, Aghajanian C, et al. Lenvatinib and pembrolizumab in patients with advanced endometrial cancer. *Ann Oncol.* 2019;30(suppl 5):abstract 992O.
49. Agahajanian C, Sill MW, Darcy KM. Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. *J Clin Oncol*. 2011;29(16):2259-2265.
50. Aghajanian C, Filiaci V, Dizon DS, et al. A phase II study of frontline paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus, or ixabepilone/carboplatin/bevacizumab in advanced/recurrent endometrial cancer. *Gynecol Oncol.* 2018;150(2):274-281.
51. Lorusso D, Ferrandina G, Colombo N, et al. Carboplatin-paclitaxel compared to Carboplatin-Paclitaxel-Bevacizumab in advanced or recurrent endometrial cancer: MITO END-2 - A randomized phase II trial. *Gynecol Oncol.* 155(3):406-412.
52. Slomovitz BM, Jiang Y, Yates MS, et al. Phase II study of everolimus and letrozole in patients with recurrent endometrial carcinoma. *J Clin Oncol*. 2015;33(8):930-936.
53. Slomovitz BM, Filiaci VL, Coleman RL, et al. GOG 3007, a randomized phase II (RP2) trial of everolimus and letrozole (EL) or hormonal therapy (medroxyprogesterone acetate/tamoxifen, PT) in women with advanced, persistent or recurrent endometrial carcinoma (EC): A GOG Foundation study. *Gynecol Oncol.* 2018;149(suppl 1).
54. Podratz KC, O'Brien PC, Malkasian GD Jr, Decker DG, Jeffries JA, Edmonson JH. Effects of progestational agents in treatment of endometrial carcinoma. *Obstet Gynecol*. 1985,66(1):106.
55. Lentz SS, Brady MF, Major FJ, Reid GC, Soper JT. High-dose megestrol acetate in advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol*. 1996;14(2):357.
56. Fiorica JV, Brunetto VL, Hanjani P, et al. Phase II trial of alternating courses of megestrol acetate and tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2004;92(1):10.
57. Ma BB, Oza A, Eisenhauer E, Stanimir G, et al. The activity of letrozole in patients with advanced or recurrent endometrial cancer and correlation with biological markers—a study of the National Cancer Institute of Canada Clinical Trials Group. *Int J Gynecol Cancer*. 2004;14(4):650.
58. Rose PG, Brunetto VL, VanLe L, Bell J, Walker JL, Lee RB. A phase II trial of anastrozole in advanced recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2000;78(2):212.
59. Salani R, Backes FJ, Fung MF, et al. Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncologists recommendations. *Am J Obstet Gynecol*. 2011;204(6):466.
60. Novetsky AP, Kuroki LM, Massad LS, et al. The utility and management of vaginal cytology after treatment for endometrial cancer. *Obstet Gynecol*. 2013;121(1):129-135.
61. Bristow RE, Purinton SC, Santillan A, Diaz-Montes TP, Gardner GJ, Guintoli RL 2nd. Cost-effectiveness of routine vaginal cytology for endometrial cancer surveillance. *Gynecol Oncol*. 2006;103(2):709.
62. Rose PG, Sommers RM, Reale FR, et al. Serial serum CA 125 measurements for evaluation of recurrence in patients with endometrial carcinoma. *Obstet Gynecol*. 1994;84:12-16.
63. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288:321-333.
64. Trope CG, Abeler VM, Kristensen GB. Diagnosis and treatment of sarcoma of the uterus. A review. *Acta Oncol*. 2012;51:694-705.
65. Amant F, Cadron I, Fuso L, et al. Endometrial carcinosarcomas have a different prognosis and pattern of spread compared to high-risk epithelial endometrial cancer. *Gynecol Oncol.* 2005;98(2):274-280.
66. Olah KS, Dunn JA, Gee H. Leiomyosarcomas have a poorer prognosis than mixed mesodermal tumours when adjusting for known prognostic factors: the result of a retrospective study of 423 cases of uterine sarcoma. *Br J Obstet Gynaecol*. 1992;99:590-594.
67. Gadducci A, Cosio S, Romanini A, et al. The management of patients with uterine sarcoma: a debated clinical challenge. *Crit Rev Oncol Hematol*. 2008;65:129-142.
68. Callister M, Ramondetta LM, Jhingran A, et al. Malignant mixed Mullerian tumors of the uterus: analysis of patterns of failure, prognostic factors, and treatment outcome. *Int J Radiat Oncol Biol Phys*. 2004;58:786-796.
69. Livi L, Paiar F, Shah N, et al. Uterine sarcoma: twenty-seven years of experience. *Int J Radiat Oncol Biol Phys*. 2003;57:1366-1373.
70. Villena-Heinsen C, Diesing D, Fischer D, et al. Carcinosarcomas–a retrospective analysis of 21 patients. *Anticancer Res*. 2006;26:4817-4823.
71. Ali S, Wells M. Mixed Mullerian tumors of the uterine corpus: a review. *Int J Gynecol Cancer*. 1993;3:1-11.
72. Morice P, Rodriguez A, Rey A, et al. Prognostic value of initial surgical procedure for patients with uterine sarcoma: analysis of 123 patients. *Eur J Gynaecol Oncol*. 2003;24:237-240.

73. Sartori E, Bazzurini L, Gadducci A, et al. Carcinosarcoma of the uterus: a clinicopathological multicenter CTF study. *Gynecol Oncol*. 1997;67:70-75.
74. Vaccarello L, Curtin JP. Presentation and management of carcinosarcoma of the uterus. *Oncology (Williston Park)*. 1992;6:45-49; discussion 53-54, 59.
75. Amant F, Dreyer L, Makin J, et al. Uterine sarcomas in South African black women: A clinicopathologic study with ethnic considerations. *Eur J Gynaecol Oncol*. 2001;22:194-200.
76. Nordal RR, Thoresen SO. Uterine sarcomas in Norway 1956-1992: incidence, survival and mortality. *Eur J Cancer*. 1997;33:907-911.
77. Yamada SD, Burger RA, Brewster WR, et al. Pathologic variables and adjuvant therapy as predictors of recurrence and survival for patients with surgically evaluated carcinosarcoma of the uterus. *Cancer*. 2000;88:2782-2786.
78. Nemani D, Mitra N, Guo M, et al. Assessing the effects of lymphadenectomy and radiation therapy in patients with uterine carcinosarcoma: a SEER analysis. *Gynecol Oncol*. 2008;111:82-88.
79. Tanner EJ, Leitao MM Jr, Garg K, et al. The role of cytoreductive surgery for newly diagnosed advanced-stage uterine carcinosarcoma. *Gynecol Oncol*. 2011;123:548-552.
80. Cantrell LA, Havrilesky L, Moore DT, et al. A multi-institutional cohort study of adjuvant therapy in stage I-II uterine carcinosarcoma. *Gynecol Oncol.* 2012;127:22-26.
81. Sutton G, Brunetto VL, Kilgore L, et al. A phase III trial of ifosfamide with or without cisplatin in carcinosarcoma of the uterus: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2000;79:147-153.
82. Homesley HD, Filiaci V, Markman M, et al. Phase III trial of ifosfamide with or without paclitaxel in advanced uterine carcinosarcoma: a Gynecologic Oncology Group study. *J Clin Oncol*. 2007;25:526-531.
83. Galaal K, van der Heijden E, Godfrey K, et al. Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma. *Cochran Database Syst Rev*. 2013;2:CD006812.
84. D'Angelo E, Prat J. Uterine sarcoma. A review. *Gynecol Oncol*. 2010;116:131-139.
85. Kaku T, Silverberg SG, Major FJ, et al. Adenosarcoma of the uterus: a Gynecologic Oncology Group clinicopathologic study of 31 cases. *Int J Gynecol Pathol*. 1992;11:75-88.
86. Clement PB, Scully RE. Mullerian adenosarcoma of the uterus: A clinicopathologic analysis of 100 cases with a review of the literature. *Hum Pathol*. 1990;21:363-381.
87. Verschraegen CF, Vasuratna A, Edwards C, et al. Clinicopathologic analysis of mullerian adenosarcoma: the M.D. Anderson Cancer Center experience. *Oncol Rep*. 1998;5:939-944.
88. Meredith RF, Eisert DR, Kaka Z, et al. An excess of uterine sarcomas after pelvic irradiation. *Cancer*. 1986;58:2003-2007.
89. Leitao MM, Tornos C, Wolfson AH, et al. Corpus: mesenchymal tumors. In: Barakat RR, Berchuck A, Randall ME, eds. *Principles and Practice of Gynecologic Oncology*. 6th ed. Lippincott Williams & Wilkins; 2013:715-749.
90. Bergman L, Beelen ML, Gallee MP, et al. Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. Comprehensive Cancer Centres' ALERT Group. Assessment of Liver and Endometrial cancer Risk following Tamoxifen. *Lancet*. 2000;356:881-887.
91. Gonzalez-Bosquet E, Martinez-Palones JM, Gonzalez-Bosquet J, et al. Uterine sarcoma: a clinicopathological study of 93 cases. *Eur J Gynaecol Oncol*. 1997;18:192-195.
92. El Husseiny G, Al Bareedy N, Mourad WA, et al. Prognostic factors and treatment modalities in uterine sarcoma. *Am J Clin Oncol*. 2002;25:256-260.
93. Bell SW, Kempson RL, Hendrickson MR. Problematic uterine smooth muscle neoplasms. A clinicopathologic study of 213 cases. *Am J Surg Pathol*. 1994;18:535-558.
94. Ip PP, Cheung AN, Clement PB. Uterine smooth muscle tumors of uncertain malignant potential (STUMP): a clinicopathologic analysis of 16 cases. *Am J Surg Pathol*. 2009;33:992-1005.
95. Guntupalli SR, Ramirez PT, Anderson ML, et al. Uterine smooth muscle tumor of uncertain malignant potential: a retrospective analysis. *Gynecol Oncol*. 2009;113:324-326.
96. Goff BA, Rice LW, Fleischhacker D, et al. Uterine leiomyosarcoma and endometrial stromal sarcoma: lymph node metastases and sites of recurrence. *Gynecol Oncol*. 1993;50:105-109.
97. Iwasa Y, Haga H, Konishi I, et al. Prognostic factors in uterine carcinosarcoma: a clinicopathologic study of 25 patients. *Cancer*. 1998;82:512-519.
98. Larson B, Silfversward C, Nilsson B, et al. Endometrial stromal sarcoma of the uterus. A clinical and histopathological study. The Radiumhemmet series 1936-1981. *Eur J Obstet Gynecol Reprod Biol*. 1990;35:239-249.
99. Hata K, Hata T, Maruyama R, et al. Uterine sarcoma: can it be differentiated from uterine leiomyoma with Doppler ultrasonography? A preliminary report. *Ultrasound Obstet Gynecol*. 1997;9:101-104.
100. Rha SE, Byun JY, Jung SE, et al. CT and MRI of uterine sarcomas and their mimickers. *AJR Am J Roentgenol*. 2003;181:1369-1374.
101. Abeler VM, Royne O, Thoresen S, et al. Uterine sarcomas in Norway. A histopathological and prognostic survey of a total population from 1970 to 2000 including 419 patients. *Histopathology*. 2009;54:355-364.
102. D'Angelo E, Spagnoli LG, Prat J. Comparative clinicopathologic and immunohistochemical analysis of uterine sarcomas diagnosed using the World Health Organization classification system. *Hum Pathol*. 2009;40:1571-1585.
103. Seagle BL, Sobecki-Rausch J, Strohl AE, et al. Prognosis and treatment of uterine leiomyosarcoma: A National Cancer Database study. *Gynecol Oncol.* 2017;145(1):61.
104. Nasioudas D, Chapman-Davis E, Frey M, Holcomb K. Safety of ovarian preservation in premenopausal women with stage I uterine sarcoma. *J Gynecol Oncol.* 2017;28(4):e46.
105. Omura GA, Blessing JA, Major F, et al. A randomized clinical trial of adjuvant adriamycin in uterine sarcomas: a Gynecologic Oncology Group study. *J Clin Oncol*. 1985;3:1240-1245.
106. Hensley ML, Ishil N, Soslow R, et al. Adjuvant gemcitabine plus docetaxel for completely resected stage I-IV high grade uterine leiomyosarcoma: results of a prospective study. *Gynecol Oncol*. 2009;112:563-567.
107. Hensley ML, Wathen JK, Maki RG, et al. Adjuvant therapy for high-grade, uterus-limited leiomyosarcoma: results of a phase 2 trial (SARC 005). *Cancer*. 2013;119:1555-1561.
108. Omura GA, Major FJ, Blessing JA, et al. A randomized study of adriamycin with and without dimethyl triazenoimidazole carboxamide in advanced uterine sarcomas. *Cancer*. 1983;52:626-632.
109. Currie J, Blessing JA, Muss HB, et al. Combination chemotherapy with hydroxyurea, dacarbazine (DTIC), and etoposide in the treatment of uterine leiomyosarcoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 1996;61:27-30.
110. Sutton G, Blessing JA, Malfetano JH. Ifosfamide and doxorubicin in the treatment of advanced leiomyosarcomas of the uterus: a Gynecologic Oncology Group study. *Gynecol Oncol*. 1996;62:226-229.
111. Edmonson JH, Blessing JA, Cosin JA, et al. Phase II study of mitomycin, doxorubicin, and cisplatin in the treatment of advanced uterine leiomyosarcoma: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2002;85:507-510.
112. Tap WD, Jones RL, Van Tine BA, et al: Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: An open-label phase 1b and randomised phase 2 trial. *Lancet.* 2016;388:488-497.

113. Tap WD, Wagner AJ, Schöffski P, et al. Effect of doxorubicin plus olaratumab vs doxorubicin plus placebo on survival in patients with advanced soft tissue sarcomas: the ANNOUNCE randomized clinical trial. *JAMA.* 2020;323(13):1266-1276.
114. Demetri GD, von Mehren M, Jones RL, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: Results of a phase III randomized multicenter clinical trial. *J Clin Oncol.* 2016;34:786-793.
115. van der Graaf WT, Blay JY, Chawla SP, et al: Pazopanib for metastatic soft-tissue sarcoma (PALETTE): A randomised, double-blind, placebocontrolled phase 3 trial. *Lancet.* 2012;379:1879-1886.
116. Dionigi A, Oliva E, Clement PB, et al. Endometrial stromal nodules and endometrial stromal tumors with limited infiltration: a clinicopathologic study of 50 cases. *Am J Surg Pathol*. 2002;26:567-581.
117. Chang KL, Crabtree GS, Lim-Tan SK, et al. Primary uterine endometrial stromal neoplasms. A clinicopathologic study of 117 cases. *Am J Surg Pathol*. 1990;14:415-438.
118. Thomas MB, Keeney GL, Podratz KC, et al. Endometrial stromal sarcoma: treatment and patterns of recurrence. *Int J Gynecol Cancer*. 2009;19:253-256.
119. Chan JK, Kawar NM, Shin JY, et al. Endometrial stromal sarcoma: a population-based analysis. *Br J Cancer*. 2008;99:1210-1215.
120. Haberal A, Kayikcioglu F, Boran N, et al. Endometrial stromal sarcoma of the uterus: analysis of 25 patients. *Eur J Obstet Gynecol Reprod Biol*. 2003;109:209-213.
121. Nordal RR, Kristensen GB, Kaern J, et al. The prognostic significance of surgery, tumor size, malignancy grade, menopausal status, and DNA ploidy in endometrial stromal sarcoma. *Gynecol Oncol*. 1996;62:254-259.
122. Gadducci A, Sartori E, Landoni F, et al. Endometrial stromal sarcoma: analysis of treatment failures and survival. *Gynecol Oncol*. 1996;63:247-253.
123. Evans HL. Endometrial stromal sarcoma and poorly differentiated endometrial sarcoma. *Cancer*. 1982;50:2170-2182.
124. Chu MC, Mor G, Lim C, et al. Low-grade endometrial stromal sarcoma: hormonal aspects. *Gynecol Oncol*. 2003;90:170-176.
125. Li AJ, Giuntoli RL 2nd, Drake R, et al. Ovarian preservation in stage I low-grade endometrial stromal sarcomas. *Obstet Gynecol*. 2005;106:1304-1308.
126. Shah JP, Bryant CS, Kumar S, et al. Lymphadenectomy and ovarian preservation in low-grade endometrial stromal sarcoma. *Obstet Gynecol*. 2008;112:1102-1108.
127. Spano JP, Soria JC, Kambouchner M, et al. Long-term survival of patients given hormonal therapy for metastatic endometrial stromal sarcoma. *Med Oncol*. 2003;20:87-93.
128. Pink D, Lindner T, Mrozek A, et al. Harm or benefit of hormonal treatment in metastatic low-grade endometrial stromal sarcoma: single center experience with 10 cases and review of the literature. *Gynecol Oncol*. 2006;101:464-469.
129. Missing reference
130. Deshmukh U, Black J, Perez-Irizarry J, et al.: Adjuvant hormonal therapy for low-grade endometrial stromal sarcoma. *Reprod Sci.* 2019;26(5):600-608.
131. Pautier P, Genestie C, Fizazi K, et al. Cisplatin-based chemotherapy regimen (DECAV) for uterine sarcomas. *Int J Gynecol Cancer*. 2002;12:749-754.
132. Li N, Wu LY, Zhang HT, et al. Treatment options in stage I endometrial stromal sarcoma: a retrospective analysis of 53 cases. *Gynecol Oncol*. 2008;108:306-311.
133. Zaloudek C, Hendrickson MR. *Mesenchymal Tumor of the Uterus*, 5th ed. New York, NY: Springer-Verlag; 2002.
134. Berchuck A, Rubin SC, Hoskins WJ, et al. Treatment of endometrial stromal tumors. *Gynecol Oncol*. 1990;36:60-65.
135. August CZ, Bauer KD, Lurain J, et al. Neoplasms of endometrial stroma: histopathologic and flow cytometric analysis with clinical correlation. *Hum Pathol*. 1989;20:232-237.
136. Tanner EJ, Garg K, Leitao MM Jr, et al. High grade undifferentiated uterine sarcoma: surgery, treatment, and survival outcomes. *Gynecol Oncol*. 2012;127:27-31.
137. Fehmian C, Jones J, Kress Y, et al. Adenosarcoma of the uterus with extensive smooth muscle differentiation: Ultrastructural study and review of the literature. *Ultrastruct Pathol*. 1997;21:73-79.
138. Carroll A, Ramirez PT, Westin SN, Soliman PT, Munsell MF, Nick AM, Schmeler KM, Klopp AH, Fleming ND. Uterine adenosarcoma: an analysis on management, outcomes, and risk factors for recurrence. *Gynecol Oncol.* 2014;135(3):455-461.
139. Moinfar F, Azodi M, Tavassoli FA. Uterine sarcomas. *Pathology*. 2007;39:55-71.
140. Seidman JD, Wasserman CS, Aye LM, et al. Cluster of uterine mullerian adenosarcoma in the Washington, DC metropolitan area with high incidence of sarcomatous overgrowth. *Am J Surg Pathol*. 1999;23:809-814.
141. Krivak TC, Seidman JD, McBroom JW, et al. Uterine adenosarcoma with sarcomatous overgrowth versus uterine carcinosarcoma: comparison of treatment and survival. *Gynecol Oncol*. 2001;83:89-94.

This page intentionally left blank

41 Tumors of the Uterine Cervix

Gloria Salvo
Mila P. Salcedo
Sol Basabe
Pedro T. Ramirez

KEY CONCEPTS

- Cancer of the cervix is the third most common gynecologic malignancy in the United States. The American Cancer Society estimated that there would be a total of 13,800 new cases of invasive cervical cancer and 4290 deaths in 2020.
- The nonavalent vaccine (Gardasil-9), which targets HPV-6, -11, -16, -18, -31, -33, -45, -52, and -58, is recommended to both boys and girls between the ages of 11 and 12 years old. A two-dose schedule with a 6- 12-month interval between doses is recommended if given before age 15 years. For people older than 15 years old or immunocompromised, three doses are required (0, 1–2, and 6 months).
- The 2018 revised International Federation of Gynecology and Obstetrics (FIGO) staging system main changes from the previous 2009 are the allowance of images and pathology, when available to allocate the stage. For stage IA only, depth of invasion (≤3 mm and >3 mm and ≤5 mm) is now considered to allocate a tumor as IA1 or IA2, respectively, because horizontal extent is no longer contemplated. Stage IB tumors are now divided according to their greatest dimension into IB1 (≤2 cm), IB2 (>2 cm and ≤4 cm), and IB3 (>4 cm). Nodal compromise is now considered part of the staging system. Positive pelvic nodes are now allocating as IIIC1 and positive paraaortic nodes are considered stage IIIC2.
- Radical hysterectomy with pelvic lymphadenectomy is the standard treatment for early-stage cervical cancer (FIGO 2018 IA2-IB2). After the results of a prospective randomized trial showing that minimally invasive surgery was associated with higher rates of locoregional recurrences (hazard ratio [HR], 4.26; 95% confidence interval [CI], 1.44-12.6; $P = .009$) and higher risk of death (HR: 6.00; 95% CI,1.77–20.3; $P = .004$], minimally invasive surgery is no longer recommended.
- First-line therapy recommended for recurrent of metastatic disease is cisplatin, paclitaxel, and bevacizumab. The Gynecologic Oncology Group 240 randomized trial showed that the addition of bevacizumab resulted in a significant improvement in overall survival compared with chemotherapy alone (median, 16.8 vs 13.3 months, respectively; HR, 0.77; 98% CI, 0.62–0.95).
- Pembrolizumab is the preferred regimen for second-line therapy in patients with recurrent or metastatic disease who are tumor programmed death-ligand 1 with an overall response rate as showed by the KEYNOTE-028 trial of 17% and duration of response was 5.4 months.

Cervical cancer is the third most common gynecologic malignancy in the United States. In 2020, the American Cancer Society estimated that there would be a total of 13,800 new cases of invasive cervical cancer and 4290 related deaths.[1] Persistent human papillomavirus (HPV) infection is the most important factor in the development of cervical cancer.[2] The incidence of this disease has decreased steadily over the past several decades because of screening tests and vaccination. Squamous cell carcinoma (SCC) and adenocarcinoma are the most common histologic subtypes.

The median age of diagnosis of cervical cancer is 50 years of age, and it is more frequently diagnosed among women age 35 to 44 years old. Cervical cancer is staged using the International Federation of Gynecology and Obstetrics (FIGO) staging system. Principal routes of spread include direct extension (uterine corpus, vagina, parametrium, bladder, or rectum), lymphatic, or hematogenous dissemination. Lymphatic metastasis is to the pelvic (obturator, external iliac, internal iliac, common iliac) or paraaortic lymph nodes (or both), and the most common sites of hematogenous spread are the lungs, liver,

and bones. In the United States, most cervical cancers are diagnosed in early stage (44%), followed by locally advanced (36%), and 15% at advanced disease[3] with 5-year survival rates of 92%, 56%, 17%, respectively.[3]

This chapter aims to describe pathogenesis of the disease, preinvasive lesions, diagnosis, and treatment in the upfront and recurrent settings.

ETIOLOGY

Risk factors associated with cervical cancer include HPV infection, immunosuppression, smoking, multiparity, increased number of sexual partners, and oral contraceptive use.[4]

Human Papillomavirus

HPV is the critical factor for the development of preinvasive and invasive cervical lesions. HPV is a small, nonenveloped, double-stranded DNA virus predominantly transmitted through sexual intercourse.[5,6]

More than 40 HPV genotypes infect the anogenital tract and other mucosal areas of the body.[7] The HPV types are further classified into low-risk or high-risk HPV depending on their oncogenic potential for cervical cancer and its precursors. Low-risk HPV genotypes include HPV-6 and -11 and usually cause benign anogenital warts.[8] Invasive lesions are much more commonly caused by high-risk HPV, including types 16, 18, 31, 45, 52, and 33.[9] Although the majority (~70%) of premalignant and invasive disease can be directly attributed to types 16 or 18, HPV DNA from any genotype is detectable in more than 99% of all cervical cancer specimens.[9,10]

In most cases, the transformed cells by the virus are managed by the individual's immune system, and the infection clears or preinvasive disease regresses. In some women, the transformed cells replicate, and if left untreated after several years, cervical cancer can develop. It is clear that women who have compromised immune systems (eg, genetic, iatrogenic, infectious, or any other cause) have a greater risk of developing a persistent HPV infection[11]; however, there is no way to predict which healthy women are unable to clear the virus spontaneously.

Other Risk Factors

Many studies have reported an increased risk of HPV infection and preinvasive and invasive cervical cancer in women who are immunocompromised, such as those with human immunodeficiency virus (HIV) infection.[12] It was found that rare high-risk HPV types are more common in cervical dysplasia of HIV-infected women, but most cases have multiple infections.[13]

Tobacco use is a well-established risk factor for cervical cancer. Cigarette smoking confers a 1.5- to 2.5-fold increase in cervix cancers. Overall, tobacco smoking is estimated to account for 21% of general cancer deaths worldwide.[14]

The number of sexual partners is an important risk factor for both preinvasive and invasive cervical cancer.[15] A collaborative study found a threefold increased relative risk of cervical cancer in women who have had six or more sexual partners, probably related to a higher risk of acquiring HPV infection.[16]

Many studies have produced controversial results on the effect of oral contraception on cervical cancer risk. The relative risk of cervical cancer is increased in current users of oral contraceptives, and it seems to decline after use ceases.[4,16]

HISTOPATHOLOGY

Squamous Cell Tumors and Precursors

Squamous Intraepithelial Lesions

Cervical SCCs are believed to develop from precursor or preinvasive lesions, which have been classified in a variety of ways but are generally based on how much of the epithelial layer contains atypical cells. The oldest system is the dysplasia–carcinoma in situ (CIS) system, with mild dysplasia, moderate dysplasia, and severe dysplasia or CIS. Another is the cervical intraepithelial neoplasia (CIN) classification, with mild dysplasia termed CIN1, moderate dysplasia termed CIN2, and CIN3 corresponding to both severe dysplasia and CIS. The Bethesda System for reporting cervical and vaginal cytologic abnormalities categorizes squamous abnormalities as follows: low-grade squamous intraepithelial lesion (LSIL), encompassing HPV infection and CIN1, and high-grade squamous intraepithelial lesion (HSIL), encompassing CIN2 and CIN3; and SCC.[17]

Invasive Cervical Cancer

Cervical cancer is classified mainly by its histologic origin, meaning from which type of cell is originated. The cervix has two different types of epithelium, the exo- and endocervix. Both epitheliums converge in what is called the transformation zone, the site where cervical cancer often develops. The principal types of cervical cancers are SCC (75%) and adenocarcinomas (25%). Other less frequent histology, such as neuroendocrine, adenoid cystic carcinoma, and carcinoid, account for 5% of all cervical cancers (Table 41–1). SCC develops from the cells of the exocervix and often begins in the transformation zone. On the other hand, adenocarcinomas develop from the glandular cells (mucus-producing cells) located in the endocervix. Less commonly, cervical cancers have features of both cell origins; these are called adenosquamous carcinomas.

TABLE 41–1 Histopathology

Classification	Subclassification
Squamous cell carcinoma	Large cell, keratinizing squamous cell carcinoma Large cell, nonkeratinizing squamous cell carcinoma Verrucous carcinoma Papillary squamous and transitional cell carcinoma Lymphoepithelioma-like carcinoma
Adenocarcinoma	Mucinous, endocervical variant Mucinous, intestinal type, signet ring variant Mucinous, adenoma malignum (minimal deviation variant) Mucinous, villoglandular adenocarcinoma (well differentiated) Endometrioid type Clear cell type Papillary serous type Mesonephric type
Adenosquamous carcinoma	
Adenoid cystic carcinoma	
Neuroendocrine	High-grade neuroendocrine (small and large cell) Low-grade neuroendocrine (carcinoid)
Undifferentiated carcinoma	
Mixed epithelial and mesenchymal tumors	

CERVICAL CANCER PREVENTION

Primary Prevention: Human Papillomavirus Vaccination

Three types of HPV preventive vaccines are currently commercially available worldwide. The bivalent vaccine (Cervarix) targets two types of high-risk HPV (HPV-16 and -18), which account for 70% of cervical cancer cases worldwide and is no longer available in the United States. The quadrivalent vaccine (Gardasil) targets HPV types 16 and 18 (high-risk HPV), as well as 6 and 11 (low-risk HPV), which usually cause genital warts. Currently in the United States, only the nonavalent vaccine (Gardasil-9) is available and targets HPV types 6, 11, 16, and 18 as the quadrivalent vaccine, as well as types 31, 33, 45, 52, and 58.[18–20] All three vaccines are most effective if given before first sexual intercourse and exposure to HPV. The vaccines have been shown in randomized clinical trials to have 93% to 98% efficacy in the prevention of cervical dysplasia (and presumably cervical cancer) in women not previously infected with HPV-16 and -18.[18–22]

The Centers for Disease Control and Prevention (CDC) recommends that the HPV vaccine be given to both boys and girls between the ages of 11 and 12 years of age, but it can be administered as early as 9 years of age.[23] A two-dose schedule with a 6- to 12-month interval between doses is recommended if given before age 15 years. For those who are 15 years or older or immunocompromised, three doses are required (0, 1–2, and 6 months).[23] Catch-up vaccination, given after the recommended age, should be offered to women and men aged 13 to 26 years who have not been previously vaccinated.[24] In 2018, the U.S. Food and Drug Administration approved the use of Gardasil-9 up to 45 years old for both men and women.[25] However, the Advisory Committee on Immunization Practices and CDC stated that vaccination between the ages of 27 and 45 years is not recommended for everyone and should be considered on a case-by-case basis.[4] The duration of immunity is not yet known, and it is not known whether a booster dose will be required. Routine cervical cancer screening is still recommended in vaccinated women.

Drolet et al[26] published a meta-analysis including data from more than 60 million individuals, demonstrating the impact of HPV vaccination to reduce HPV infections, anogenital warts, and CIN2 and higher lesions. In approximately 5 to 8 years after vaccination, the prevalence of HPV-16 and -18 decreases more than 80% in girls aged 13 to 19 years and approximately 66% among women aged 20 to 24 years. The reductions in anogenital warts were 67% among girls 15 to 19 years, 54% in young women (20–24 years), 48% in boys (15–19 years), and 32% in young adult men (20–24 years). After 5 to 9 years of vaccination, there was also a reduction of more than 50% in CIN2+ among girls aged 15 to 19 years and 31% among young women aged 20 to 24 years.[26]

Secondary Prevention

Cervical Cytology

Cervical cytology (Pap test) became available in the 1950s. It is known that cervical cytology has a low sensitivity; however, a widespread Pap testing has reduced the incidence of cervical cancer by 50% to 70%. This is partly because it takes many years for invasive cancer to develop after a persistent HPV infection and the development of dysplasia and because most women are tested repeatedly.[27]

Primary Human Papillomavirus Testing

There is evidence that HPV testing is effective for cervical cancer screening. HPV testing is more sensitive than cervical cytology.[28–30] Cervical cytology is still the most used screening test in developed countries; however, co-testing with HPV is now also recommended. HPV DNA testing has been recommended in countries or regions of the world in any level of resources available.[31] A large, randomized study in Canada including 19,009 women screened for cervical cancer with HPV testing versus liquid-based cytology concluded that HPV primary testing had significantly lower likelihood of CIN3+ at 48 months than liquid-based cytology.[32]

Guidelines for screening by the American Society of Colposcopy and Cervical Pathology (ASCCP) include[1]

- Screening for cervical cancer is recommended between the ages of 21 and 65 years.
- Cervical cancer screening should begin at age 21 years regardless of the age of onset of sexual activity.
- 21 to 29 years: cervical cytology every 3 years; no HPV testing
- 30 to 65 years: co-testing with cervical cytology and HPV every 5 years (preferred) or cervical cytology testing alone every 3 years
- Screening is NOT recommended for women older than 65 years of age who have had three consecutives negative cytology test results or two consecutives negative co-tests within 10 years before stopping screening (most recent test within past 5 years), provided they have no history of high-grade dysplasia (CIN2/3) or cancer (CIN2+) in the past 20 years. However, women presenting at age 65 years of age or older who have not had previous screening should undergo cervical cytology and HPV testing.
- Screening with cervical cytology or HPV testing is not recommended for women who have had a hysterectomy with removal of the cervix and who do not have a history of CIN2+.

The Bethesda System was developed in 1988 and last updated in 2001 and is now used widely.[17] The Bethesda System first states whether the sample is satisfactory or unsatisfactory, meaning that the sample is appropriate for diagnosis. The report next indicates whether the cellular material is normal. If other than normal, the abnormalities are further divided into squamous and glandular. The cytologist may also comment on whether there is evidence of infection (Table 41–2).

TABLE 41–2 The Bethesda System

Specimen adequacy	Satisfactory for evaluation Unsatisfactory for evaluation
General categorization (*optional*)	Negative for intraepithelial lesion or malignancy Epithelial cell abnormality Other
Interpretation or result	**Negative for intraepithelial lesion or malignancy** Organisms Other non-neoplastic findings (optional to report; list not comprehensive) Reactive cellular changes associated with (descriptive findings) Glandular cells status post hysterectomy Atrophy
	Epithelial cell abnormalities Squamous cell Atypical squamous cells (ASC) of undetermined significance (ASC-US) cannot exclude HSIL (ASC-H) Low-grade squamous intraepithelial lesion (LSIL) High-grade squamous intraepithelial lesion (HSIL) Squamous cell carcinoma Glandular cell Atypical glandular cells (AGCs; specific endocervical, endometrial, or not otherwise specified) AGCs, favor neoplastic (specific endocervical, or not otherwise specified) Endocervical adenocarcinoma in situ Adenocarcinoma **Other** (list not comprehensive) Endometrial cells in a woman 40 years of age or older

Data from Solomon D, Davey D, Kurman R, et al: The 2001 Bethesda System: terminology for reporting results of cervical cytology, *JAMA*. 2002 Apr 24;287(16):2114-2119.

TREATMENT OF PREINVASIVE DISEASE

Management of Patients with Abnormal Cervical Screening Test Results

The current consensus guidelines from the ASCCP for the management of patients with abnormal cervical cancer screening test results (primary HPV screening, co-testing with HPV testing and cervical cytology, and cervical cytology alone) and treatment of cervical dysplasia in women 25 years or older are summarized next.[33,34]

In the recently published guidelines, the recommendations are based on risk of CIN3+ (CIN3, adenocarcinoma in situ [AIS], or cancer) determined by current tests results combined with patient's past history (Fig. 41–1). It has aligned the understanding of HPV natural history and cervical carcinogenesis based on the principle that persistent HPV infection is necessary for developing precancer or invasive cancer. The duration of the HPV infection and the HPV type are important for risk stratification. Thus, a negative HPV test result immediately preceding a low-grade abnormal co-test result reduces the estimated risk of CIN3+.[34]

If primary HPV screening is used and the results are positive for HPV, it is recommended to perform both a reflex HPV genotyping test, if not previously done, and a reflex cytology test. (Laboratories should perform a specific additional triage test in the setting of a positive screening test result.) If this is not feasible, referral for colposcopy is acceptable. If positive HPV-16 or -18 and negative cytology (negative for intraepithelial lesion or malignancy, NILM) is documented, a colposcopy is recommended.[34]

If minimally abnormal screening results (HPV-positive and -negative cytology, HPV-negative and LSIL with unknown previous screening history) are found, the recommendation is for surveillance with close follow up at 1 year.[34]

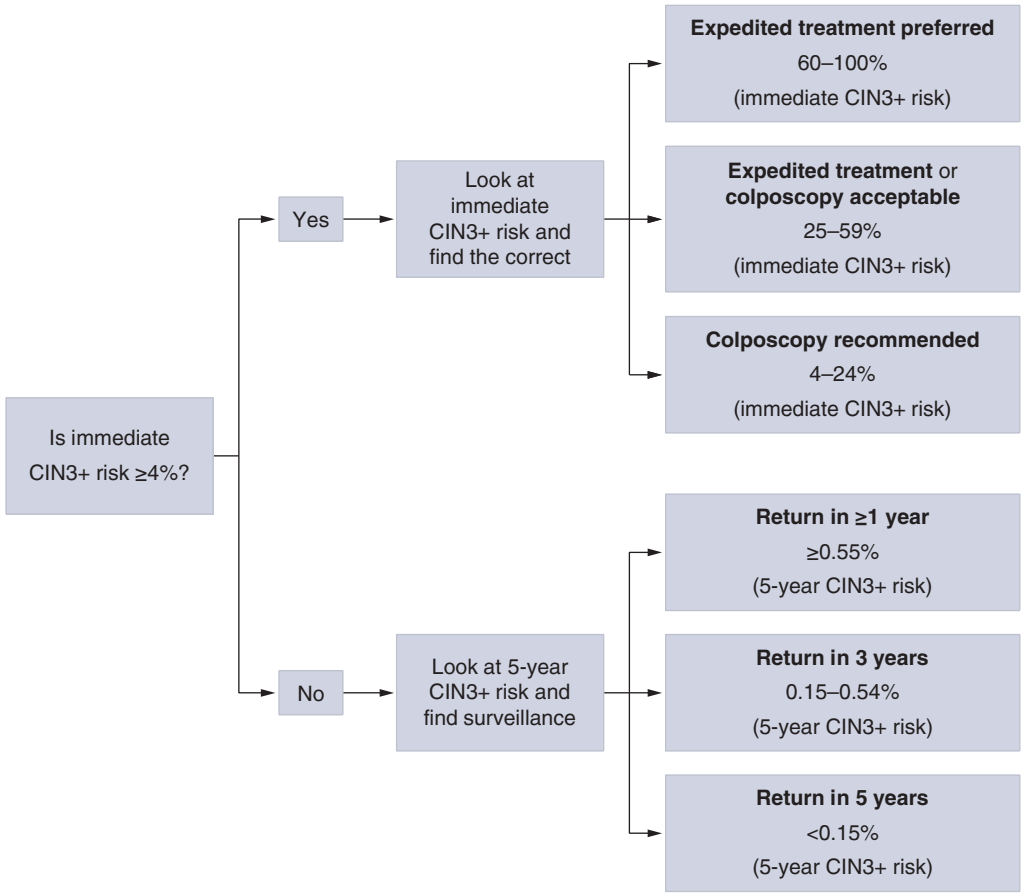


FIGURE 41–1 **Algorithm for management based on calculated risk, for given current results and history combination, the immediate cervical intraepithelial neoplasia (CIN) 3+ risk is examined. If this risk is 4% or greater, immediate management via colposcopy or treatment is indicated. If the immediate risk is less than 4%, the 5-year CIN3+ risk is examined to determine whether patients should return in 1, ,3 or 5 years. (Reproduced with permission from Perkins RB, Guido RS, Castle PE, et al: 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors, *J Low Genit Tract Dis.* 2020 Apr;24(2):102-131.)**

Atypical Squamous Cells

Treatment depends on the subcategory based on the HPV test and cervical cytology: atypical squamous cells of undetermined significance (ASC-US) or cannot exclude a higher grade lesion (ASC-H).

1. ASC-US: ASCs of undetermined significance are the most common cytologic abnormalities.[35] Women with HPV-positive ASC-US cytology in their initial screening should undergo colposcopy because their immediate risk of CIN3+ is approximately 4.5%. Women with HPV-negative ASC-US cytology screening in the setting of an unknown history can be reevaluated at 3 years (estimated 5-year CIN3+ risk, 0.40%).[33,34]
2. ASC-H: Approximately 5% to 10% of ASC cases are classified at ASC-H.[35] For women with ASC-H cytology, colposcopy is recommended regardless of HPV result.[34]

Low-Grade Squamous Intraepithelial Lesion

LSIL has a greater likelihood of resolving spontaneously; however, in some cases, it might progress to more severe dysplasia.[35] Schlecht and colleagues[36] analyzed 118 women with LSIL who were followed for approximately 53 months; 88.1% regressed to a lower grade (ASC-US or negative cytology), and half of these abnormalities regressed within 6 months.

Colposcopy is recommended after an HPV-positive LSIL screening results in the general population with unknown previous screening history. Follow-up in 1 year is recommended if HPV-negative and LSIL cytology is documented with unknown previous screening history. A 1-year follow-up period is also recommended in a patient with a new positive HPV test result and LSIL cytology after a documented negative HPV test or co-test within an appropriate screening interval or colposcopic examination less than CIN2 within the previous year. Surveillance is recommended rather than immediate colposcopy for low-grade abnormalities (HPV-positive ASC-US or LSIL) if a patient has at least one previous negative HPV-based test result.[34]

Regarding long-term follow-up after a low-grade cytology (HPV-positive and -negative for intraepithelial lesion or malignancy cytology, ASC-US, or LSIL) without evidence of cytologic or histologic HSIL, continued surveillance according to risk estimation using available data is recommended.

High-Grade Squamous Intraepithelial Lesion

A diagnosis of HSIL indicates CIN2/3 or more severe dysplasia.[35] Women with HSIL cytology undergoing expedited treatment (without biopsy confirmation) are diagnosed with CIN3+ in 49% to 75% of cases.[34] Expedited treatment is preferred, but colposcopy with biopsy is acceptable in nonpregnant patients 25 years or older when the risk of CIN3+ is 60% or higher. If HSIL cytology and HPV-16 positive are presented, the immediate CIN3+ risk is 60%, and cancer risk is 8.1%. thus, expedited treatment is preferred.[34]

Atypical Glandular Cells and Adenocarcinoma in Situ

Although uncommonly diagnosed, atypical glandular cells (AGCs) and AIS carries an underlying risk of CIN2+ of approximately 9% and of invasive cancer in approximately 2% to 3%. Cytologic AGCs is associated with a histologic diagnosis of AIS in 3% to 4%.[34,35,37] The recommendation is for colposcopy with endocervical sampling except in pregnancy. Endometrial sampling should also be performed in women who are older than 35 years or at risk for endometrial cancer (abnormal uterine bleeding, obesity, conditions suggesting chronic anovulation). For women presenting atypical endometrial cells specified, initial evaluation with endometrial and endocervical sampling is preferred, with colposcopy acceptable at initial evaluation.[34]

Treatment of Cervical Intraepithelial Neoplasia

The consensus recommendation is to qualify histologic HSIL using the CIN nomenclature, specifying CIN2 or CIN3, when it is possible. Treatment is preferred to observation if histologic HSIL cannot be specified when it is reported as histologic HSIL only or CIN2/3 (not specified). Excisional therapy consists of loop electrosurgical excision procedure (LEEP or large loop excision of the transformation zone), cold knife conization, and laser cone biopsy. Ablation treatment includes cryotherapy, laser ablation, and thermal ablation. The choice of treatment modality depends on the availability of equipment and experience and expertise of the clinician. Hysterectomy is unacceptable as primary therapy solely for the treatment of patients with histologic HSIL.[34]

Expedited treatment (treatment without preceding colposcopic biopsy) is preferred for nonpregnant patients who are 25 years or older with HSIL cytology and concurrent positive testing for HPV-16 and for those never or rarely screened patients with HPV-positive HSIL cytology regardless of HPV genotype. Shared decision making for expedited treatment should be used, especially for patients with concerns about the potential impact of treatment on pregnancy outcomes.[34]

Cervical Intraepithelial Neoplasia Grade 1

CIN1 is a histologic expression of HPV infection. Histologic LSIL (CIN1) and cytologic ASC-US/HPV-positive

and cytology showing LSIL are biologically the same and should be managed similarly.

When CIN1 or no lesion are found on histology (colposcopy with biopsy) after HPV-positive and cytology with ASC-US or LSIL, there is a 5-year risk of CIN3+ of approximately 2%. One-year surveillance is recommended after colposcopy with biopsies of histologic LSIL (CIN1) or less, preceded by a low-grade co-test result (HPV-positive and LSIL cytology, HPV-positive and ASC-US cytology, or repeated HPV-positive and negative for intraepithelial lesion or malignancy cytology).[34]

Observation is preferred to treatment for histologic CIN1. For women 25 years or older, if histologic LSIL (CIN1) persists for more than 2 years, observation is preferred but treatment is acceptable. If treatment is selected and the entire squamocolumnar junction and all lesions are fully visualized on colposcopy, either excision or ablation treatments are acceptable. Treatment of CIN1 in less than 2-year follow-up is an acceptable option based on patient preference, after shared decision making, but it is considered a special situation because the immediate estimated CIN3+ risk is less than 25%.[34]

The 1-year risk of CIN3+ of a woman with a diagnosis of histologic LSIL (CIN1) after ASC-H cytology is 1.4% and after HSIL cytology is 3.9%. When CIN1 is preceded by ASC-H, observation in 1 year with HPV-based testing is recommended if the colposcopic examination can visualize the entire squamocolumnar junction and the upper limit of lesions and the endocervical sampling, if collected, is negative. When CIN1 is preceded by HSIL, it is acceptable to review the cytologic, histologic, and colposcopic findings. If the review changes the diagnosis, the guidelines should be followed for management. If cytology shows HSIL and biopsy shows histology CIN1 or less, either a diagnostic excisional procedure or observation with HPV-based testing and colposcopy in 1 year is acceptable (only if colposcopy visualized the entire squamocolumnar junction and upper limit of lesions and endocervical sampling is less than CIN2).[34]

Cervical Intraepithelial Neoplasia Grades 2 and 3

Approximately 40% of CIN2 lesions and 30% of CIN3 lesions regress spontaneously.[28] Approximately 22% of CIN2 lesions progress to CIN3, and 5% progress to cancer. Furthermore, approximately 15% of CIN3 lesions progress to cancer.[35,37] Because CIN3 is considered an immediate cancer precursor, treatment is recommended in women presenting with HSIL (CIN3), and observation is unacceptable.[34] Treatment is recommended in women presenting with HSIL (CIN2) unless the patient's concerns about the effect of treatment on future pregnancy outweigh concerns about cancer; then either treatment or observation is acceptable. If observation is the management option, then it should include colposcopy and HPV-based testing every 6 months for up to 2 years. Observation is unacceptable if the entire squamocolumnar junction or the upper limit of lesions is not visualized or when the results of an endocervical sampling, if performed, is CIN2+ or higher.[34]

Regarding treatment for HSIL histology (CIN2 or CIN3), the excisional treatment is preferred to ablative. After treatment, HPV-based testing at 6 months is preferred. If HPV-based tests are positive, colposcopy and appropriate biopsies should be performed. Follow-up at 6 months with colposcopy and endocervical curettage is acceptable. After this, annual HPV or co-testing is preferred until three consecutive negative test results have been obtained. Long-term follow-up with HPV testing or co-testing for at least 25 years is recommended in patients treated for histologic or cytologic HSIL even if this extends screening past age 65 years.[34]

Of note, these guidelines do not apply to rare abnormalities or special populations such as women younger than 25 years and pregnant women, with additional risk factors or other complicating history. After immediate treatment, surveillance and the next steps in the management should follow ASCCP guidelines.

Adenocarcinoma in Situ

An initial diagnostic conization excisional procedure to rule out invasive adenocarcinoma is recommended if a histologic AIS is presented in a cervical biopsy. If the margins of the specimen are involved or endocervical sampling obtained above the conization bed is positive, re-excision to increase the likelihood of complete excision is preferred even if hysterectomy is planned. After the initial management, hysterectomy is preferred. Fertility-sparing management for appropriately selected patients is acceptable. Long-term follow-up is recommended for women who do not undergo hysterectomy.[34]

The new Society of Gynecologic Oncology (SGO) guidelines recommend that simple hysterectomy is preferred for patients with confirmed diagnosis of AIS with negative margins on the conization specimen. Either modified radical hysterectomy or simple hysterectomy is acceptable for patients with confirmed diagnosis of AIS with positive margins on the conization specimen. Surgical assessment of lymph nodes is acceptable at the time of hysterectomy but not required and should be guided by the surgeon's risk assessment, which may include factors such as margin status of the preceding excisional specimen or postexcisional endocervical sampling results, pathologist concern for malignancy, HPV results (HPV-16– or -18–positive vs other high-risk HPV type), and patient risk factors.[38]

INVASIVE CERVICAL CANCER

Clinical Presentation

Patients with early-stage disease are frequently asymptomatic; their lesions may be discovered incidentally after an abnormal Pap smear. In patients with gross lesions, the most common presenting symptom is abnormal vaginal bleeding or postcoital bleeding. Other symptoms such as malodorous vaginal caused by tumor necrosis with superimposed infection by anaerobic organisms can be present. In more advanced disease, leg swelling caused by compression of the venous or lymphatic system, lower back pain caused by nerve compression or bone involvement, and or bowel symptoms caused by cancer invasion may be present. If the tumor protrudes into the vagina, bladder, or rectum, vaginal passage of urine or stool can occur.

Diagnosis and Staging

Pelvic Examination

Pelvic examination including visualizing the cervix using a speculum may reveal a normal cervix or a cervical lesion. Any abnormal finding in the cervix should undergo a biopsy even with a normal Pap smear. Visible lesions may appear as an exophytic tumor, a superficial ulceration, or a lesion extending from the endocervix. A rectovaginal examination gives an estimate of tumor size and vaginal and parametrial compromise.

Biopsy

Histologic evaluation of a cervical biopsy to confirm invasive cervical carcinoma is mandatory. If there is a visible lesion, the biopsy should be from the most suspicious zone, avoiding necrotic areas that are often nondiagnostic. In women with no visible lesion but who are symptomatic or with abnormal Pap smear, a colposcopy and directed biopsy is indicated. Cervical conization and LEEP are diagnostic tools in patients with suspected malignancy not found on a biopsy or inadequate colposcopy, patients with high-grade cervical neoplasia, patients with moderate to severe dysplasia in an endometrial curettage, and in microinvasive disease for treatment decision making.

Staging

Cervical carcinomas are staged using the FIGO staging system. Tumor stage is allocated at the time of diagnosis and is not altered, even upon recurrence. The 2018 revised FIGO staging system allows images and pathology, when available, to allocate the stage.[39–41] In the previous staging system, cervical cancer was only staged clinically. Other changes mostly embrace early-stage disease. Horizontal extent is no longer considered for stage IA1 and IA2, and only depth of invasion is now considered. Stage IB is now divided into IB1 (tumors ≤2 cm), IB2 (tumors >2 to ≤4 cm), and IB3 (tumors >4 cm) rather than IB1 and IB2 as was previously based on tumor size 4 or smaller and larger than 4 cm. Nodal compromise, although known to be a mayor prognostic factor, did not change the stage in the previous system. In the FIGO 2018 classification, positive pelvic nodes allocate tumors into stage IIIC1 and positive paraaortic nodes in stage IIIC2. Sentinel lymph nodes (SLNs) with macro- or micrometastasis are considered as IIIC tumors (Table 41–3).

Images

Image studies such as pelvic ultrasound (vaginal or transrectal), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET)–CT play an important role in the pretreatment evaluation of patients with cervical cancer because they have shown to be more accurate than pelvic examination in determining tumor size, location of the tumor within the cervix, lymph node compromise, and vaginal and parametrial invasion.[42,43]

MRI is significantly more accurate in measuring tumor size and delineating cervical tumor boundaries and local tumor extension compared with CT scan because of its distinctive tissue contrast and multiplanar capability.[44,45] It is also indicated in the pretreatment evaluation of young women with small-volume disease who wish to preserve fertility.

Several studies have found that the accuracy of pelvic ultrasound, when performed by expert radiologists, is comparable to that of MRI with the advantages of being low cost and widely available.[43] CT is able to identify extrauterine spread of disease, including enlarged pelvic and paraaortic lymph nodes, extension to the pelvic sidewalls and hydronephrosis, bladder rectum compromise, and the presence of distant metastases. PET-CT is useful in the detection of lymph node metastases, with sensitivities of 75% to 100% and specificities of 87% to 100%, demonstrating abnormal tracer uptake even in normal-size nodes.[46] PET-CT (preferred) or chest, abdomen, and pelvic CT scan should be performed in patients with tumors stage IB1 or greater and when an invasive tumor is an incidental finding on a simple hysterectomy specimen.

Tumor Markers

Squamous cell carcinoma antigen (SCC-Ag) is the most commonly used serum marker in patients with cervical cancer. Recent studies have shown that the abnormal cut-off value used for serum SCC-Ag is 1.5 ng/mL.[47,48] However, different cut-off values are used for

TABLE 41–3 Revised 2018 International Federation of Gynecology and Obstetrics Staging System for Cervical Cancer

Stage	Subclassification
Stage I: the carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded)	**IA:** invasive carcinoma that can be diagnosed only by microscopy with maximum depth of invasion ≤5 mm[a] **IA1:** measured stromal invasion ≤3 mm in depth **IA2:** measured stromal invasion >3 mm and ≤5 mm in depth **IB:** invasive carcinoma with measured deepest invasion >5 mm (greater than stage IA); lesion limited to the cervix uteri with sized measured by maximum tumor diameter[b] **IB1:** invasive carcinoma >5 mm depth of stromal invasion and ≤2 cm in greatest dimension **IB2:** invasive carcinoma >2 cm and ≤4 cm in greatest dimension **IB3:** invasive carcinoma >4 cm in greatest dimension
Stage II: the cervical carcinoma invades beyond the uterus but has not extended onto the lower third of the vagina or to the pelvic wall	**IIA:** involvement limited to the upper two thirds of the vagina without parametrial invasion **IIA1:** invasive carcinoma ≤4 cm in greatest dimension **IIA2:** invasive carcinoma >4 cm in greatest dimension **IIB:** with parametrial invasion but not up to the pelvic wall
Stage III: the carcinoma invades the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or a nonfunctioning kidney and/or involves pelvic and/or paraaortic lymph nodes	**IIIA:** carcinoma involves lower third of the vagina, with no extension to the pelvic wall **IIIB:** extension to the pelvic wall and/or hydronephrosis or a nonfunctioning kidney (unless known to be from another cause) **IIIC:** involvement of pelvic and/or paraaortic lymph nodes (including micrometastases),[c] irrespective of tumor size and extent (with r and p notations)[d] **IIIC1:** pelvic lymph node metastasis only **IIIC2:** paraaortic lymph node metastasis
Stage IV: the carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum; a bullous edema, as such, does not permit a case to be allotted to stage IV	**IVA:** spread of the growth to adjacent organs **IVB:** spread to distant organs

[a]Imaging and pathology can be used, when available, to supplement clinical findings with respect to tumor size and extent in all stages. Pathological findings supersede imaging and clinical findings.
[b]The involvement of vascular or lymphatic spaces should not change the staging. The lateral extent of the lesion is no longer considered.
[c]Isolated tumor cells do not change the stage but their presence should be recorded.
[d]Adding notation of r (imaging) or p (pathology) to indicate the finding that are used to allocate the case to stage IIIC. For example, if imaging indicates pelvic lymph node metastasis, the stage allocation would be stage IIIC1r; if confirmed by pathological findings, it would be stage IIIC1p. The type of imaging modality or pathology technique used should always be documented. When in doubt, the lower staging should be assigned.
Adapted with permission from Corrigendum to "Revised FIGO staging for carcinoma of the cervix uteri" [Int J Gynecol Obstet 145(2019) 129-135], *Int J Gynaecol Obstet* 2019 Nov;147(2):279-280.

serum SCC-Ag to evaluate the clinical significance, and these vary among studies. Hong et al[49] noted that persistently elevated serum SCC-Ag level (>10 ng/mL in a 2-year follow-up with at least one serum SCC-Ag measurement between the first 1–3 months and serial SCC-Ag evaluations when SCC-Ag >2 ng/mL) after radiotherapy is a strong predictor of treatment failure. Furthermore, another study that included patients with SCC of the uterine cervix who had achieved complete remission after primary treatment showed that patients with pretreatment SCC-Ag greater than 1.86 ng/mL or posttreatment SCC-Ag >greater than 0.9 ng/mL should be considered at high risk for cancer recurrence.[48] Davelaar et al[50] reported that in patients with early-stage SCC of the cervix poor overall survival (OS) and poor disease-free survival (DFS) were associated with an SCC-Ag level higher than 1.1 ng/mL. Similarly, other studies reported that in patients with stage IB to IIIB cervical SCC who underwent neoadjuvant chemotherapy followed by radical surgery, SCC-Ag level greater than 3 ng/mL could be considered an independent poor prognostic factor for progression-free survival (PFS) and OS.[51,52]

Although the ranges of sensitivity and specificity of this marker for recurrence were 56% to 86% and 83% to 100%, respectively; the majority of studies showed that the sensitivity of this tumor marker is low.[51,53,54] The investigators suggested that future research may need to focus on larger sample studies and the combination of SCC-Ag and other tumor markers, such as

cytokeratin fraction 21-1 (CYFRA 21-1), carbohydrate antigen 19-9 (CA 19-9), and carcinoembryonic antigen (CEA), to assess its limitations and improve its accuracy for future screening purposes.

Cancer antigen 125 (CA-125) is a gynecologic tumor marker most frequently used in ovarian and advanced endometrial cancer. In cervical cancer, Ngan et al[55] found that higher stage disease was associated with increased levels of CA-125 (>35 U/mL). Abnormal levels of CA-125 were detected in 15% of patients with stage I cervical adenocarcinoma, 25% of patients with stage II cervical adenocarcinoma, 33% of patients with stage III to IV cervical adenocarcinoma, and 75% of patients with recurrent adenocarcinoma of the cervix. Because this tumor marker has shown a sensitivity of 20% to 75% for cervical adenocarcinoma and because of its low negative predictive value, it is not considered a diagnostic tool to help assess patients with cervical cancer.[51,56]

CA 19-9 is associated primarily with hepatocellular carcinoma and pancreatic adenocarcinoma. It reflects inflammatory processes among epithelial cells and indicates poor prognosis when elevated in serum. Borras et al[57] reported that the CA 19-9 level was significantly higher in patients with cervical adenocarcinoma than in those with cervical SCC. Although studies have shown that CA19-9 could be a useful tumor marker in the early detection of tumor relapse in cervical cancer patients undergoing radiation therapy, the overall sensitivity of this tumor marker was found to be only 41.7%.[58] Investigators concluded that it is not commonly used in patients with cervical adenocarcinoma.

CYFRA 21-1 is an enzyme-immunoassay that measures serum fragments of cytokeratin 19. Studies have shown that elevated levels of CYFRA 21-1 have been found in 63% of patients with advanced SCC of the cervix.[59,60] CYFRA 21-1 elevation was found to have a correlation with tumor stage, tumor size, depth of stromal invasion, lymphovascular invasion, parametrial involvement, and lymph node status. Because the sensitivity of CYFRA 21-1 was lower than that of SCC-Ag, it was reported that in combination, it may be more useful in predicting disease recurrence. However, the clinical relevance of CYFRA 21-1 is still debated as with SCC-Ag.

CEA is a set of related glycoproteins involved in cell adhesion that is normally produced by gastrointestinal (GI) tissue during fetal development; however, production generally stops after birth. However, the serum levels are elevated in some cancers such as colorectal and gastric carcinoma, as well as some non-neoplastic conditions such as ulcerative colitis and pancreatitis. Borras et al[57] found that the overall sensitivity of this tumor antigen for detecting carcinoma of the uterine cervix was 33%. In this study, CEA showed a higher sensitivity for cervical adenocarcinoma (38.5%) compared with 32% for cervical SCC. Investigators determined that CEA levels decreased in 20% to 33% of patients with advanced cervical cancer that responded to therapy and was elevated in 36% of patients with cervical cancer who developed recurrent disease and was also elevated in 75% of all patients, including those with adenocarcinoma and adenosquamous and squamous carcinoma with metastatic disease. No prognostic value was found for its correlation with OS, and it was suggested that this tumor marker could reach a higher percentage of detection of cervical adenocarcinoma in combination with CA-125 and CA19-9. Conversely, a recent study showed that abnormal levels of CEA suggested a high probability (86.1%) of having parametrial and nodal invasion, which play a significant role in the stage of the disease and further treatment decision.[61]

Tumor Markers Under Investigation

Mathur et al[62] conducted a study including 15 different groups of patients with preinvasive and invasive cervical cancer at different stages of the disease and compared them with a control group with persistently normal Pap smears. The aim of the study was to verify the diagnostic importance of measuring serum levels of *insulinlike growth factor II (IGF-II)* and other tumor markers (Insulin Like Growth Factor Binding Protein 3 (IGFBP3), vascular endothelial growth factor [VEGF]-B and -C) for the early detection of cervical cancer. This study showed that serum measurements of IGF-II are useful in the assessment of patients with noninvasive disease, such as Atypical squamous cells of undetermined significance (ASCUS) with CIN or CIN1 (100% sensitivity and specificity). In women with ASCUS and CIN on biopsy, pretherapy CIN and persistent CIN (all grades) had IGF-II ranging from 1036 to 1128 ng/mL, which was significantly elevated in contrast to control participants. Of note, levels greater than 1300 ng/mL (824 ng/mL is considered the clinically significant cut-off value) seemed to be associated with advanced cervical cancer because this concentration was seen in the persistent and late cervical cancer groups. The investigators also demonstrated that measuring IGF-II levels could be useful for monitoring efficacy of therapy in patients with cervical cancer. (Surgical therapy was the standard of care for all patients with CIN, but adjuvant chemoradiation was administered to women with recurrent or persistent cervical cancer.) Investigators concluded that measuring serum IGF-II levels could be considered a useful screening tool for the detection of an early noninvasive lesions and a diagnostic tool for ASCUS and CIN.

VEGF-C is a proangiogenic cytokine that plays a specific role in the process of neoangiogenesis, which is involved in the progression of the disease and metastasis. Mathur et al[62] found that the serum and tissue levels of this particular VEGF were significantly higher

in patients with advanced cervical cancer. Franc et al[63] showed that VEGF-C is expressed in SCC of the uterine cervix, especially in clinical stage IB to IIIB disease, and that this expression is primarily involved in lymphangiogenesis. VEGF-C expression increases as the clinical stage increases. Similarly, another study showed that the expression of VEGF-C, along with other cytokines, may be associated with lymph node metastasis and may have synergistic effects on the malignant progression in patients with cervical cancer.[64] This tumor marker, as many others, fails in cervical cancer screening when considered individually and shows the greatest utility as a diagnostic tool when combined with other tumor markers, such as SCC-Ag.[54]

YKL-40 (amino acids tyrosine, lysine, and leucine), also known as CHI3L1 or human cartilage glycoprotein-39, is a group of proteins that act as growth factors for several cell types. YKL-40 has been suggested to play a pathophysiological role in tissue remodeling and inflammation, but its true function remains to be determined. Several studies have revealed that elevated serum levels of YKL-40 are present in numerous solid tumors and that it is a potential biomarker in the detection and management of adenocarcinoma of several organs, including the colon, ovary, lung, and breast.[65–68] Mitsuhashi et al[69] showed that increased serum preoperative levels of YKL-40 correlated with the persistence of disease or relapse, independent from the clinical stage and age of patients with cervical adenocarcinoma. It was demonstrated that serum YKL-40 level was elevated in early-stage SCC and adenocarcinoma of the cervix. The sensitivity of YKL-40 for adenocarcinoma was shown to be 78% for all disease and 68% for stage I tumors, suggesting that accuracy was insufficient for screening purposes. A more recent study showed that there is a correlation between CHI3L1 expression and vascular mimicry formation (an alternative microvascular system that develops tumor vascular networks that correlate with tumor growth, metastasis, and short survival time of patients with a number of cancers) in cervical cancer.[70] This suggested that increased CHI3L1 expression mediates not only angiogenesis but also vascular mimicry formation, thereby facilitating cancer aggressiveness and metastasis. This study proposed a feasible therapeutic strategy for targeting CHI3L1 expression in cervical cancer with both classic angiogenesis and vascular mimicry formation, other than considering it a tumor marker for screening.

Thymidine kinase (TK) is a pyrimidine pathway enzyme involved in nucleic acid synthesis and is considered to be a marker of proliferation. It has been studied in hematologic malignancies and colorectal and breast cancers, among others.[71–74] Recently, it was found that the salvage and de novo DNA synthesis pathways may be involved in cell proliferation of cervical carcinoma, mechanisms in which TK plays an essential role.[75] This study showed that serum TK level was significantly higher in patients with invasive cervical carcinoma than in normal women and patients with CIS. In patients who underwent pelvic lymph node dissection, high serum TK levels could not predict pelvic lymph node metastasis. Additionally, high serum TK levels were found to be an independent prognostic factor with no correlation to any other clinicopathologic factors such as patient age, clinical stage, or histologic type. TK may play a role in influencing the malignant behavior of invasive cervical carcinoma, and the investigators concluded that high serum TK levels are significantly associated with poorer survival in patients with advanced cervical carcinoma.

Macrophage colony-stimulating factor (M-CSF) constitutes a group of cytokines called hematopoietic growth factors that stimulate the proliferation and differentiation of monocytes to macrophages, playing a role in the inflammatory response. Increased expression of M-CSF and its receptor is correlated with poor prognoses in breast, ovarian, and prostate cancers. Recent studies have found an autologous production in various human cell lines in vitro and by some tumors in vivo, such as uterine cervix cancer.[76] Sidorkiewicz et al[77] demonstrated that M-CSF plasma levels were significantly higher than SCC-Ag and CA-125 in patients with cervical cancer and that this could be clinically useful in the initial assessment of cervical cancer. However, they concluded that the greatest diagnostic value is demonstrated when combined with other tumor markers, such as VEGF, CA-125, and SCC-Ag. Zajkowska et al[78] showed that high levels of M-CSF were found in stages II to IV of patients with cervical cancer with a sensitivity of 72% to 77%. Nevertheless, their conclusion was that combining M-CSF and SCC-Ag measurements might improve early detection of cervical cancer compared with the use of either marker alone.

Epigenetics are described as genomic structural modifications that affect gene expression but do not alter the underlying DNA sequence. Over the years, it has been shown that epigenetic changes play an important role in tumorigenesis. Epigenetic mechanisms for the regulation of gene expression include DNA methylation, histone modifications, and noncoding RNAs. Recently, it has become apparent that the non–protein-coding portion of the genome may play a major biological role in health and disease, particularly in cancer. The two broad classes of these noncoding RNAs (ncRNAs) include microRNAs (miRNAs) and long noncoding RNAs (lncRNAs). miRNAs are endogenously expressed small RNA sequences that act as posttranscriptional regulators of gene expression, and their role in cancer has been extensively studied. Several miRNAs have been found to be related to cervical cancer (miR-361-5p,

miR-29a, miR-99, miR-196a, miR-126, miR-125) and its carcinogenetic role (overexpression, downregulation, upregulation).[79] Laengsri et al[80] concluded that the detection of miRNAs in circulating blood is a means for reducing the number of invasive specimen collections. The differences in biological properties of cell lines and primary tissue from cervical biopsy affect miRNA expression levels. Also, host genetic variation, aging, and duration and type of viral infection also impact cervical cancer susceptibility. To increase accuracy, profiles of miRNAs in serum would need to be verified in large sample sizes. Finally, the construction of panels of candidate miRNAs from blood specimens—for use as screening, diagnostic, or prognostic markers and for prediction of risk of cervical cancer by single nucleotide polymorphism (SNP) in miRNAs—might be useful for future clinical application. Similarly, another study concluded that in the context of invasive cervical cancer screening, an important issue to be investigated is whether miRNA signatures could be associated with current and future risk of high-grade CIN, most likely in combination with other different markers, to improve risk stratification. The investigation of miRNA levels in cervical exfoliated cells certainly opens new possibilities for studying molecular markers in the context of screening programs.[81]

TREATMENT OF INVASIVE CERVICAL CANCER

Early-Stage Disease: FIGO 2018 Stages IA1, IA2, IB1, IB2, and IIA1

Overall, for early-stage cervical cancer, radical surgery and radiation therapy are both acceptable treatment options (Fig. 41–2).[82] In young patients, radical hysterectomy with ovarian preservation to avoid premature menopause is preferred because radiation is associated with long-term sexual and ovarian dysfunction. Because ovarian metastases in early stage are infrequent (0.8% for squamous and 1.5% for adenocarcinomas),[83] the ovaries are typically preserved in premenopausal women. There are two hysterectomy classifications used among gynecologic oncologists, the Piver-Rutledge-Smith classification[84] and the Querleu-Morrow-Cibula classification[85] (Table 41–4).

For patients with stage IA1 without lymph vascular space invasion (LVSI), the recommendation is a nonfragmented cone biopsy with 3-mm negative margins (negative for invasive disease and HSIL without any further treatment). If margins are positive, an extrafascial hysterectomy with pelvic lymphadenectomy with or without SLN mapping is recommended. As a fertility-sparing option, a reconization or trachelectomy can be done.[82]

In patients with stage IA1 with LVSI and IA2, the indication is a modified radical hysterectomy with pelvic lymphadenectomy with or without SLN mapping or, in nonsurgical candidates, external-beam radiation therapy (EBRT) and brachytherapy.

For patients wishing to preserve fertility a cone biopsy with negative margins with pelvic lymphadenectomy (if margins are positive, a reconization or trachelectomy should be performed) or a radical trachelectomy with pelvic lymphadenectomy, SLN mapping, or both.

For stages IB1, IB2, and IIA1, the indication is a radical hysterectomy with pelvic lymph node dissection with or without SLN mapping with or without paraaortic lymphadenectomy or pelvic radiation and brachytherapy with concurrent platinum-containing chemotherapy (cisplatin). Many centers around the world perform only SLN mapping and not a full pelvic lymphadenectomy as the nodal assessment in patients with early-stage cervical cancer. Currently, some have recommended class II hysterectomy rather than conventional class III hysterectomy in stages IB and IIA disease only for tumors smaller than 2 cm because it has fewer complications with no difference in the 5-year survival rate.[86]

With regards to the approach, radical hysterectomy was routinely performed through a minimally invasive approach (laparoscopy or robotics). However, in 2018, a multicenter, prospective, randomized trial (Laparoscopic Approach to Cervical Cancer (LACC) trial) compared oncologic outcomes in patients with early-stage cervical cancer (FIGO 2009 stage IA1 with LVSI-IB1) who underwent radical hysterectomy by an open versus a minimally invasive approach. The investigators found that DFS rate at 4.5 years was 86% with minimally invasive radical hysterectomy and 96.5% with open surgery. The study also showed that minimally invasive surgery was associated with higher rates of locoregional recurrences (hazard ratio [HR], 4.26; 95% confidence interval [CI], 1.44–12.6; P = .009) and higher risk of death (HR, 6.00; 95% CI, 1.77–20.3; P = .004).[87] A propensity score study of women with FIGO 2009 stage IA2 or IB1 cervical cancer who underwent radical hysterectomy (minimally invasive, 1225 and open, 1236) showed similar results.[88] With a median follow-up period of 45 months, the minimally invasive approach was associated with a higher 4-year mortality rate (9.1 vs 5.3%). Several retrospective studies were subsequently published showing similar results.[89,90] The most recent National Comprehensive Cancer Network (NCCN) 2020 guideline do not recommend the minimally invasive approach and support the use of open radical hysterectomy.[82] Secondary analysis from the LACC trial showed no difference in overall perioperative complications[91] with similar quality of life outcomes between groups (minimally invasive vs open radical hysterectomy).[92]

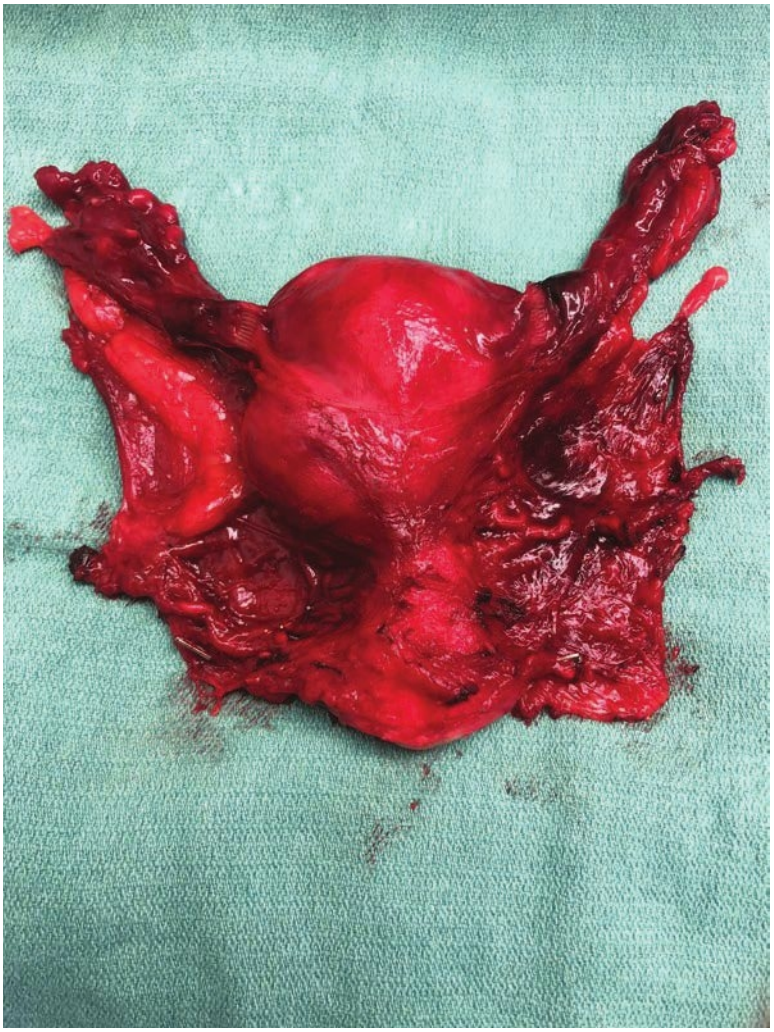


FIGURE 41–2 Radical hysterectomy specimen demonstrating the uterus and cervix, bilateral parametrial tissue, and upper vagina.

Cut-Through Hysterectomy

Invasive cervical cancer may be coincidentally diagnosed in the specimen of a simple hysterectomy, an event reported in approximately 15% of patients.[93] The NCCN guidelines recommend that after careful review of the pathological specimen, patients with stage IA1 disease without LVSI need no further treatment. For higher stages (IA1 with LVSI, IA2, IB1), positive margins, or gross residual disease after imaging studies, pelvic radiation with brachytherapy (with or without concurrent chemotherapy) is recommended. Optional radical parametrectomy with or without adjuvant treatment is recommended by the guideline.[82] A radical parametrectomy consists in removal of the upper vagina, parametrium, and regional lymph nodes. However, a recent study by Pareja et al[94] of 30 patients who underwent radical parametrectomy showed that in patients with low-risk factors (squamous, adenocarcinoma, or adenosquamous; lesions <2 cm in size and invading <10 mm), no radical parametrectomy specimen had residual tumor. None of the patients received adjuvant therapy. After a median follow-up of period 99 months (range, 6–160 months), only one patient recurred. The authors concluded that radical parametrectomy may be avoided in patients with low-risk early-stage cervical cancer detected after a simple hysterectomy because the rates of residual disease (parametrial or vaginal) and the need for adjuvant treatments or recurrences are very low.[94]

Adjuvant Treatment

When there is a combination of risk factors such as large tumor size (>4 cm), deep stromal invasion (>one third stromal invasion), or LVSI, EBRT with concurrent chemotherapy is recommended. The Sedlis criteria are used to guide adjuvant treatment decisions, include (1) greater than one third stromal invasion, (2) LVSI, and

TABLE 41–4 Hysterectomy Classifications

Piver-Rutledge-Smith Classification	
Class	**Description**
Class I: simple hysterectomy	Removal of the uterus along with the cervix
Class II: modified radical hysterectomy	Removal of the uterus with part of the paracervical and parametrial tissue in the lateral aspect of the cervix after dissecting the ureters away. Half of the cardinal ligament (lateral aspect), the uterosacral ligament (posterior aspect), and one third of the upper vagina are all removed.
Class III: radical hysterectomy	Removal of the uterus similar to that of class II, but the tissue structure is removed to a greater extent, generally close to the pelvic sidewall laterally and sacrum posteriorly; the upper half of the vagina is also removed.
Class IV: extended radical hysterectomy	Complete removal of the cervix, uterus, parametrial tissue, cardinal, and uterosacral ligaments. In addition, the ureter is completely dissected from the vesicouterine ligament, and the superior vesical artery is transected.
Class V: partial exenteration	Partial excision of the involved organs. In addition to the above procedures, this encompasses the removal of the distal ureter and urinary bladder.
Querleu-Morrow-Cibula Classification	
Type	**Description**
Type A: extrafascial hysterectomy	The paracervix is transected medial to the ureter but lateral to the cervix. The uterosacral and vesicouterine ligaments are not transected at a distance from the uterus. Vaginal resection is generally at a minimum, routinely <10 mm, without removal of the vaginal part of the paracervix (paracolpos).
Type B: modified radical hysterectomy	Partial resection of the uterosacral and vesicouterine ligaments is a standard part of this category. The ureter is unroofed and rolled laterally, permitting transection of the paracervix at the level of the ureteral tunnel. The caudal (posterior, deep) neural component of the paracervix caudal to the deep uterine vein is not resected. At least 10 mm of the vagina from the cervix or tumor is resected.
Type C: radical hysterectomy	**Type C1**, which corresponds to the nerve-sparing modification, requires separation of two parts of the dorsal parametria; the medial part, which entails rectouterine and rectovaginal ligaments; and the lateral laminar structure, also called mesoureter, which contains the hypogastric plexus. Furthermore, type C1 requires only a partial dissection of the ureter from the ventral parametria, which is usually asymmetric toward more extensive resection of the medial leaf of the cranial (above the ureter) part of the ventral parametria. **Type C2**, which aims for a complete parametrial resection. The ureter is completely dissected from the ventral parametria up to the urinary bladder wall. Defining the resection limits on the longitudinal (deep parametrial or vertical) plane is crucial for distinguishing between types C1 and C2.
Type D: laterally extended hysterectomy	This type differs from type C2 only in the lateral extent of the lateral parametria resection. Ureteral dissection and resection of both dorsal and ventral parametria is identical to the type C2. Laterally, however, it requires ligation and removal of the internal iliac artery and vein, together with their branches, including the gluteal, internal pudendal, and obturator vessels.

Data from Piver MS, Rutledge F, Smith JP. Five classes of extended hysterectomy for women with cervical cancer. *Obstet Gynecol*. 1974;44(2):265-272 and Cibula D, Abu-Rustum NR, Benedetti-Panici P, et al. New classification system of radical hysterectomy: emphasis on a three-dimensional anatomic template for parametrial resection. *Gynecol Oncol*. 2011;122(2):264-268.

(3) tumor size larger than 4 cm.[95] The risks of recurrence and death in the presence of these factors are up to 30% after surgery alone.[95,96] Other risk factors such as positive margins or pathologically confirmed positive pelvic lymph nodes or microscopic involvement of the parametrium (sometimes referred to as Peters' criteria)[97,98] are considered high-risk factors. For patients with these criteria, the recurrence risk is approximately 40% with a risk of death up to 50% after surgery alone.[98,99] If high-risk features are found, metastatic disease should be excluded (CT or PET-CT), and radiation therapy with concurrent chemotherapy

and brachytherapy are recommended. The benefit of adjuvant radiation therapy was shown in a 2012 meta-analysis that compared adjuvant radiotherapy with no further treatment after hysterectomy in 397 women with early-stage cervical cancer. Adjuvant therapy resulted in a reduction in the risk of disease progression (relative risk [RR], 0.58; 95% CI, 0.37–0.91) with no difference in the risk of death at 5 years (RR, 0.84; 95% CI, 0.3–2.36).[100]

Data suggest that chemoradiation may improve the risk of recurrence. A retrospective analysis of 129 patients with intermediate-risk disease treated over a 13-year period compared outcomes after treatment with platinum-based chemoradiation (n = 89) or radiation alone (n = 40).[101] Compared with radiation alone, chemoradiation resulted in a lower recurrence rate (9 vs 23%; P = .049) and a trend toward improved PFS at 5 years (90 vs 78%; HR, 2.82; 95% CI, 0.99–8.02). However, the authors reported there was no difference in OS between groups. There is an ongoing prospective study, Gynecologic Oncology Group (GOG) 263, to evaluate the benefits and risks of radiotherapy versus chemoradiation as adjuvant treatment in women with stage I or II cervical cancer.

Fertility-Sparing Surgery in Early-Stage Cervical Cancer

Thirty-seven percent of cervical cancers are diagnosed in women younger than the age of 45 years, with disease confined to the cervix in 46% of cases[3]; therefore, fertility-sparing surgery has emerged as an alternative without compromising oncologic outcomes. Fertility-sparing surgeries include conization, simple trachelectomy, and radical trachelectomy. Whereas a conization is a resection of the cervix in a cone-shape manner, a simple trachelectomy involves a more extensive removal of most of the cervix in a cylinder shape. Both procedures are performed vaginally. The difference between a radical and a simple trachelectomy is that a radical trachelectomy involves the removal of the parametrium, in addition to the cervix. It is reassuring that a recent Surveillance, Epidemiology, and End Results (SEER) data analysis (n = 2571) showed that uterine-preserving surgery such as cone or trachelectomy is not associated with a higher risk of death compared with non–uterine-preserving surgery (hysterectomy).[102]

Tumor size, FIGO stage, additional risk factors, and location of the lesion within the cervix and its proximity to other structures as the vaginal fornix are key in choosing the appropriate surgical technique. The goal is to remove a large portion of the cervix to remove the entire lesion, with adequate margins, and to allow adequate pathologic evaluation. Most experts agree that at least 5 mm of free margins from the level of the tumor to the endocervical cut margin is required to reduce the risk of local recurrence. If 5 mm of free margin is not obtained, an additional "slice" of cervix should ideally be removed; otherwise, a definitive hysterectomy should be performed.

Candidates for fertility-sparing treatment are women wishing to preserve future fertility; 40 years of age or younger; with tumors smaller than 2 cm; with FIGO 2018 stage IA1 to IB1; and with squamous, adenosquamous, or adenocarcinomas; and with negative nodes. The rationale behind this recommendation is that risk factors such as positive lymph nodes, deep infiltration, and lymphovascular space invasion are more likely to occur with increased tumor size and with other histology (eg, neuroendocrine carcinomas). As tumor size increases, so does the need of adjuvant therapy as shown by Park et al[103] (13.6% vs 34.0%; P <.001) when comparing tumors smaller than 2 and 2 to 4 cm. The need for adjuvant therapy precludes the possibility of maintaining fertility. Because patients who meet the criteria for fertility preservation treatment have a highly curable disease, it is of paramount importance that conservative procedures are accompanied by meticulous review of the preoperative pelvic MRI with an experienced radiologist, rigorous preoperative counseling, and a pathologic evaluation of the cone or simple trachelectomy specimen by an experienced gynecologic pathologist.

For women with FIGO 2018 stage IA1 cervical cancer without LVSI and who have no evidence of intermediate- or high-risk features, conization alone is a standard treatment option regardless of fertility interests with no need for nodal assessment.[104] A study analyzing data from a national cancer database (n = 1409) of women ages 40 years and younger with stage IA1 cervical cancer found no significant difference in 5-year survival rate between those who underwent conization versus hysterectomy (98 vs 99%); data regarding LVSI was not available.[105]

For patients with 2018 FIGO stage IA1 with LVSI, IA2, or IB1, fertility-sparing surgery requires some form of lymph node assessment in addition to the cervical procedure. Radical trachelectomy is the treatment of choice. To date, simple trachelectomy as an alternative to radical trachelectomy has been studied only in retrospective studies and is not the suggested surgery.

The best available data comparing conization with radical trachelectomy is a meta-analysis of 60 studies including 2854 patients, most with stage IA1 to IB1 disease (some studies included patients with stage IB2 or IIA). The results were pooled for each procedure, conization and radical trachelectomy, but tests of significance were not performed comparing the two procedures. For conization and radical trachelectomy, recurrence rates were as follows: stage IA (0.4 and 0.7%) and stage IB (IB1;0.6 vs 2.3%), with mortality rates of 0% and 0.7%; respectively. The pregnancy

and preterm delivery rates for conization were 36% and 7%, respectively, and for radical trachelectomy were 21% and 27%.[106]

Recurrence rate of patients undergoing different fertility-sparing options were evaluated by Pareja et al.[107] The recurrence rate for abdominal radical trachelectomy (all sizes), vaginal radical trachelectomy (all sizes), neoadjuvant chemotherapy, and abdominal radical trachelectomy (tumors <2 cm) ranged from 3.8% to 7.6%. The authors found that the recurrence rate after vaginal and laparoscopic radical trachelectomy in patients with tumors larger than 2 cm was 17% and 21%, respectively, and hence concluded that the procedure is not recommended for patients with tumors 2 to 4 cm in size.[107] A large systematic review by Bentivegna et al[108] evaluated oncologic outcomes in six different fertility-sparing techniques. The study included 1364 patients who underwent vaginal trachelectomies, 230 who underwent simple trachelectomy or conizations, 99 who underwent neoadjuvant chemotherapy followed by conservative surgery, and 987 who underwent abdominal radical trachelectomies (660 laparotomic, 238 laparoscopic, and 89 robotic). Recurrent disease was found in 58, 4, 6, 48 patients, respectively, with 24, 0, 2, and 12 patients dying from the disease in each treatment group, respectively.[108]

Fertility-Sparing Options for Tumors 2 to 4 cm in Size

Currently, standard treatment for patients with 2- to 4-cm cervical cancers is radical hysterectomy. There is not a well-defined strategy for patients with lesions larger than 2 cm who wish to preserve fertility. The rate of positive nodes varies from 10% to 45%, which is an indication for adjuvant treatment that precludes fertility preservation. Neoadjuvant chemotherapy to reduce tumor size followed by a fertility-sparing procedure may be an option. Five studies of neoadjuvant chemotherapy followed by fertility-sparing surgery showed a 71% response rate and better obstetric outcome than upfront trachelectomy.[109] A very recent meta-analysis of 86 patients who underwent neoadjuvant chemotherapy followed by fertility-sparing surgery confirmed that more radical surgery results in less favorable pregnancy outcome compared with less radical surgery.[110] The potential use of this approach is being evaluated in a multicenter, prospective, single-arm, phase II trial Neo-Adjuvant Chemotherapy and Conservative Surgery in Cervical Cancer to Preserve Fertility (CONTESSA) addressing the safety of neoadjuvant chemotherapy followed by fertility-sparing surgery in young women (40 years and younger) with FIGO 2018 stage IB2 cervical cancer with tumors measuring 2 to 4 cm. The primary endpoint is to assess the rate of successful fertility-sparing surgery and no adjuvant therapy. Eligible patients should undergo three cycles of platinum-based chemotherapy in combination with paclitaxel. After three cycles of neoadjuvant chemotherapy, a clinical examination and pelvic MRI should be performed to assess tumor response. Patients with complete or partial response (lesions <2 cm) should then proceed to fertility-sparing surgery (simple trachelectomy or large cone).[111]

Obstetric Outcomes After Fertility-Sparing Surgery

Bentivegna et al,[112] published a systematic review including 2777 patients who underwent five different fertility-sparing surgical procedures and 944 subsequent pregnancies. The overall fertility, live birth, and prematurity rates after these procedures were 55%, 70%, and 38%, respectively. The pregnancy rate was higher in patients after vaginal (63%) or minimally invasive radical trachelectomy (59%) compared with a laparotomic radical trachelectomy (49%). The choice among fertility-saving procedures depends first and foremost on the oncologic characteristics of the tumor.

Open versus Minimally Invasive Approach in Fertility-Sparing Surgery

Radical trachelectomy has been shown to be safe and feasible by open and minimally invasive approaches.[113–115] In the United States, there has been a significant increase in the use of minimally invasive radical trachelectomy from 29% in 2010 to 75% in 2015 (P <.001).[116] Oncologic outcomes among approaches has only been evaluated in small retrospectives studies. A review by Bentivegna et al[108] showed a 5% recurrence rate for the open and 6% for the laparoscopic approach. More recently, a retrospective national database study including 246 patients undergoing open or minimally invasive radical trachelectomy showed a 4-year OS rate of 92% (95% CI, 83.5%–96.5%) for the open and 96% (95% CI, 88.7%–98.4%) for the minimally invasive approach.[116] An ongoing (International radical trachelectomy assessment: **IRTA study**), international, retrospective registry is comparing DFS between patients who underwent open versus minimally invasive radical trachelectomy.[117] Preliminary results have been presented and showed that among 698 patients (open, 388; minimally invasive, 310), there was no difference in intraoperative complications (P = .23) or postoperative complications (23% in the open and 25% in the minimally invasive group; P = .56). There was higher rate of readmission (2% vs 11%; P <.001) and reoperation (2% vs 5%; P = .01) in the minimally invasive group. With a median follow-up time of 50.9 months (range, <1–179 months), overall, there was no difference in DFS between approaches with a 5.4% recurrence rate in the open versus 6.4% in the minimally

invasive group (P = .37). The 4.5-year DFS (open vs minimally invasive) was 93.6% (95% CI, 92.2%–95.0%) versus 91.1% (95% CI, 89.1%–93.2%), respectively. OS was similar between groups (P = .91). Recurrence rate based on tumor size showed that patients who underwent minimally invasive surgery and had tumors 1 to 2 cm in size before surgery were more likely to have a recurrence compared with those who underwent open surgery (12.1% vs 8.3%; P = .010). The authors concluded that minimally invasive radical trachelectomy was found to have worse oncologic outcomes in tumors 1 to 2 cm in size. However, no difference was noted in patients with smaller tumors.

More Conservative Options

The possibility of less radical surgery including simple hysterectomy, simple trachelectomy, or cervical conization with or without SLN biopsy and/or pelvic lymph node dissection may be an option not only for patients desiring future fertility but also for all patients with low-risk early-stage cervical cancer. Low-risk tumors include squamous carcinoma, adenocarcinoma, or adenosquamous carcinoma; lesions smaller than 2 cm; stromal invasion less than 10 mm; and no LVSI.

Only retrospective studies have reported on the oncologic safety of more conservative surgery in this group of patients.[118] Three ongoing prospective trials are evaluating the role of conservative management of patients with low-risk cervical cancer. The first is the ConCerv trial, which evaluates the safety and feasibility of performing conservative surgery in women with early-stage cervical cancer. This is a prospective single-arm study evaluating 100 patients. Surgical options include conization with pelvic lymph node assessment only, simple hysterectomy and pelvic node assessment, or patients who had undergone an "inadvertent" simple hysterectomy with a postoperative diagnosis of cancer.

Two ongoing studies are addressing conservative management of patients with low-risk cervical cancer. The Radical Versus Simple Hysterectomy and Pelvic Node Dissection With Low-risk Early Stage Cervical Cancer (SHAPE) trial is a randomized phase III trial comparing radical hysterectomy with pelvic lymphadenectomy versus simple hysterectomy with pelvic lymphadenectomy in patients with low-risk early-stage (IA2-IB1) cervical cancer (adenocarcinoma, squamous, or adenosquamous carcinomas; ≤2 cm tumors; with ≤10 mm stromal invasion; with or without LVSI). The primary endpoint of the study is pelvic relapse-free survival. The study aimed to enroll 700 patients and is to be completed by 2023. GOG 278 is a multicenter prospective cohort study that is evaluating the physical function and quality of life before and after surgery in patients with stage I cervical cancer treated with non-radical surgery. It includes stage IA1 (LVSI present) and IA2-IB1 (≤2 cm) with no radiologic metastatic disease.

Sentinel Lymph Node Mapping

Lymphatic mapping is based on the principle that if the SLN that is the first lymph node draining from the tumor is negative, more extensive lymphadenectomy may be avoided (Fig. 41–3).

The SLN mapping technique consists of a tracer, a dye or radiocolloid technetium 99m (Tc99), injected

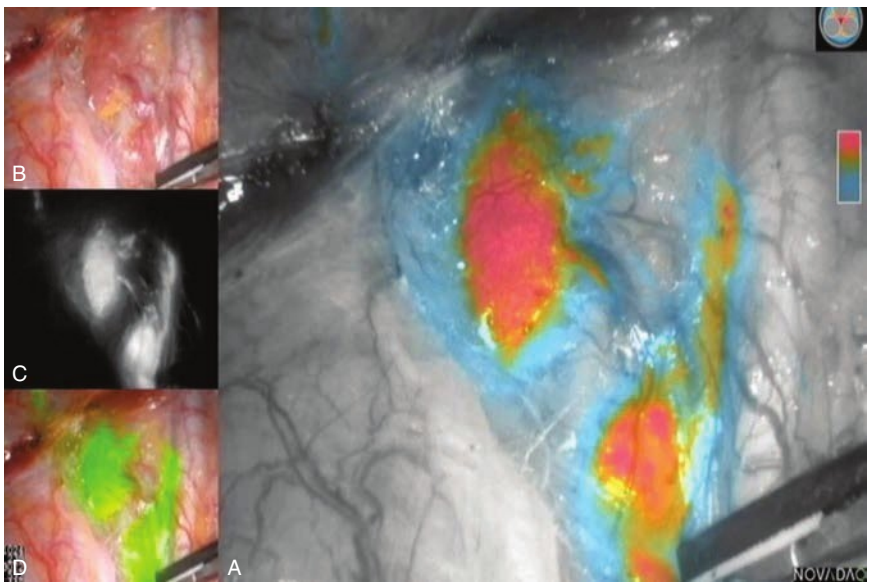


FIGURE 41–3 **Image of sentinel lymph node (SLN) mapping performed through a minimally invasive surgery. A. SLN with use of color-segmented fluorescence. The *left panel* demonstrates image with regular white light (B), "night vision" (C), and green fluorescent imaging (D).**

into the cervix. A mapping algorithm[82] should be followed, removing all SLNs. If there is a grossly suspicious node even without uptake of the tracer, it should be removed. Because the cervix is a central structure and can drain to either the left or right hemipelvis, if a SLN is detected in both hemipelves (bilateral detection), no further nodal removal is needed. If only one hemipelvis was mapped, a pelvic lymphadenectomy should be performed in the nonmapping hemipelvis.

Over the past 20 years, SLN mapping in patients with cervical cancer has been evaluated in both retrospective and prospective studies, which have collectively shown that in well-selected patients, the sensitivity is approximately 99%.[119] The (SENTICOL [Ganglion Sentinelle dans le Cancer du Col]) I trial was prospective study, aimed to determine if bilateral negative SLNs accurately predicted absence of lymph node metastasis in early cervical cancer patients. A total of 139 patients were included. Unilateral and bilateral detection rates were 97.8% and 77%, respectively. No false-negative results were observed in patients whom SLNs were identified bilaterally, concluding that SLN biopsy was reliable when SLNs were detected bilaterally.[120]

SLN biopsy appears to perform better than imaging studies in detecting metastatic disease. A meta-analysis of 72 studies, including 5042 women with cervical cancer, evaluated several approaches to identify metastatic nodes. The sensitivity and specificity for the detection of lymph node metastases were 91% and 100% for SLN mapping, 75% and 98% for PET-CT, 56% and 93% for MRI, and 58% and 92% for CT.[121]

Low-Volume Disease

Positive SLNs are classified according to the size of the nodal metastases as macrometastases (>2 mm), micrometastases (0.2–2 mm), and isolated tumor cells (ITCs) (<0.2 mm). Ultrastaging, which mandates serial sectioning of each node at multiple levels, and immunohistochemical staining with pancytokeratin antibodies (AE1/AE3) is performed if metastases are not identified with hematoxylin and eosin (H&E) stains. Ultrastaging increases the probability of finding low-volume disease (micrometastases and ITCs). It has been shown to identify 15% to 22% positive nodes that would have been missed by only a pelvic lymphadenectomy and regular H&E. The impact of low-volume disease in oncologic outcomes is still under review. A study by Cibula et al[122] retrospectively evaluated 645 patients with early-stage disease who underwent SLN and pelvic lymphadenectomy with ultrastaging. Macrometastasis, micrometastasis, and ITC were detected in 14.7%, 10.1%, and 4.5% patients, respectively. The presence of ITC was not associated with significant risk, both for recurrence free survival and OS. OS was significantly reduced in patients with macrometastasis and micrometastasis. The presence of micrometastasis was associated with significant reduction of OS, which was equivalent to patients with macrometastasis, with no prognostic significance for ITC. A subanalysis of patients included in the (SENTICOL [Ganglion Sentinelle dans le Cancer du Col]) 1 trial concluded that evidence of micrometastasis or ITCs in the SLN of untreated patients with early cervical cancer did not impact PFS.[123] Two ongoing prospective trials Sentinel Lymph Node Biopsy in Patients With Early Stages Cervical Cancer (SENTIX and SENTICOL III) will shed some light on the significance of low-volume disease. Data on the oncological outcome from both trials will not be available until 2020 and 2025, respectively.[120,124]

Frozen Section

The concept of frozen section evaluation of SLNs has been proposed as a means to determine whether to abandon or continue the intended procedure based on lymph node status of disease. Several studies have reported the sensitivity of SLN frozen section to be as low as 53%.[125–128] The SENTICOL study failed to detect lymph node involvement intraoperatively in 15 of 20 patients, including not only low-volume disease (12 cases) but also three cases of macrometastasis.[125] There remains significant controversy as to the value of this approach.

Locally Advanced Disease: FIGO 2018 Stages IB3, IIA2, IIB, IIIC1, IIIC2, and IVA

In locally advanced disease, the standard recommendation is EBRT with concurrent weekly platinum-based chemotherapy and brachytherapy.[98,129,130]

In stages IB3 and IIA2, CT scan or PET-CT should be performed to rule out nodal disease. In patients with radiologically positive nodes ($IIIC_r$), the treatment depends on the location of the compromised nodes. If only pelvic nodes are positive (IIIC1), chemoradiation and brachytherapy are indicated. If paraaortic nodes are positive ($IIIC2_p$ with positive or negative pelvic nodes), extended-field chemoradiation with brachytherapy is the treatment of choice. If distant metastatic disease is found, biopsy to confirm it and systemic chemotherapy are indicated.

Neoadjuvant Chemotherapy for Locally Advanced Cervical Cancer

Although chemoradiation therapy with cisplatin remains the standard treatment for patients with locally advanced disease, the overall recurrence rate is approximately 40%. Therefore, additional treatment strategies are being studied to improve oncologic outcomes. A phase III trial including 633 women with locally

advanced (FIGO 2009 stage IB2, IIA, or IIB) squamous cervical cancer were randomly assigned to either three cycles of neoadjuvant chemotherapy (paclitaxel and carboplatin once every 3 weeks) followed by radical hysterectomy or to standard chemoradiation. Compared with standard chemoradiation, those receiving neoadjuvant chemotherapy followed by surgery had worse 5-year DFS (69.3 vs 76.7%, respectively; HR, 1.38; 95% CI, 1.02–1.87) with similar 5-year OS between the two groups (75.4 vs 74.7%; respectively; HR, 1.025; 95% CI, 0.75–1.40). Delayed toxicities at 2 years or later after treatment completion were worse in the group treated with chemoradiation.[131] Similarly, the preliminary results of a phase III trial (European Organization for Research and Treatment of Cancer 55994), including 620 patients with stage IB2 to IIB cervical cancer, showed that patients randomly assigned to neoadjuvant chemotherapy followed by surgery experienced worsened 5-year PFS rates (57 vs 66%; difference, 9%; 95% CI, 2%–18%) and comparable 5-year OS rates (72 vs 76%; HR, 0.87; 95% CI, 0.65–0.15) as those receiving concomitant chemoradiation. Although short-term grade 3 or greater toxicities were higher with neoadjuvant therapy followed by surgery (41% and 23%, respectively), long-term toxicities were less frequent compared with chemoradiation (15% vs 21%).[132]

In summary, neoadjuvant chemotherapy before definitive hysterectomy does not offer an OS advantage relative to primary chemoradiation, and it has been associated with inferior DFS. Therefore, if chemoradiation is available, it should be recommended.

Radiation Therapy

Radiation therapy is used in cervical cancer as (1) definitive (upfront primary) treatment for patients with locally advanced disease or nonsurgical candidates and (2) adjuvant treatment after surgery in patients with high-risk factors (positive nodes, positive margins, deep stromal invasion, parametrial compromise, large tumor size, LVSI).

CT-based treatment planning is considered standard in EBRT. Brachytherapy is a critical component in patients that do not undergo surgery as part of primary treatment. It is also used as part of adjuvant therapy.

External-Beam Radiation Therapy

EBRT to the pelvis is delivered using multiple conformal fields or intensity-modulated volumetric techniques. Typically, the whole pelvis is treated with external-beam radiation to 45 Gy in 25 once-daily fractions of 1.8 Gy.

For patients with locally advanced disease, the primary tumor and regional lymphatics at risk are typically treated with EBRT to a dose of 40 to 50 Gy. The primary tumor is then boosted using brachytherapy with an additional 30 to 40 Gy for a total point A (represents a paracervical reference point and is used as a dosing parameter) dose of 80 Gy for small-volume tumors and 85 Gy or more for larger volume tumors. Grossly involved unresected nodes may be boosted with an additional 10 to 20 Gy.[82] For locally advanced disease, a total of 86 to 90 Gy with EBRT and brachytherapy is the usual recommended dose.

As adjuvant treatment (after primary surgery), EBRT is recommended at a dose of 45 to 50 Gy. Grossly involved unresected nodes may be treated with a boost of 10 to 20 Gy.[82]

Intensive-modulated radiation therapy (IMRT) can deliver the nodal boost simultaneous to the EBRT and better spare normal tissues, but randomized data evaluating the efficacy are pending. The Standard Versus Intensity-Modulated Pelvic Radiation Therapy in Treating Patients With Endometrial or Cervical Cancer (TIME-C) trial compared patients with endometrial and cervical cancer ($n = 278$) receiving four-field radiation to IMRT after radical hysterectomy, showing that IMRT was associated with significantly lower scores for GI and urinary toxicity than standard radiation therapy.[133] For patients undergoing radiation therapy, it is important to avoid treatment breaks because prolonged treatment is associated with worse oncologic outcomes.[134,135] Extending the overall treatment beyond 6 to 8 weeks results in a 0.5% to 1% decrease in pelvic control and decreases specific survival for each extra day of overall treatment. For brachytherapy, time to completion of brachytherapy longer than 56 days was associated with a higher rate of pelvic failure (HR, 2.8; 95% CI, 1.2–16; $P = .02$). The 3-year pelvic failure for longer than 56 days versus 56 days or less was 26% vs 9% ($P = .04$).[136]

It is important during treatment planning to minimize the potential impact on surrounding tissues such as sigmoid colon, rectum, bladder, small bowel, bone, and bone marrow because side effects may be magnified by concurrent chemotherapy. To avoid early menopause in young women with cervical cancer, ovarian transposition (moving the ovaries upper into the abdomen to avoid the area of EBRT) may be considered. However, a systematic review showed that the proportion of women with preserved ovarian function after ovarian transposition was 65% (95% CI, 56–74; 95% CI, 85–106).[137]

In the recurrent setting, stereotactic body radiotherapy allows for delivery of very high doses of focused external-beam radiation and may be applied to isolated metastatic sites.[138,139]

Concurrent Chemotherapy with Radiation Therapy (Chemoradiation)

Three landmark publications in the *New England Journal of Medicine* in 1999 changed practice regarding

radiation therapy for cervical cancer because all three studies demonstrated that the combination of EBRT with chemotherapy (chemoradiation) improved oncologic outcomes in patients with locally advanced cervical cancer.

Rose et al,[140] published a GOG randomized trial of EBRT in combination with concurrent chemotherapy (group1, cisplatin alone; group 2, cisplatin, fluorouracil, and hydroxyurea; and group 3, hydroxyurea alone) in 526 patients with locally advanced cervical cancer (stage IIB–IVA with negative lymph nodes). All patients received EBRT and were randomized to receive one of three chemotherapy regimens. The median follow-up period was 35 months. Both groups that received cisplatin regimen had a higher rate of PFS than the group that received hydroxyurea alone (P <.001). The relative risks of progression of disease or death were 0.57 (95% CI, 0.42–0.78) in group 1 and 0.55 (95% CI, 0.40–0.75) in group 2 compared with group 3. The OS rate was significantly higher in groups 1 and 2 than in group 3, with relative risks of death of 0.61 (95% CI, 0.44–0.85) and 0.58 (95% CI, 0.41–0.81), respectively. The study concluded that EBRT with concurrent chemotherapy regimens that contain cisplatin improved OS and PFS rates among women with locally advanced cervical cancer.

A second study by Morris et al,[141] compared pelvic and paraaortic EBRT alone (n = 193) versus pelvic EBRT and concurrent chemotherapy with fluorouracil and cisplatin (n = 193) in women with locally advanced cervical cancer confined to the pelvis (stages IIB–IVA or stage IB or IIA with a tumor diameter of ≥5 cm or involvement of pelvic lymph nodes). Patients were then to receive one or two applications of low-dose-rate intracavitary radiation, with a third cycle of chemotherapy planned for the second intracavitary procedure in the combined-therapy group. With a median follow-up time of 43 months, the estimated cumulative rates of survival at 5 years were 73% for patients treated with combined therapy (EBRT and chemotherapy) and 58% for those treated with EBRT alone (P = .004). Cumulative rates of DFS at 5 years were 67% and 40%, respectively (P <.001). The rates of both distant metastases (P <.001) and locoregional recurrences (P <.001) were significantly higher among patients treated with EBRT alone. The study concluded that the addition of chemotherapy to EBRT and brachytherapy significantly improved survival among women with locally advanced cervical cancer.

The third study by Keys et al,[142] a GOG trial, aimed to determine whether weekly cisplatin during EBRT improve PFS and OS among patients with bulky (≥4-cm) stage IB cervical cancer. Patients were randomly assigned to receive EBRT alone (n = 186) or in combination with weekly cisplatin for up to six doses (n = 183) followed in all patients by adjuvant hysterectomy. The relative risks of progression of disease and death were 0.51 (95% CI, 0.34–0.75) for combined EBRT and cisplatin and 0.54 (95% CI, 0.34–0.86) for EBRT alone. The rates of both PFS (P <.001) and OS (P = .008) were significantly higher in the combined-therapy group at 4 years. In the combined-therapy group, there were higher frequencies of transient grade 3/4 adverse hematologic (21% vs 2% in the EBRT group) and GI effects (14% vs 5%). The study concluded that adding weekly cisplatin to pelvic EBRT followed by hysterectomy significantly reduced the risk of disease recurrence and death in women with bulky stage IB cervical cancers.

Brachytherapy

Brachytherapy is the local application of radiation to the cervix and vagina, a critical component of locally advanced cervical cancer treatment allowing for a higher dose to the cervix, sparing the surrounding tissue. The role of brachytherapy was shown in a 2013 SEER database study including 7000 women with FIGO 2009 stage IB2 (>4 cm) to IVA cervical cancer. Using a matched cohort analysis of patients treated between 2000 and 2009, the use of brachytherapy resulted in significantly higher rates of cancer-specific survival (64 vs 52%) and OS (58 vs 46%) at 4 years.[143] Brachytherapy may be delivered with either a low-dose rate (LDR), pulse-dose rate, or high-dose rate (HDR) system. HDR and LDR brachytherapy appear to have similar efficacy and late complications.[144] LDR brachytherapy requires one or two insertions and HDR is given in three to six insertions. Multiple brachytherapy schemas have been used when combined with EBRT. One of the most common is HDR dose of 30 Gy in five fractions, which is equivalent to 40 Gy, to point A using LDR brachytherapy.

Treatment of Paraaortic Nodes

The recommendation for patients with common iliac or paraaortic nodal compromise is extended-field radiation therapy. This entails extending the superior pelvic field border to the level of the renal vessels.[82] This treatment is associated with a high risk of serious acute and late toxicity.[145] The use of IMRT, at least to the paraaortic nodal region, helps decrease morbidity. Extended-field radiation therapy to the paraaortic nodes (for occult or macroscopic compromised nodes) should provide a dose of 45 Gy.[82]

Advanced Stage: FIGO IVB

The preferred treatment is platinum-based chemotherapy with cisplatin or carboplatin. Many patients

with stage IVB disease may also have significant pelvic disease burden and EBRT in addition to systemic chemotherapy was proposed in a multi-institutional retrospective study.[146] A total of 95 patients with stage IVB who underwent EBRT and systemic chemotherapy ($n = 34$) or systemic chemotherapy alone ($n = 61$) from 2005 to 2015 were evaluated. The study showed that the OS was significantly longer in the EBRT with chemotherapy group (42 vs 18 months; $P < .01$). The authors concluded that EBRT in addition to chemotherapy gives a significant OS benefit and that further study is warranted to determine which subgroups may benefit the most from this treatment strategy.[146]

SURVEILLANCE

Surveillance recommendations as provided by the SGO[147] and the NCCN[82] are as follows. During the first 2 years after treatment, physical examination is recommended every 3 to 6 months. From years 3 to 5, this should be done every 6 to 12 months and annually after 5 years. Patients with high-risk disease (positive lymph nodes, parametrial compromise, or positive margins) can be evaluated more frequently, especially during the first 2 years, when most relapses occur. A recommended frequency is every 3 months for the first 2 years. The role of annual cervical or vaginal cytology is controversial because some studies have shown that Pap smear does not detect recurrences in asymptomatic patients with stage I or II disease.[147,148] If low-grade squamous dysplasia is diagnosed during surveillance, treatment is not recommended.

Imaging has a limited role in the follow-up of asymptomatic patients, and it should not be performed as part of routine surveillance in asymptomatic patients with stage I disease with no clinical suspicion of recurrence. In fertility-sparing surgical patients, pelvic MRI should be considered 6 months after surgery and yearly for 2 to 3 years. PET-CT should be considered if metastatic disease is suspected.[149]

For stage II or greater, PET-CT (preferred) or CT scan is recommended after 3 to 6 months of completing treatment. Cervical cancer survivors are at risk for secondary cancers (HPV-related malignancies, such as oropharyngeal cancer and anal cancer).[150]

RECURRENT CERVICAL CANCER

It is generally accepted that any lesions detected and documented as disease within 6 months after treatment should be considered persistent disease. The diagnosis of recurrence is usually made after 6 months.

Recurrent cervical cancer is frequently classified as locoregional or distant or metastatic recurrent disease. Most locoregional and distant recurrences (75%) are symptomatic, and 62% to 89% of cervical cancer recurrences are detected within 2 years of primary treatment. By year 5, 89% to 99% of recurrent disease has been detected.[151]

For women who underwent curative-intent therapy, the predominant site of disease recurrence is local (at the vaginal apex) or regional (pelvic sidewall). The risk of persistent or recurrent pelvic disease increases with more advanced stage. Some retrospective studies reported the distribution of anatomic sites of recurrence to be central (22%–56%) (vaginal apex or pelvis without sidewall involvement), pelvic sidewall (28%–37%), and distant metastases or multiple recurrence sites (15%–61%).[152–155] The estimated prevalence of organ site involvement by metastatic cervical cancer was pelvic or paraaortic nodes (75 and 62%, respectively), lung (33%–38%), liver (33%), peritoneum (5%–27%), adrenal gland (14%–16%), intestines (12%), or skin (10%).[153]

Locoregional recurrent usually presents with vaginal discharge, bleeding, dyspareunia, or pain. Patients with metastatic disease usually present with no symptoms, nonspecific complaints (fatigue, nausea, or weight loss), or symptoms related to the site of metastases. Patients with suspicion of recurrence should undergo a confirmatory biopsy. Images should be performed to determine site of recurrence. CT scan and PET-CT are the most frequently used. PET-CT for evaluation of local and distant disease has a sensitivity of 93% to 96% and specificity of 93% to 95%.[155]

Treatment of Locoregional Recurrent Disease

Options for therapy depend on the type of primary treatment received. For patients previously treated with EBRT with a local recurrence, surgical resection with curative intent (hysterectomy or pelvic exenteration) is recommended. Candidates for surgery include those with a central pelvic recurrence without sidewall fixation or associated hydronephrosis, with long disease-free interval (>12 months), and a recurrence size of less than 3 cm.[156] For patients who received primary EBRT, surgery including radical hysterectomy or pelvic exenteration is recommended with survival rates approaching 50%.[157,158] Exenteration is an ultraradical surgical procedure consisting of an en bloc resection of the female reproductive organs, lower urinary tract, and a portion of the rectosigmoid. Total exenteration refers to removal of the uterus, tubes, ovaries, parametrium,

bladder, rectum or rectal segment, vagina, urethra, and a portion of the levator muscles. In an anterior exenteration, the rectum is spared, but in a posterior exenteration, the bladder and urethra are preserved. A perineal phase, infralevator exenteration, resecting the anus, urethra, and portions of the vulva, may also be required. The choice of procedure is based on the location of the cancer. Reconstruction of the urinary tract (ileal conduit or continent diversion) or the GI tract (end colostomy, temporary ileostomy, double-barrel wet colostomy) may be required. A neovagina reconstruction can be offered in some cases to all types of pelvic exenteration. The potential for cure by exenterative surgery requires that the tumor be resected with negative margins. For patients successfully undergoing exenterative surgery (negative margins and no metastatic disease), the cure rate is approximately 50%.[159] Careful patient selection is required given the perioperative surgical morbidity. A recently published population-based retrospective study including 2647 patients from 2011 to 2015 who underwent pelvic exenteration for gynecologic cancers showed a perioperative complication rate of 68% with a mortality rate of 2%.[160]

For patients who have not received radiation therapy as primary treatment, have a relapse outside the radiated field, or are not surgical candidates, the recommendation is for radiation with or without chemotherapy (cisplatin or carboplatin) with or without brachytherapy.

For patients who have been previously treated with radiation and are not candidates for surgical resection, chemotherapy is recommended. Patients who experience recurrence after second-line therapy, either surgery or radiation, have a poor prognosis.[161] They can be treated with chemotherapy or best supportive care or can be enrolled in a clinical trial.

Treatment for Distant or Metastatic Recurrent Disease

First-Line Therapy

First-line therapy recommended for recurrent of metastatic disease is cisplatin, paclitaxel, and bevacizumab. The addition of bevacizumab to combined chemotherapy was evaluated in a randomized phase III trial (GOG 240). A total of 452 women with metastatic, persistent, or recurrent cervical carcinoma were randomly assigned to chemotherapy (cisplatin–paclitaxel or topotecan–paclitaxel) with or without bevacizumab. The addition of bevacizumab resulted in a significant improvement in OS compared with chemotherapy alone (median, 16.8 vs 13.3 months, respectively; HR, 0.77; 98% CI, 0.62–0.95). OS in women who did not receive prior radiation was higher in both groups (24.5 vs 16.8 months). Postprogression survival was not significantly different across groups (8.4 vs 7.1 months; HR, 0.83; 95% CI, 0.66–1.05). Significant improvement in PFS (median, 8.2 vs 6.0 months; HR, 0.68; 95% CI, 0.54–0.82) and significant improvement in overall response rate (49 vs 36%) were also seen.[162,163]

A 2017 systematic review and metanalysis including data from 19 trials of chemotherapy for patients with recurrent, persistent, or metastatic cervical cancer found a trend toward improved OS for the addition of bevacizumab to cisplatin–paclitaxel and topotecan–paclitaxel versus all other nonbevacizumab regimens.[164]

Because of toxicity related to cisplatin, carboplatin is a reasonable substitute particularly for patients with medical comorbidities and those previously treated with cisplatin-based chemoradiation. This is based on the results of the Japanese Clinical Oncology Group 0505 trial (JCOG 0505)[165] in which 253 women with stage IVB, persistent or recurrent cervical cancer were randomly assigned to receive cisplatin–paclitaxel or carboplatin–paclitaxel. Prior cisplatin therapy (primarily with chemoradiation) was noted in 43% and 50% of each group, respectively. The carboplatin–paclitaxel regimen was noninferior to cisplatin–paclitaxel in terms of median OS (18.3 months vs 17.5 months; $P = .032$) with a similar overall response rate (63 vs 60%). The carboplatin arm had significantly less serious (grade 4) neutropenic events (45 vs 75%; $P < .0001$) and less serious (grade 3/4) incidences of renal insufficiency (0 vs 2.4%). A systematic review including 1181 patients supports carboplatin as a reasonable alternative to cisplatin.[166]

Second-Line Therapy

Pembrolizumab is the preferred regimen for second-line therapy in patients with recurrent or metastatic disease who are positive for tumor programmed death-ligand 1 (PDL-1) or microsatellite instability high or deficient mismatch repair. In the phase Ib KEYNOTE-028 trial, among 24 women with PD-L1 metastatic or recurrent treatment-refractory cervical cancer, the overall response rate was 17%, and duration of response was 5.4 months.[167] Toxicities of pembrolizumab and other checkpoint inhibitors include rash, colitis, and pneumonitis. Other recommended agents as second-line therapy are bevacizumab, albumin-bound paclitaxel, docetaxel, fluorouracil, gemcitabine, ifosfamide , irinotecan, mitomycin, pemetrexed, topotecan, vinorelbine, and in certain circumstances, larotrectinib or entrectinib for *NTRK* gene fusion-positive tumors.[82]

MD ANDERSON PRACTICE TIPS

- The HPV DNA testing is effective for cervical cancer screening and has been recommended in countries or regions of the world in any level of resources available.
- Patients with stage IA2-IB1 cervical cancer seeking fertility preservation should be offered a radical trachelectomy.
- When performing a radical hysterectomy for stage IA2-IB2 FIGO 2018 cervical cancer, the open approach is the new standard of care.
- In patients with metastatic or recurrent cervical cancer, the combination of carboplatin, paclitaxel, and bevacizumab is the preferred treatment regimen.
- In patients with recurrent cervical cancer, molecular testing and PDL-1 status are routinely recommended.

REFERENCES

1. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *Am J Clin Pathol*. 2012;137(4):516-542.
2. Dugue PA, Rebolj M, Garred P, Lynge E. Immunosuppression and risk of cervical cancer. *Expert Rev Anticancer Ther*. 2013;13(1):29-42.
3. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer stat facts: cervical cancer. https://seer.cancer.gov/statfacts/html/cervix.html
4. Division of Cancer Prevention and Control, Centers for Disease Control and Prevention Centers for Disease Control and Prevention. Cervical cancer: what are the risk factors for cervical cancer? https://www.cdc.gov/cancer/cervical/basic_info/risk_factors.htm
5. Chang F. Role of papillomaviruses. *J Clin Pathol*. 1990;43(4):269-276.
6. Wolf JK, Ramirez PT. The molecular biology of cervical cancer. *Cancer Invest*. 2001;19(6):621-629.
7. Trottier H, Franco EL. The epidemiology of genital human papillomavirus infection. *Vaccine*. 2006;24(suppl 1):S1-S15.
8. Schiffman M, Castle PE, Jeronimo J, et al. Human papillomavirus and cervical cancer. *Lancet*. 2007;370(9590):890-907.
9. Joste NE, Ronnett BM, Hunt WC, et al. Human papillomavirus genotype-specific prevalence across the continuum of cervical neoplasia and cancer. *Cancer Epidemiol Biomarkers Prev*. 2015;24(1):230-240.
10. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol*. 1999;189(1):12-19.
11. Ahdieh L. Prevalence, incidence, and type-specific persistence of human papillomavirus in human immunodeficiency virus (HIV)–positive and HIV-negative women. *J Infect Dis*. 2001:682-90
12. Ferenczy A, Coutlee F, Franco E, Hankins C. Human papillomavirus and HIV coinfection and the risk of neoplasias of the lower genital tract: a review of recent developments. *CMAJ*. 2003;169(5):431-434.
13. McKenzie ND, Kobetz EN, Ganjei-Azar P, et al. HPV in HIV-infected women: implications for primary prevention. *Front Oncol*. 2014;4:179.
14. Lee YC, Hashibe M. Tobacco, alcohol, and cancer in low and high income countries. *Ann Glob Health*. 2014;80(5):378-383.
15. Juneja A, Sehgal A, Mitra AB, Pandey A. A survey on risk factors associated with cervical cancer. *Indian J Cancer*. 2003;40(1):15-22.
16. International Collaboration of Epidemiological Studies of Cervical Cancer. Comparison of risk factors for invasive squamous cell carcinoma and adenocarcinoma of the cervix: collaborative reanalysis of individual data on 8,097 women with squamous cell carcinoma and 1,374 women with adenocarcinoma from 12 epidemiological studies. *Int J Cancer*. 2007;120(4):885-891.
17. Solomon D, Davey D, Kurman R, et al. The 2001 Bethesda system: terminology for reporting results of cervical cytology. *JAMA*. 2002;287(16):2114-2119.
18. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med*. 2007;356(19).
19. Joura EA, Giuliano AR, Iversen OE, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *N Engl J Med*. 2015;372(8):711-723.
20. Paavonen J, Naud P, Salmerón J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet*. 2009;374(9686):301-314.
21. Scheller NM, Svanstrom H, Pasternak B, et al. Quadrivalent HPV vaccination and risk of multiple sclerosis and other demyelinating diseases of the central nervous system. *JAMA*. 2015;313(1):54-61.2015/01/07.
22. Šterbenc A, Triglav T, Poljak M. An update on prophylactic human papillomavirus (HPV) vaccines: a review of key literature published between September 2018 and September 2019. Presented at: Acta Dermatovenerologica Alpina Pannonica et Adriatica, 2019;28(4).
23. National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention. Immunization schedules. https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html
24. Meites E, Kempe A, Markowitz LE. Use of a 2-dose schedule for human papillomavirus vaccination—updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2016;65(49):1405-1408.
25. U.S. Food and Drug Administration. Human papillomavirus 9-valent vaccine, recombinant. https://www.fda.gov/vaccines-blood-biologics/vaccines/gardasil-9
26. Drolet M, Bénard É, Pérez N, et al. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. *Lancet*. 2019;394(10197):497-509.
27. Papanicolaou GN, Traut HF. The diagnostic value of vaginal smears in carcinoma of the uterus. 1941. *Arch Pathol Lab Med*. 1997;121(3):211-224.
28. Castle PE, Stoler MH, Wright TC, et al. Performance of carcinogenic human papillomavirus (HPV) testing and HPV16 or HPV18 genotyping for cervical cancer screening of women aged 25 years and older: a subanalysis of the ATHENA study. *Lancet Oncol*. 2011;12(9):880-890.
29. Huh WK, Ault KA, Chelmow D, et al. Use of primary high-risk human papillomavirus testing for cervical cancer screening: interim clinical guidance. *Obstet Gynecol*. 2015;125(2):330-337.
30. Monsonego J, Cox JT, Behrens C, et al. Prevalence of high-risk human papilloma virus genotypes and associated risk of cervical precancerous lesions in a large U.S. screening population: data from the ATHENA trial. *Gynecol Oncol*. 2015;137(1):47-54.
31. Jeronimo J, Castle PE, Temin S, et al. Secondary prevention of cervical cancer: ASCO resource-stratified clinical practice guideline. *J Glob Oncol*. 2016;3(5):635-657.
32. Ogilvie GS, van Niekerk D, Krajden M, et al. Effect of screening with primary cervical HPV testing vs cytology testing on high-grade cervical intraepithelial neoplasia at 48 months: the HPV FOCAL randomized clinical trial. *JAMA*. 2018;320(1):43-52.
33. Egemen D, Cheung LC, Chen X, et al. Risk estimates supporting the 2019 ASCCP Risk-based management consensus guidelines. *J Low Genit Tract Dis*. 2020;24(2):132-143.
34. Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP risk-based management consensus guidelines for abnormal cervical cancer screening tests and cancer precursors. *J Low Genit Tract Dis*. 2020;24(2):102-131.
35. Massad LS, Einstein MH, Huh WK, et al. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *Obstet Gynecol*. 2013;121(4):829-846.
36. Schlecht NF, Platt RW, Duarte-Franco E, et al. Human papillomavirus infection and time to progression and regression of cervical intraepithelial neoplasia. *J Natl Cancer Inst*. 2003;95(17):1336-1343.
37. American College of Obstetricians and Gynecologists. Practice Bulletin No. 140: management of abnormal cervical cancer screening test results and cervical cancer precursors. *Obstet Gynecol*. 2013;122(6):1338-1367.
38. Teoh D, Musa F, Salani R, et al. Diagnosis and management of adenocarcinoma in situ: a Society of Gynecologic Oncology

evidence-based review and recommendations. *Obstet Gynecol*. 2020;135(4):869-878.
39. Corrigendum to "Revised FIGO staging for carcinoma of the cervix uteri" [Int J Gynecol Obstet 145(2019) 129-135]. *Int J Gynaecol Obstet*. 2019;147(2):279-280.
40. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri. *Int J Gynaecol Obstet*. 2018;143(suppl 2):22-36.
41. Bhatla N, Berek JS, Cuello Fredes M, et al. Revised FIGO staging for carcinoma of the cervix uteri. *Int J Gynaecol Obstet*. 2019;145(1):129-135.
42. Mitchell DG, Snyder B, Coakley F, et al. Early invasive cervical cancer: tumor delineation by magnetic resonance imaging, computed tomography, and clinical examination, verified by pathologic results, in the ACRIN 6651/GOG 183 Intergroup Study. *J Clin Oncol*. 2006;24(36):5687-5694.
43. Testa AC, Di Legge A, De Blasis I, et al. Imaging techniques for the evaluation of cervical cancer. *Best Pract Res Clin Obstet Gynaecol*. 2014;28(5):741-768.
44. Mayr NA, Magnotta VA, Ehrhardt JC, et al. Usefulness of tumor volumetry by magnetic resonance imaging in assessing response to radiation therapy in carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys*. 1996;35(5):915-924.
45. Subak LL, Hricak H, Powell CB, et al. Cervical carcinoma: computed tomography and magnetic resonance imaging for preoperative staging. *Obstet Gynecol*. 1995;86(1):43-50.
46. Loft A, Berthelsen AK, Roed H, et al. The diagnostic value of PET/CT scanning in patients with cervical cancer: a prospective study. *Gynecol Oncol*. 2007;106(1):29-34.
47. Jeong BK, Huh SJ, Choi DH, et al. Prognostic value of different patterns of squamous cell carcinoma antigen level for the recurrent cervical cancer. *Cancer Res Treat*. 2013;45(1):48-54.
48. Ryu HK, Baek JS, Kang WD, Kim SM. The prognostic value of squamous cell carcinoma antigen for predicting tumor recurrence in cervical squamous cell carcinoma patients. *Obstet Gynecol Sci*. 2015;58(5):368-376.
49. Hong JH, Tsai CS, Chang JT, et al. The prognostic significance of pre- and posttreatment SCC levels in patients with squamous cell carcinoma of the cervix treated by radiotherapy. *Int J Radiat Oncol Biol Phys*. 1998;41(4):823-830.
50. Davelaar EM, van de Lande J, von Mensdorff-Pouilly S, et al. A combination of serum tumor markers identifies high-risk patients with early-stage squamous cervical cancer. *Tumour Biol*. 2008;29(1):9-17.
51. Gaducci A. The prognostic relevance of pretreatment serum immunosuppressive acidic protein (IAP) in patients with squamous cell carcinoma of the uterine cervix: a comparison with squamous cell carcinoma antigen (SCC). *Cancer J*. 1994;7:241-247.
52. Strauss HG, Laban C, Lautenschlager C, et al. SCC antigen in the serum as an independent prognostic factor in operable squamous cell carcinoma of the cervix. *Eur J Cancer*. 2002;38(15):1987-1991.
53. Duk JM, de Bruijn HW, Groenier KH, et al. Cancer of the uterine cervix: sensitivity and specificity of serum squamous cell carcinoma antigen determinations. *Gynecol Oncol*. 1990;39(2):186-194.
54. Liu Z, Shi H. Prognostic role of squamous cell carcinoma antigen in cervical cancer: a meta-analysis. *Dis Markers*. 2019;2019:6710352.
55. Ngan HY, Cheung AN, Lauder IJ, et al. Tumour markers and their prognostic value in adenocarcinoma of the cervix. *Tumour Biol*. 1998;19(6):439-444.
56. Dolscheid-Pommerich RC, Keyver-Paik M, Hecking T, et al. Clinical performance of LOCI-based tumor marker assays for tumor markers CA 15-3, CA 125, CEA, CA 19-9 and AFP in gynecological cancers. *Tumour Biol*. 2017;39(10):1010428317730246.
57. Borras G, Molina R, Xercavins J, et al. Tumor antigens CA 19.9, CA 125, and CEA in carcinoma of the uterine cervix. *Gynecol Oncol*. 1995;57(2):205-211.
58. Abe A, Nakano T, Morita S, Oka K. Clinical evaluation of serum and immunohistochemical expression of SCC and CA19-9 in radiation therapy for cervical cancer. *Anticancer Res*. 1999;19(1b):829-836.
59. Chmura A, Wojcieszek A, Mrochem J, et al. [Usefulness of the SCC, CEA, CYFRA 21.1, and CRP markers for the diagnosis and monitoring of cervical squamous cell carcinoma]. *Ginekol Pol*. 2009;80(5):361-366.
60. Piao X, Kong TW, Chang SJ, et al. Pretreatment serum CYFRA 21-1 level correlates significantly with survival of cervical cancer patients: a multivariate analysis of 506 cases. *Gynecol Oncol*. 2015;138(1):89-93.
61. Molina R. CYFRA 21.1 in patients with cervical cancer: comparison with SCC and CEA. *Anticancer Res*. 2005.
62. Mathur SP, Mathur RS, Gray EA, et al. Serum vascular endothelial growth factor C (VEGF-C) as a specific biomarker for advanced cervical cancer: relationship to insulin-like growth factor II (IGF-II), IGF binding protein 3 (IGF-BP3) and VEGF-A [corrected]. *Gynecol Oncol*. 2005;98(3):467-483.
63. Franc M, Kachel-Flis A, Michalski B, et al. Lymphangiogenesis in cervical cancer evaluated by expression of the VEGF-C gene in clinical stage IB-IIIB. *Prz Menopauzalny*. 2015;14(2):112-117.
64. Dai Y, Tong R, Guo H, et al. Association of CXCR4, CCR7, VEGF-C and VEGF-D expression with lymph node metastasis in patients with cervical cancer. *Eur J Obstet Gynecol Reprod Biol*. 2017;214:178-183.
65. Cintin C, Johansen JS, Christensen IJ, et al. High serum YKL-40 level after surgery for colorectal carcinoma is related to short survival. *Cancer*. 2002;95(2):267-274.
66. Dehn H, Hogdall EV, Johansen JS, et al. Plasma YKL-40, as a prognostic tumor marker in recurrent ovarian cancer. *Acta Obstet Gynecol Scand*. 2003;82(3):287-293.
67. Jensen BV, Johansen JS, Price PA. High levels of serum HER-2/neu and YKL-40 independently reflect aggressiveness of metastatic breast cancer. *Clin Cancer Res*. 2003;9(12):4423-4434.
68. Johansen JS, Drivsholm L, Price PA, Christensen IJ. High serum YKL-40 level in patients with small cell lung cancer is related to early death. *Lung Cancer*. 2004;46(3):333-340.
69. Mitsuhashi A, Matsui H, Usui H, et al. Serum YKL-40 as a marker for cervical adenocarcinoma. *Ann Oncol*. 2009;20(1):71-77.
70. Ngernyuang N, Shao R, Suwannarurk K, Limpaiboon T. Chitinase 3 like 1 (CHI3L1) promotes vasculogenic mimicry formation in cervical cancer. *Pathology*. 2018;50(3):293-297.
71. Hallek M, Wanders L, Strohmeyer S, Emmerich B. Thymidine kinase: a tumor marker with prognostic value for non-Hodgkin's lymphoma and a broad range of potential clinical applications. *Ann Hematol*. 1992;65(1):1-5.
72. O'Neill KL, Hoper M, Odling-Smee GW. Can thymidine kinase levels in breast tumors predict disease recurrence? *J Natl Cancer Inst*. 1992;84(23):1825-1828.
73. Scanlon K. Overexpression of DNA replication and repair enzymes in cisplatin-resistant human colon carcinoma HCT8 cells and circumvention by azidothymidine. *Cancer Commun*. 1989;1:269-275.
74. Svobodova S, Topolcan O, Holubec L, et al. Prognostic importance of thymidine kinase in colorectal and breast cancer. *Anticancer Res*. 2007;27(4a):1907-1909.
75. Fujiwaki R, Hata K, Moriyama M, et al. Clinical value of thymidine kinase in patients with cervical carcinoma. *Oncology*. 2001;61(1):47-54.
76. Ławicki S. Plasma levels and diagnostic utility of macrophage colony-stimulating factor, matrix metalloproteinase-9, and tissue inhibitor of metalloproteinases-1 as new biomarkers of breast cancer. *Ann Lab Med*. 2016;36:38-42.

77. Sidorkiewicz I, Zbucka-Kretowska M, Zareba K, et al. Plasma levels of M-CSF and VEGF in laboratory diagnostics and differentiation of selected histological types of cervical cancers. *BMC Cancer*. 2019;19(1):398.
78. Zajkowska M, Zbucka-Kretowska M, Sidorkiewicz I, et al. Plasma levels and diagnostic utility of macrophage-colony stimulating factor, matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 as tumor markers in cervical cancer patients. *Tumour Biol*. 2018;40(7):1010428318790363.
79. Fang J, Zhang H, Jin S. Epigenetics and cervical cancer: from pathogenesis to therapy. *Tumour Biol*. 2014;35(6):5083-5093.
80. Laengsri V, Kerdpin U, Plabplueng C, et al. Cervical cancer markers: epigenetics and microRNAs. *Lab Med*. 2018;49(2):97-111.
81. Pardini B, De Maria D, Francavilla A, et al. MicroRNAs as markers of progression in cervical cancer: a systematic review. *BMC Cancer*. 2018;18(1):696.
82. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology cervical cancer, version I. https://www.nccn.org/professionals/physician_gls/default.aspx
83. Shimada M, Kigawa J, Nishimura R, et al. Ovarian metastasis in carcinoma of the uterine cervix. *Gynecol Oncol*. 2006;101(2):234-237.
84. Piver MS, Rutledge F, Smith JP. Five classes of extended hysterectomy for women with cervical cancer. *Obstet Gynecol*. 1974;44(2):265-272.
85. Cibula D, Abu-Rustum NR, Benedetti-Panici P, et al. New classification system of radical hysterectomy: emphasis on a three-dimensional anatomic template for parametrial resection. *Gynecol Oncol*. 2011;122(2):264-268.
86. Landoni F, Maneo A, Cormio G, et al. Class II versus class III radical hysterectomy in stage IB-IIA cervical cancer: a prospective randomized study. *Gynecol Oncol*. 2001;80(1):3-12.
87. Ramirez PT, Frumovitz M, Pareja R, et al. Minimally invasive versus abdominal radical hysterectomy for cervical cancer. *N Engl J Med*. 2018;379(20):1895-1904.
88. Melamed A, Margul DJ, Chen L, et al. Survival after minimally invasive radical hysterectomy for early-stage cervical cancer. *N Engl J Med*. 2018;379(20):1905-1914.
89. Cusimano MC, Baxter NN, Gien LT, et al. Impact of surgical approach on oncologic outcomes in women undergoing radical hysterectomy for cervical cancer. *Am J Obstet Gynecol*. 2019;221(6):619 e1-e24.
90. Uppal S, Gehrig PA, Peng K, et al. Recurrence rates in patients with cervical cancer treated with abdominal versus minimally invasive radical hysterectomy: a multi-institutional retrospective review study. *J Clin Oncol*. 2020;38(10):1030-1040.
91. Obermair A, Asher R, Pareja R, et al. Incidence of adverse events in minimally invasive vs open radical hysterectomy in early cervical cancer: results of a randomized controlled trial. *Am J Obstet Gynecol*. 2020;222(3):249 e1- e10.
92. Frumovitz M. Plenary session best orals IGCS8-0506 quality of life assessment in early-stage cervical cancer patients in undergoing radical hysterectomy via minimally invasive surgery or open approach: the LACC trial. *Int J Gynecol Cancer*. 2018;28.
93. Munstedt K, von Georgi R, Zygmunt M, et al. Shortcomings and deficits in surgical treatment of gynecological cancers: a German problem only? *Gynecol Oncol*. 2002;86(3):337-343.
94. Pareja R, Echeverri L, Rendon G, et al. Radical parametrectomy after 'cut-through' hysterectomy in low-risk early-stage cervical cancer: time to consider this procedure obsolete. *Gynecol Oncol*. 2018;149(3):520-524.
95. Sedlis A, Bundy BN, Rotman MZ, et al. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a Gynecologic Oncology Group Study. *Gynecol Oncol*. 1999;73(2):177-183.
96. Rotman M, Sedlis A, Piedmonte MR, et al. A phase III randomized trial of postoperative pelvic irradiation in stage IB cervical carcinoma with poor prognostic features: follow-up of a gynecologic oncology group study. *Int J Radiat Oncol Biol Phys*. 2006;65(1):169-176.
97. Monk BJ, Tian C, Rose PG, Lanciano R. Which clinical/pathologic factors matter in the era of chemoradiation as treatment for locally advanced cervical carcinoma? Analysis of two Gynecologic Oncology Group (GOG) trials. *Gynecol Oncol*. 2007;105(2):427-433.
98. Peters WA 3rd, Liu PY, Barrett RJ 2nd, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol*. 2000;18(8):1606-1613.
99. Monk BJ, Wang J, Im S, et al. Rethinking the use of radiation and chemotherapy after radical hysterectomy: a clinical-pathologic analysis of a Gynecologic Oncology Group/Southwest Oncology Group/Radiation Therapy Oncology Group trial. *Gynecol Oncol*. 2005;96(3):721-728.
100. Rogers L, Siu SS, Luesley D, et al. Radiotherapy and chemoradiation after surgery for early cervical cancer. *Cochrane Database Syst Rev*. 2012(5):CD007583.
101. Okazawa M, Mabuchi S, Isohashi F, et al. Impact of the addition of concurrent chemotherapy to pelvic radiotherapy in surgically treated stage IB1-IIB cervical cancer patients with intermediate-risk or high-risk factors: a 13-year experience. *Int J Gynecol Cancer*. 2013;23(3):567-575.
102. Tseng JH, Aloisi A, Sonoda Y, et al. Less versus more radical surgery in stage IB1 cervical cancer: a population-based study of long-term survival. *Gynecol Oncol*. 2018;150(1):44-49.
103. Park JY, Kim DY, Kim JH, et al. Outcomes after radical hysterectomy according to tumor size divided by 2-cm interval in patients with early cervical cancer. *Ann Oncol*. 2011;22(1):59-67.
104. Bisseling KC, Bekkers RL, Rome RM, Quinn MA. Treatment of microinvasive adenocarcinoma of the uterine cervix: a retrospective study and review of the literature. *Gynecol Oncol*. 2007;107(3):424-430.
105. Wright JD, NathavithArana R, Lewin SN, et al. Fertility-conserving surgery for young women with stage IA1 cervical cancer: safety and access. *Obstet Gynecol*. 2010;115(3):585-590.
106. Zhang Q, Li W, Kanis MJ, et al. Oncologic and obstetrical outcomes with fertility-sparing treatment of cervical cancer: a systematic review and meta-analysis. *Oncotarget*. 2017;8(28):46580-46592.
107. Pareja R, Rendon GJ, Sanz-Lomana CM, et al. Surgical, oncological, and obstetrical outcomes after abdominal radical trachelectomy—a systematic literature review. *Gynecol Oncol*. 2013;131(1):77-82.
108. Bentivegna E, Gouy S, Maulard A, et al. Oncological outcomes after fertility-sparing surgery for cervical cancer: a systematic review. *Lancet Oncol*. 2016;17(6):e240-e253.
109. Plante M. Bulky early-stage cervical cancer (2-4 cm lesions): upfront radical trachelectomy or neoadjuvant chemotherapy followed by fertility-preserving surgery: which is the best option? *Int J Gynecol Cancer*. 2015;25(4):722-728.
110. Laios A, Kasius J, Tranoulis A, et al. Obstetric outcomes in women with early bulky cervical cancer downstaged by neoadjuvant chemotherapy to allow for fertility-sparing surgery: a meta-analysis and metaregression. *Int J Gynecol Cancer*. 2018;28(4):794-801.
111. Plante M, van Trommel N, Lheureux S, et al. FIGO 2018 stage IB2 (2-4 cm) Cervical cancer treated with Neo-adjuvant chemotherapy followed by fertility Sparing Surgery (CONTESSA); Neo-Adjuvant Chemotherapy and Conservative Surgery in Cervical Cancer to Preserve Fertility (NEOCON-F). A PMHC, DGOG, GCIG/CCRN and multicenter study. *Int J Gynecol Cancer*. 2019;29(5):969-975.

112. Bentivegna E, Maulard A, Pautier P, et al. Fertility results and pregnancy outcomes after conservative treatment of cervical cancer: a systematic review of the literature. *Fertil Steril*. 2016;106(5):1195-211 e5.
113. Kim JH, Park JY, Kim DY, et al. Fertility-sparing laparoscopic radical trachelectomy for young women with early stage cervical cancer. *BJOG*. 2010;117(3):340-347.
114. Persson J, Kannisto P, Bossmar T. Robot-assisted abdominal laparoscopic radical trachelectomy. *Gynecol Oncol*. 2008;111(3):564-567.
115. Smith JR, Boyle DC, Corless DJ, et al. Abdominal radical trachelectomy: a new surgical technique for the conservative management of cervical carcinoma. *Br J Obstet Gynaecol*. 1997;104(10):1196-1200.
116. Cui RR, Chen L, Tergas AI, et al. Trends in use and survival associated with fertility-sparing trachelectomy for young women with early-stage cervical cancer. *Obstet Gynecol*. 2018;131(6):1085-1094.
117. Ramirez PT, Pareja R, Eriksson AGZ, Frumovitz M. International Gynecologic Cancer Society 2019 meeting summary. *Int J Gynecol Cancer*. 2020;30(2):167-173.
118. Ramirez PT, Pareja R, Rendon GJ, et al. Management of low-risk early-stage cervical cancer: should conization, simple trachelectomy, or simple hysterectomy replace radical surgery as the new standard of care? *Gynecol Oncol*. 2014;132(1):254-259.
119. Tax C, Rovers MM, de Graaf C, et al. The sentinel node procedure in early stage cervical cancer, taking the next step; a diagnostic review. *Gynecol Oncol*. 2015;139(3):559-567.
120. Lecuru FR, McCormack M, Hillemanns P, et al. SENTICOL III: an international validation study of sentinel node biopsy in early cervical cancer. A GINECO, ENGOT, GCIG and multicenter study. *Int J Gynecol Cancer*. 2019;29(4):829-834.
121. Selman TJ, Mann C, Zamora J, et al. Diagnostic accuracy of tests for lymph node status in primary cervical cancer: a systematic review and meta-analysis. *CMAJ*. 2008;178(7):855-862.
122. Cibula D, Abu-Rustum NR, Dusek L, et al. Prognostic significance of low volume sentinel lymph node disease in early-stage cervical cancer. *Gynecol Oncol*. 2012;124(3):496-501.
123. Guani B, Dorez M, Magaud L, et al. Impact of micrometastasis or isolated tumor cells on recurrence and survival in patients with early cervical cancer: SENTICOL trial. *Int J Gynecol Cancer*. 2019;29(3):447-452.
124. Cibula D, Dusek J, Jarkovsky J, et al. A prospective multicenter trial on sentinel lymph node biopsy in patients with early-stage cervical cancer (SENTIX). *Int J Gynecol Cancer*. 2019;29(1):212-215.
125. Bats AS, Buenerd A, Querleu D, et al. Diagnostic value of intraoperative examination of sentinel lymph node in early cervical cancer: a prospective, multicenter study. *Gynecol Oncol*. 2011;123(2):230-235.
126. Roy M, Bouchard-Fortier G, Popa I, et al. Value of sentinel node mapping in cancer of the cervix. *Gynecol Oncol*. 2011;122(2):269-274.
127. Slama J, Dundr P, Dusek L, Cibula D. High false negative rate of frozen section examination of sentinel lymph nodes in patients with cervical cancer. *Gynecol Oncol*. 2013;129(2):384-388.
128. Sonoda K, Yahata H, Okugawa K, et al. Value of intraoperative cytological and pathological sentinel lymph node diagnosis in fertility-sparing trachelectomy for early-stage cervical cancer. *Oncology*. 2018;94(2):92-98.
129. Yamashita H, Okuma K, Kawana K, et al. Comparison between conventional surgery plus postoperative adjuvant radiotherapy and concurrent chemoradiation for FIGO stage IIB cervical carcinoma: a retrospective study. *Am J Clin Oncol*. 2010;33(6):583-586.
130. Yessaian A, Magistris A, Burger RA, Monk BJ. Radical hysterectomy followed by tailored postoperative therapy in the treatment of stage IB2 cervical cancer: feasibility and indications for adjuvant therapy. *Gynecol Oncol*. 2004;94(1):61-66.
131. Gupta S, Maheshwari A, Parab P, et al. Neoadjuvant chemotherapy followed by radical surgery versus concomitant chemotherapy and radiotherapy in patients with stage Ib2, IIa, or IIb squamous cervical cancer: a randomized controlled trial. *J Clin Oncol*. 2018;36(16):1548-1555.
132. Kenter G, Greggi S, Vergote I, et al. Results from neoadjuvant chemotherapy followed by surgery compared to chemoradiation for stage Ib2-IIb cervical cancer, EORTC 55994. *J Clin Oncol*. 2019;37(15 suppl):5503.
133. Klopp AH, Yeung AR, Deshmukh S, et al. Patient-reported toxicity during pelvic intensity-modulated radiation therapy: NRG Oncology-RTOG 1203. *J Clin Oncol*. 2018;36(24):2538-2544.
134. Perez CA, Grigsby PW, Castro-Vita H, Lockett MA. Carcinoma of the uterine cervix. I. Impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy. *Int J Radiat Oncol Biol Phys*. 1995;32(5):1275-1288.
135. Petereit DG, Sarkaria JN, Chappell R, et al. The adverse effect of treatment prolongation in cervical carcinoma. *Int J Radiat Oncol Biol Phys*. 1995;32(5):1301-1307.
136. Song S, Rudra S, Hasselle MD, et al. The effect of treatment time in locally advanced cervical cancer in the era of concurrent chemoradiotherapy. *Cancer*. 2013;119(2):325-331.
137. Gubbala K, Laios A, Gallos I, et al. Outcomes of ovarian transposition in gynaecological cancers; a systematic review and meta-analysis. *J Ovarian Res*. 2014;7:69.
138. Choi CW, Cho CK, Yoo SY, et al. Image-guided stereotactic body radiation therapy in patients with isolated para-aortic lymph node metastases from uterine cervical and corpus cancer. *Int J Radiat Oncol Biol Phys*. 2009;74(1):147-153.
139. Higginson DS, Morris DE, Jones EL, et al. Stereotactic body radiotherapy (SBRT): technological innovation and application in gynecologic oncology. *Gynecol Oncol*. 2011;120(3):404-412.
140. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med*. 1999;340(15):1144-1153.
141. Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med*. 1999;340(15):1137-1143.
142. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med*. 1999;340(15):1154-1161.
143. Han K, Milosevic M, Fyles A, et al. Trends in the utilization of brachytherapy in cervical cancer in the United States. *Int J Radiat Oncol Biol Phys*. 2013;87(1):111-119.
144. Liu R, Wang X, Tian JH, et al. High dose rate versus low dose rate intracavity brachytherapy for locally advanced uterine cervix cancer. *Cochrane Database Syst Rev*. 2014(10):CD007563.
145. Small W Jr, Winter K, Levenback C, et al. Extended-field irradiation and intracavitary brachytherapy combined with cisplatin chemotherapy for cervical cancer with positive para-aortic or high common iliac lymph nodes: results of ARM 1 of RTOG 0116. *Int J Radiat Oncol Biol Phys*. 2007;68(4):1081-1087.
146. Perkins V, Moore K, Vesely S, et al. Incorporation of whole pelvic radiation into treatment of stage IVB cervical cancer: a novel treatment strategy. *Gynecol Oncol*. 2020;156(1):100-106.
147. Salani R, Khanna N, Frimer M, et al. An update on post-treatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncology (SGO) recommendations. *Gynecol Oncol*. 2017;146(1):3-10.
148. Morice P, Deyrolle C, Rey A, et al. Value of routine follow-up procedures for patients with stage I/II cervical cancer treated with combined surgery-radiation therapy. *Ann Oncol*. 2004;15(2):218-223.
149. Gee MS, Atri M, Bandos AI, et al. Identification of distant metastatic disease in uterine cervical and endometrial cancers

with FDG PET/CT: analysis from the ACRIN 6671/GOG 0233 Multicenter trial. *Radiology*. 2018;287(1):176-184.
150. Raspagliesi F, Ditto A, Solima E, et al. Microinvasive squamous cell cervical carcinoma. *Crit Rev Oncol Hematol*. 2003;48(3):251-261.
151. Elit L, Fyles AW, Devries MC, et al. Follow-up for women after treatment for cervical cancer: a systematic review. *Gynecol Oncol*. 2009;114(3):528-535.
152. Chung HH, Jo H, Kang WJ, et al. Clinical impact of integrated PET/CT on the management of suspected cervical cancer recurrence. *Gynecol Oncol*. 2007;104(3):529-534.
153. Fulcher AS, O'Sullivan SG, Segreti EM, Kavanagh BD. Recurrent cervical carcinoma: typical and atypical manifestations. *Radiographics*. 1999;19 Spec No:S103-16; quiz S264-5.
154. Pallardy A, Bodet-Milin C, Oudoux A, et al. Clinical and survival impact of FDG PET in patients with suspicion of recurrent cervical carcinoma. *Eur J Nucl Med Mol Imaging*. 2010;37(7):1270-1278.
155. Patel CN, Nazir SA, Khan Z, et al. 18F-FDG PET/CT of cervical carcinoma. *AJR Am J Roentgenol*. 2011;196(5):1225-1233.
156. Friedlander M, Grogan M. Guidelines for the treatment of recurrent and metastatic cervical cancer. *Oncologist*. 2002;7(4):342-347.
157. Maneo A, Landoni F, Cormio G, et al. Radical hysterectomy for recurrent or persistent cervical cancer following radiation therapy. *Int J Gynecol Cancer*. 1999;9(4):295-301.
158. Rutledge S, Carey MS, Prichard H, et al. Conservative surgery for recurrent or persistent carcinoma of the cervix following irradiation: is exenteration always necessary? *Gynecol Oncol*. 1994;52(3):353-359.
159. Höckel M, Dornhöfer N. Pelvic exenteration for gynaecological tumours: achievements and unanswered questions. *Lancet Oncol*. 2006;7(10):837-847.
160. Matsuo K, Mandelbaum RS, Adams CL, et al. Performance and outcome of pelvic exenteration for gynecologic malignancies: a population-based study. *Gynecol Oncol*. 2019;153(2):368-375.
161. Lorusso D, Ferrandina G, Pignata S, et al. Evaluation of pemetrexed (Alimta, LY231514) as second-line chemotherapy in persistent or recurrent carcinoma of the cervix: the CERVIX 1 study of the MITO (Multicentre Italian Trials in Ovarian Cancer and Gynecologic Malignancies) Group. *Ann Oncol*. 2010;21(1):61-66.
162. Tewari KS, Sill MW, Long HJ 3rd, et al. Improved survival with bevacizumab in advanced cervical cancer. *N Engl J Med*. 2014;370(8):734-743.
163. Tewari KS, Sill MW, Penson RT, et al. Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). *Lancet*. 2017;390(10103):1654-1663.
164. Kitagawa R, Katsumata N, Shibata T, et al. Paclitaxel Plus carboplatin versus paclitaxel plus cisplatin in metastatic or recurrent cervical cancer: the open-label randomized phase III Trial JCOG0505. *J Clin Oncol*. 2015;33(19):2129-2135.
165. Saito I, Kitagawa R, Fukuda H, et al. A phase III trial of paclitaxel plus carboplatin versus paclitaxel plus cisplatin in stage IVB, persistent or recurrent cervical cancer: Gynecologic Cancer Study Group/Japan Clinical Oncology Group Study (JCOG0505). *Jpn J Clin Oncol*. 2010;40(1):90-93.
166. Lorusso D, Petrelli F, Coinu A, et al. A systematic review comparing cisplatin and carboplatin plus paclitaxel-based chemotherapy for recurrent or metastatic cervical cancer. *Gynecol Oncol*. 2014;133(1):117-123.
167. Frenel JS, Le Tourneau C, O'Neil B, et al. safety and efficacy of pembrolizumab in advanced, programmed death ligand 1-positive cervical cancer: results from the phase Ib KEYNOTE-028 trial. *J Clin Oncol*. 2017;35(36):4035-4041.

42 Gestational Trophoblastic Disease

Han T. Cun
Aaron Shafer

KEY CONCEPTS

- Gestational trophoblastic disease (GTD) is a spectrum of rare tumors that arise from abnormal placental trophoblastic tissue, including benign disease such as complete and partial hydatidiform moles, as well as malignant tumors such as invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor.
- Risk factors for GTD include geography, socioeconomic status, dietary factors, maternal age, and previous GTD history.
- GTD is historically diagnosed based on pathology, but due to earlier detection because of routine early ultrasonography, diagnosis of a molar pregnancy based on histology alone may be difficult, and cytogenetic techniques can assist in diagnosis.
- The diagnosis of malignant disease, or gestational trophoblastic neoplasia, is based on increase or plateau of human chorionic gonadotropin (hCG) levels, tissue diagnosis of choriocarcinoma, or evidence of metastatic disease.
- After the diagnosis of malignant disease, it is imperative that patients be staged and scored using International Federation of Gynecology and Obstetrics 2000 staging incorporating the modified World Health Organization scoring system to determine whether single- or multiagent therapy is appropriate.
- Throughout the course of treatment, patients should be monitored with every 1- to 2-week serum hCG levels to determine response.

Gestational trophoblastic disease (GTD) is a spectrum of rare tumors arising from abnormal placental trophoblastic tissue. It ranges from benign disease, including complete and partial hydatidiform moles, to malignant tumors such as invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT). The malignant disease is otherwise known at gestational trophoblastic neoplasia (GTN) or gestational trophoblastic tumor.

Our knowledge of hydatidiform moles dates back to 400 B.C., when Hippocrates was the first to describe them as "dropsy of the uterus."[1] By the mid-20th century, similar to other malignancies, survival rates were dismal. During this time, the mortality rate for invasive moles neared 15% because of hemorrhage, sepsis, embolic disease, or complications from surgery.[2] Additionally, choriocarcinoma had a mortality rate close to 100% when metastases were present and approached 60% even when hysterectomy was performed for nonmetastatic disease. Even benign hydatidiform moles had poor prognoses because of life-threatening hemorrhage and other medical complications. However, because of the identification of a specific and accurate biomarker used for follow-up as well as the development of an effective chemotherapy treatment, current management of patients with GTD yields cure rates approaching 100%.

EPIDEMIOLOGY

GTD is rare accounting for fewer than 1% of all gynecologic tumors. However, the exact rate of prevalence is difficult to determine because of the rarity of the disease, inconsistent use of definitions, and a lack of centralized databases.[3] Despite this, various studies have identified a number of risk factors associated with GTD. These include but are not limited to geography, socioeconomic status, dietary factors, maternal age, and previous GTD history.

GTD is variable throughout different regions of the world. In the United States, GTD occurs in roughly

1 in 1000 pregnancies, with the majority being benign hydatidiform moles, whereas the incidence of choriocarcinoma ranges from 2 to 7 in 100,000 pregnancies.[4] In a broader sense, the rate of GTD in North America, South America, and Europe is approximately 1 in 500 to 1000 pregnancies, but in East Asia, incidence reaches 1 in 120 pregnancies.[3,5] For malignant disease, the reported incidence of choriocarcinoma ranges from as low as 1 in 40,000 pregnancies in North America and Europe to 9.2 in 40,000 pregnancies in Southeast Asia.[2] These regional differences may reflect genetics and ethnicity as potential risk factors for GTD, but other causative factors such as socioeconomic status and diet may also play a role. For instance, in East Asia, the Middle East, the United States, and Brazil, women of lower socioeconomic status have up to a 10-fold higher rate of molar pregnancy compared with women of higher socioeconomic status.[6,7] Additionally, diets with low consumption of carotene and animal fat are associated with increased risk of complete hydatidiform moles[8,9] but not partial moles.[10]

Risk for GTD increases at the extremes of reproductive age as well. Specifically, the risk increases after the age of 35 years with a 5- to 10-fold increased risk after age 45 years.[11] However, women younger than 15 years of age also have a 2-fold risk of developing a molar pregnancy. Additionally, a history of previous molar pregnancy also increases the risk of subsequent GTD up to 10 times compared with the occurrence of sporadic moles.[12] Although various risk factors associated with the development of GTD have been identified, there are currently no prevention or risk reduction strategies available to decrease the development of GTD.

The majority, 80%, of GTDs are benign hydatidiform moles, 15% are invasive moles, and 5% are choriocarcinoma.[13] PSTT, a rare form of GTD, only accounts for 0.2 to 2% of GTDs and has the highest rate of morality because of its relative chemoresistence.[13] Choriocarcinoma is associated with an antecedent complete hydatidiform mole in 50% of cases, a history of abortion in 25%, term delivery in 20%, and an ectopic pregnancy in 5%. Choriocarcinoma after a partial mole is rare.[3,6]

PATHOGENESIS

All GTDs arise from placental tissue from a pregnancy with abnormal fertilization. In normal fertilization, the union of a sperm with an ovum initiates rapid cellular division and the development of a diploid embryo. Embryonic differentiation leads to the development of trophoblasts, specialized epithelial cells that support the development of the placenta and the villi. Normal trophoblasts are comprised of cytotrophoblasts, syncytiotrophoblasts, and intermediate trophoblasts. In GTD, abnormal fertilization results in a complex interplay of genetic and chromosomal abnormalities, leading to trophoblastic hyperplasia and cell cycle dysregulation.

Genetics

GTD is a unique lesion arising from fetal rather than maternal tissue. This occurs after the abnormal union of sperm and ovum, resulting in an imbalance or excess of paternal genetic material compared with maternal material.

In a complete mole, the maternal genetic material is lost during meiosis, and the empty ovum is fertilized by one sperm that duplicates its chromosomes or two separate sperm (dispermy). For instance, 80% to 92% of complete moles have a 46,XX karyotype after fertilization of an empty ovum by a haploid sperm (23X) that then undergoes duplication to create a diploid set of identical chromosomes (46,XX).[14] Additionally, complete moles may also develop after postzygotic diploidization of a triploid conception. Approximately 4% to 20% of complete moles result from dispermy, in which two sperm, fertilize an empty ovum, resulting in a 46,XX or 46,XY karyotype containing all paternal nuclear chromosomes.[6,15] Most are 46,XY, but approximately 5% of all complete moles result from dispermy with heterozygous 46,XX karyotype. Of note, a 46,YY mole has not been reported, suggesting that the X chromosome is required for survival.

Ultimately, these aberrations in fertilization result in nuclear chromosomes with sole paternal origin. The only maternal contribution is maternal mitochondrial DNA.[6,16] This is further supported by the finding that when paternal heterozygotes for the human leukocyte antigen (HLA) locus give rise to a hydatidiform mole, the HLA expression of the molar tissue is homozygous.[17]

In contrast to a complete mole, a partial mole results from the abnormal union of two sperm with one ovum with intact chromosomes, resulting in a triploid karyotype. Occasionally, a normal ovum can be fertilized by an abnormal diploid sperm.[6] Thus, the classic partial mole has a triploid karyotype (69 chromosomes), and both paternal and maternal chromosomes are present. The most common sex chromosome arrangement is XXY, but XXX and XYY also exist.[6] Of note, in triploid pregnancies, a partial mole results when the extra haploid chromosomes are of paternal origin, and a fetus develops when the extra haploid chromosomes are of maternal origin. Caution is used in the event that a partial mole is reported as diploid because the diagnosis is usually a misidentified complete mole, hydropic abortion, or twin pregnancy.

Malignant GTN may have contributions from both paternal and maternal genetic material. Choriocarcinoma

may be either paternal or biparental; however, the latter is more often associated with an intraplacental choriocarcinoma.[18]

Imprinting, Growth Factors, and Oncogenes

Imprinting is known to play a role in the development of GTD. Because paternal genetics impact placental growth but maternal genetics regulate fetal growth, the excess of paternal chromosomes leads to excessive placental or trophoblastic proliferation. The genomic imbalance contributes to changes in various growth factor gene expression and paternal antigen expression, leading to growth dysregulation and immunologic changes. Additionally, the malignant potential of moles may vary depending on its heterozygous or homozygous nature. For instance, one study found there was a Y chromosome detected in only 9% of hydatidiform moles but 50% of invasive moles and 74% of choriocarcinomas.[19]

Genetic mutations and instability have also been implicated in the development of GTD. For instance, one study evaluating samples from hydatidiform moles and choriocarcinoma found somatic point mutations and mitochondrial DNA instability.[20] These genetic aberrations lead to the potential changes in oncogenes, tumor suppressive genes, and various molecular pathways that affect malignant transformation.

Various oncogene products have been found to be elevated in GTD (Table 42–1). For instance, cell lines from choriocarcinoma have abundant expression of epidermal growth factor receptor (EGFR). This is driven by the paracrine effect of certain macrophage-derived cytokines such as interleukin-1 (IL-1-α, IL-1-β) and tumor necrosis factor, which can suppress cell growth and increase the expression of EGFR.[21] Additional studies have demonstrated the amplification and overexpression of oncogene products such as c-erbB-2, c-myc, c-fms, and mdm-2, which have been shown to be associated with higher proliferation index, more aggressive behavior, and malignant transformation of GTD.[22-24] Human placental growth hormone has also been detected in GTD and has been proposed as a possible biomarker.[25]

The downregulation of tumor suppressor genes may also play a role in disease development (see Table 42–1). For instance, GTD has been shown to downregulate p53, p21, and Rb,[26] and it has been shown that p53-dependent apoptosis likely mitigates trophoblastic proliferation.[27] Furthermore, other studies have also suggested that telomerase activity may also support the development of GTD and GTN.[22] Other molecules such as cell–cell adhesion molecules as well as matrix metalloproteinases and their tissue inhibitors also regulate invasion and thus may play a role in pathogenesis.[22]

TABLE 42–1 Genes Implicated in Gestational Trophoblastic Disease

p53
p21$^{WAF1/C1P1}$
mdm2
Rb (retinoblastoma)
c-myc7q21-q31
c-fms
c-erbB2
Bcl-2
Telomerase

Like many other diseases, the malignant transformation of GTD is likely a multistep process that involves many genetic changes that support tumor proliferation and invasion.

Familial Recurrent Hydatidiform Mole Syndrome

Familial recurrent hydatidiform mole syndrome is a rare disorder that leads to recurrent molar pregnancies. It is an autosomal recessive disorder with mutations in NLRP7 (70% of cases) or KHDC3L (5% of cases) that result in diploid complete moles of biparental origin compared with exclusively paternal origin.[28,29] Women with this disorder have a high rate of complete hydatidiform mole (74%), but partial moles (4%) are also possible. For these women, only 5% of pregnancies are normal; the rest are spontaneous abortions (17%).[30] Normal live birth may be difficult to achieve for these women and may require use of oocyte donation and reproductive endocrinology referral.

PATHOLOGY AND CYTOGENETIC TECHNIQUES

Historically, GTD was diagnosed based on pathology alone. Each histologic subtype has its own specific pathologic criteria and characteristics. However, because of the use of routine ultrasonography in early pregnancy, tissue is often obtained in an earlier gestation, and the diagnosis of molar pregnancy based on histology alone is difficult. Thus, diagnostic criteria has shifted to include cytogenetic techniques along with pathology to diagnosis GTD. Overall, recognizing moles and distinguishing complete from partial moles is important because of differing risk of persistent trophoblastic disease and malignancy, which is considerably higher after a complete mole (15%–20%) than a partial mole (<5%).

Complete Mole

Hydatidiform moles are confined to the uterus. Complete hydatidiform moles are characterized by total hydatidiform enlargement of the villi surrounded by hyperplastic and atypical trophoblasts. Fetal parts, fetal blood vessels, and fetal blood are absent (Table 42–2). Traditionally, this was typically seen and diagnosed in the second trimester, but because of early detection, hydatidiform moles are now often suspected in the first trimester. Early-gestation complete moles lack the characteristic hydropic villi. Instead, they demonstrate villi with characteristic redundant bulbous terminal villi, hypercellular myxoid stroma, budding typically with nonpatchy trophoblastic hyperplasia, stromal karyorrhectic debris, and collapsed abnormal villous blood vessels.[31]

When pathologic signatures are difficult to detect, cytogenetic techniques may be used. Chromosomal banding and restriction fragment length polymorphism (RFLP) analysis of DNA allow unique chromosomal patterns of complete molar pregnancies to be identified and differentiated.[27,32] Immunohistochemistry (IHC) detection of p57,[KIP2] an imprinted gene expressed only by maternal alleles, is also helpful. A negative screen result is diagnostic for a complete mole because the placenta of all other gestations demonstrate nuclear staining of cytotrophoblast and villous mesenchyme.[33]

Partial Mole

In contrast, partial hydatidiform moles typically include hydatidiform changes of the villi accompanied by identifiable embryonic tissue or amniotic membranes. They typically have less pronounced histopathologic features such as less edema and trophoblast proliferation compared with complete moles. The hydatidiform changes to the villi tend to be focal rather than diffuse (see Table 42–2). They demonstrate patchy villous hydrops with scarred, abnormally shaped and scalloped, irregular villi with trophoblastic pseudo-inclusions and patchy trophoblastic hyperplasia. Their villous capillaries are more functional because they possess the same proportion of nucleated fetal erythrocytes as an embryo. In partial moles, hydatidiform changes occur at a slower rate compared with complete moles.

Again, chromosomal banding and RFLP may be used to identify unique chromosomal patterns of partial molar pregnancies. Chromosomal ploidy analysis may also be helpful to distinguish between partial (triploid) from complete (diploid) moles, although this cannot determine other etiologies of triploidy. This may be particularly helpful during a missed abortion that has developed hydropic villi suggestive but not diagnostic of partial mole.

TABLE 42–2 Features of Complete and Partial Hydatidiform Moles

	Complete	Partial
Fetal or embryonic tissue	Absent	Present
Hydatidiform swelling of chorionic villi	Diffuse	Focal
Trophoblastic hyperplasia	Diffuse	Focal
Trophoblastic stromal inclusions	Absent	Present
Genetic parentage	Paternal	Biparental
Karyotype	46,XX or 46,XY	69,XXY or 69,XYY
p57KIP2	Absent	Present
Persistent β-hCG elevation (%)	20	0.5

β-hCG, β human chorionic gonadotropin.

Invasive Mole

Invasive moles demonstrate the same histologic features as complete hydatidiform moles but are characterized by enlarged hydropic villi invasion into the myometrium. They are typically diagnosed after molar evacuation when serum human chorionic gonadotropin (hCG) levels remain elevated. They can invade locally, causing hemorrhage and necrosis, although uterine perforation rarely occurs. Although metastasis is rare, hematogenous metastases may occur and when it does, it is most often to the lungs. Approximately 10% to 17% of hydatidiform moles result in invasive moles, and roughly 15% of these metastasize to the lungs or vagina.[34] Occasionally, metastatic deposits demonstrate hydropic villi rather than sheets of anaplastic cells characteristic of metastatic choriocarcinoma.

Choriocarcinoma

Choriocarcinoma is a highly malignant tumor with a distinct histology. It can arise from any type of trophoblastic tissue but rarely after a partial mole. Grossly, these tumors are bulky with hemorrhagic and necrotic areas. Genetically, highly complex karyotypes have been reported, and most have XX karyotype.[12] Microscopically, these lesions consist of disordered sheets of anaplastic cytotrophoblasts and syncytiotrophoblasts without chorionic villi, with frequent mitoses and multinucleated giant cells. There is often direct invasion into the myometrium, which may result in disease found in the fallopian tubes and ovaries as well. Additionally, it is often accompanied by vascular invasion and thus may result in distant metastasis, such as in the lungs, brain, or liver.[3]

Placental Site Trophoblastic Tumor

PSTT is an extremely rate tumor that most often develops after nonmolar pregnancies but can also develop after the evacuation of a complete mole.[35,36] These tumors occur at the placental implantation site. Grossly, it appears as a white-tan to yellow nodular mass in the endomyometrium, with half the cases invading deep into the myometrium.[12] Histologically, it demonstrates monophasic extravillous trophoblast, which dissects between bundles of smooth muscle, sometimes with syncytial elements.[37] Intermediate trophoblastic cells have oval nuclei with abundant eosinophilic cytoplasm, and no chorionic villi are present. Syncytiotrophoblasts and cytotrophoblastic populations are also absent. PSTT has a nonaggressive behavior with less vascular invasion, necrosis, and hemorrhage than choriocarcinoma.[37] Even though it is usually a uterine-confined tumor, metastatic disease may occur, likely because of its propensity for lymphatic metastasis.

Molecular analysis may be performed. IHC staining reveals diffuse presence of cytokeratin, human placental lactogen, MUC-4, HSD3B1, HLA-G, and Mel-CAM (CD146).[12] hCG and inhibin may be present but only focally.[12] Most cells have a low mitotic count, and the proliferation index is modestly increased, with a ki-67 index of 14%.[38] PSTT shows rare genetic imbalances and instead are typically diploid.[3,6]

Epithelioid Trophoblastic Tumor

ETT is also a rare disease derived from chorionic-type extravillous trophoblasts, often characterized as a variant of PSTT. Grossly, the tumor appears as white-tan to brown discrete nodules or cystic hemorrhage masses invading deep into the surrounding tissues. Nearly half arise in the cervix or lower uterine segment, but some in the fundus and broad ligament. It develops from neoplastic transformation of chorionic-type intermediate trophoblasts.[2,39,40] Its mitotic count ranges from 0 to 9 per 10 high-powered field.[12] Extensive or geographic necrosis is often present. ETT often exists with other trophoblastic disease and is rather chemoresistant.[38] Most present many years after a full-term delivery.[2,39,40]

CLINICAL PRESENTATION

Complete Moles

The classic signs of a molar pregnancy were once vaginal bleeding in the absence of fetal heart sounds and a uterus larger than expected for gestational age.[6] However, because of the rise in early diagnosis from routine use of ultrasonography, these signs and symptoms occur less frequently. Nonetheless, 80% to 90% of complete hydatidiform moles present with vaginal bleeding between 6 to 16 weeks of gestation.[2]

For patients who do present at a later gestation, they may exhibit a constellation of signs and symptoms historically associated with molar pregnancy. Patients with complete moles often demonstrate a pre-evacuation hCG level greater than 100,000 mIU/mL. They may present with abdominal pain related to the enlarged uterus or the pathognomonic prune juice–like vaginal discharge produced from the liquefaction of intrauterine blood clots. Because of heavy and recurrent bleeding, patients may also present with iron-deficiency anemia more severe than expected for a normal pregnancy, and 50% of patients had symptomatic anemia at the time of diagnosis. Patients may also develop theca lutein cysts, which are ovarian cysts caused by hCG-induced hyperstimulation. Bilateral cysts occur in 15% of cases[2] and may cause pelvic pressure and fullness. Typically, these cysts regress spontaneously after uterine evacuation, but their rupture or tension can cause acute abdominal symptoms that may require surgical intervention.

A variety of other signs and symptoms can be identified at the time of diagnosis. Pregnancy-related hypertension may occur in the first or second trimester. Historically, 20% to 30% of patients present with early preeclampsia, thought be to precipitated by the release of large amounts of vasoactive substance from necrotic trophoblastic tissue.[41] Seizure activity is rare. Roughly 10% of patients may present with hyperemesis gravidarum, and 7% present with hyperthyroidism because of the structural analogy of hCG to thyroid-stimulating hormone.[42,43] Thyroid storm has been reported. Other rare presentations include respiratory distress, disseminated intravascular coagulation (DIC), or microangiopathic hemolytic anemia. Many of these symptoms were more common in the past before the routine use of early ultrasound examination in the first and second trimesters of pregnancy.

Partial Moles

Aside from vaginal bleeding seen in 75% of patients with partial hydatidiform moles, the clinical presentation is otherwise different compared with a complete mole. Patients with partial moles often have symptoms related to an incomplete or missed abortion, and diagnosis is made solely after histologic evaluation of the curettage specimen. Other symptoms such as excessive uterine enlargement, hyperemesis, hypertension, preeclampsia, hypothyroidism, and theca lutein cysts occur less frequently in partial hydatidiform moles.[42] Fewer than 10% of patients with partial moles present with an enlarged uterus.

An intact fetus can coexist with a partial mole, although this occurs in fewer than 1 in 100,000 pregnancies. A minority of patients, fewer than 10%, have a pre-evacuation hCG levels greater than 100,000 mIU/mL.[2] Thus, hormonal symptoms are less common for patients with partial moles compared with patients with complete moles.

Malignant Gestational Trophoblastic Disease

After surgical evacuation, 80% of patients with GTD demonstrate spontaneous remission. However, all patients should be observed closely for malignant transformation by monitoring for symptoms, signs, and serum hCG levels. Malignant GTN is diagnosed after evacuation by a rising or plateaued hCG level, evidence of metastatic disease, tissue diagnosis of choriocarcinoma, or postevacuation bleeding not caused by retained tissue.[6,12,44]

Metastatic GTN occurs in roughly 20% of patients after molar evacuation. It most often arises from choriocarcinoma, a highly vascular tumor with hematogenous spread. It can demonstrate extensive metastasis with spontaneous hemorrhage and subsequent symptoms. Some of these metastases may histologically appear identical to molar disease, but the vast majority are histologically more similar to choriocarcinomas.

As described earlier, 50% of GTN cases are found after a complete molar pregnancy, but it may also develop after a normal pregnancy, ectopic pregnancy, or abortion. For nonmetastatic GTN, patients may present with recurrent symptoms such as irregular vaginal bleeding, theca lutein cysts, asymmetric uterine enlargement, or persistently elevated serum β-hCG levels. Although rare, perforation by the tumor into the myometrium can cause intraperitoneal bleeding. Vaginal bleeding caused by tumor invasion into the uterine vessels, a vascular uterine mass, or vaginal metastasis may be a presenting symptom. Patients rarely may also present with sepsis and abdominal pain, particularly because the uterine mass may be a nidus for infection.[6]

Pulmonary metastases occur in 80% of patients with metastatic disease, arising from trophoblastic tissue that entered the circulation by uterine venous sinuses[45] (Table 42–3). This occurs spontaneously but may also happen after molar surgical evacuation. Because of its vascular nature, hemoptysis is common with lung involvement, but patients may also demonstrate chest pain, dyspnea, and cough. Pulmonary hypertension and pleural effusions may also develop. More commonly, patients are asymptomatic, and these are only be detected following diagnostic imaging such as a chest radiography or computed tomography (CT) scan. On imaging, these findings may be subtle and include alveolar, nodular, and military patterns.[46]

TABLE 42–3 Common Metastatic Sites in Gestational Trophoblastic Neoplasm

Lungs	80%
Vagina	30%
Pelvis	20%
Brain	10%
Liver	10%
Bowel, kidney, or spleen	<5%
Other	<5%
Serum[a]	<5%

[a]Persistent human chorionic gonadotropin after hysterectomy
Data from Berkowitz RS, Goldstein DP. Pathogenesis of gestational trophoblastic neoplasms. *Pathol Annu.* 1981;11:391-411.

However, when extensive, pulmonary metastases can in extreme cases cause respiratory failure and death.

Other sites of metastasis may include the vagina (30%), pelvis (20%), brain (10%), liver (10%), or gastrointestinal (GI) tract (<5%)[47] (see Table 42–3). Vaginal metastasis may cause bleeding or may be visualized as bluish deposits upon vaginal examination. In a patient with known or suspected GTD, it is important to not biopsy vaginal lesions because they can be highly vascular and lead to hemorrhage, which can be difficult to control. Patients may experience right upper quadrant pain with hepatic metastasis caused by stretching of the Glisson capsule. GI lesions can cause severe hemorrhage or perforation with peritonitis, both of which would require emergent surgical intervention. Biopsy of these metastatic lesions is contraindicated because uncontrolled bleeding may occur.

Central nervous system (CNS) metastasis suggests widespread disease. This occurs in 7% to 28% of patients with metastatic choriocarcioma.[45,46] Patients often present with headache, hemiparesis, vomiting, dizziness, coma, grand mal seizures, visual disturbances, aphasia, and slurred speech. Weight loss and anorexia may also occur. Of note, in one third of cases with CNS metastasis, there is no vaginal bleeding.[6]

PSTT and ETT present in similar ways as invasive moles and nearly always demonstrate abnormal vaginal bleeding because the disease typically remains localized to the uterus.[35] These tumors produce only small amounts of hCG relative to their size, and in some cases, hCG levels may even be normal.[6] Human placental lactogen may be elevated in PSTT and ETT and in some patients may be a better tumor marker. Lymphatic metastasis may occur but is rare, occurring in 5% of PSTT cases.[13]

DIAGNOSIS

Diagnosis of a hydatidiform mole is made by histologic examination of a surgically excised specimen,

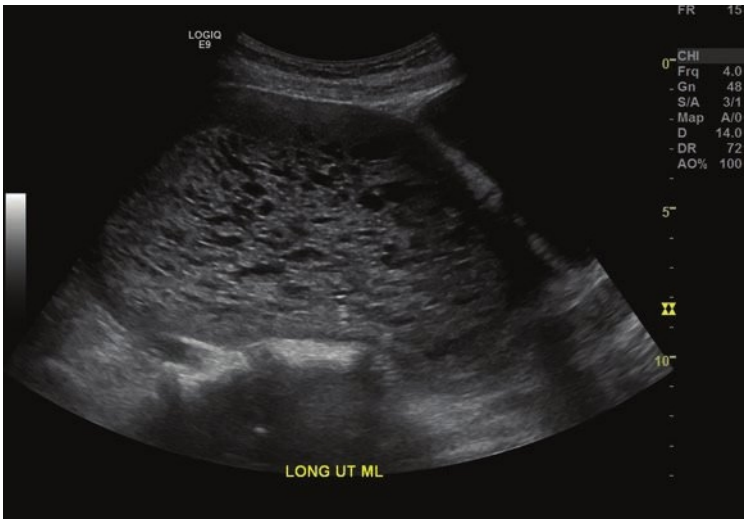


FIGURE 42–1 **Pelvic ultrasound of patient with complete hydatidiform mole. Note the classic "snowstorm" appearance caused by numerous chorionic villi with diffuse hydatidiform swelling.**

typically a curettage specimen. After curettage, the patient is monitored with serial hCG levels. The diagnosis of persistent GTN or malignant GTN is then made by plateauing or rising hCG levels during this surveillance.

Histologic diagnosis of extrauterine metastases from an invasive mole or choriocarcinoma should never be attempted because a biopsy can cause massive, life-threatening hemorrhage. Instead, hCG levels are sensitive and adequate to make the diagnosis of malignant GTN without histologic confirmation.

Because PSTT and ETT do not typically arise after molar pregnancy, their diagnosis is usually made upon examination of the curettage, biopsy, or hysterectomy specimen.[6]

Radiologic Imaging

Pelvic ultrasonography plays a central role in assisting in diagnosis but is not diagnostic of GTD. Upon sonographic evaluation, a complete hydatidiform mole has heterogeneous intrauterine material with multiple cysts, or the classic "snowstorm" appearance, because of numerous chorionic villi with diffuse hydatidiform swelling[48] (Fig. 42–1). In contrast, an early complete mole may appear similar to an embryonic death, an incipient pregnancy, or blighted ovum on ultrasonography.[49] But as gestational age increases, molar pregnancies may take on a more classic appearance of a complete hydatidiform mole on ultrasound. As a result, the rate of ultrasound detection of complete moles increases with gestational age. Additionally, theca lutein cysts on the ovaries may also be seen on pelvic sonographic evaluation, often when hCG levels are high.[50] The presentation of partial hydatidiform moles on ultrasonographic evaluation is also dependent on gestational age, and these may be more difficult to evaluate because of the presence of fetal parts mimicking an early pregnancy. Thus, partial moles may be typically suspected later in the first trimester, when a thickened placenta is visualized.[49]

After the diagnosis of malignant GTN, additional imaging is imperative for staging purposes and to determine the presence or absence of metastatic disease. The most common site of metastatic disease is the lung, and thus a chest x-ray examination should be performed in all patients. This is able to detect lung metastases larger than 1 cm and that present as multiple, well-defined, dense, and rounded opacities.[49] Although a normal chest x-ray examination does not necessarily need to be followed by a chest CT, given modern CT scans with lower dosages, a CT of the chest, abdomen, and pelvis is also appropriate and in higher resource settings is recommended because it can assess for pulmonary as well as abdominal and pelvic metastases all at once (Fig. 42–2). When using a chest CT for staging, though, only those greater than 1 cm should be counted because micrometastases are not associated with change in prognosis for patients[51,52] (Fig. 42–3).

If initial chest imaging findings are abnormal with an elevated hCG, further evaluation should be undertaken to assess for additional metastasis such as in the liver and brain. If not already done, this should include CT of the abdomen and pelvis, and CT or magnetic resonance imaging (MRI) of the brain. Although brain metastases can be seen by brain CT, it is better assessed using MRI.[49] Although MRI is not routinely used for the extracranial evaluation of GTN, it may be helpful as an ancillary tool in an atypical presentation,

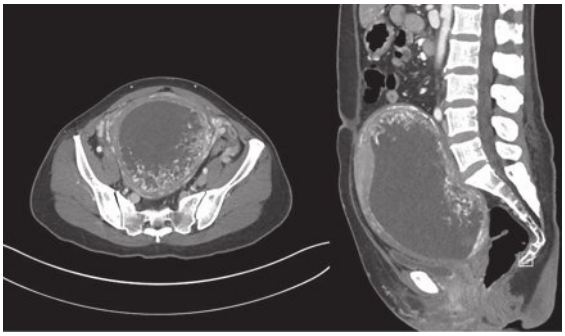


FIGURE 42–2 Computed tomography scan of the pelvis of a patient with gestational trophoblastic disease. Note the enlarged uterus. A. Axial section of the pelvis. B. Sagittal section of the pelvis.



FIGURE 42–3 Computed tomography scan of the lung of a patient with metastatic choriocarcinoma. The *arrow* indicates a metastatic lung lesion.

recurrent disease, or PSTT or ETT or to evaluate the primary tumor and local disease invasion in patients who are undergoing surgical treatment.[49]

Laboratory Tests

During pregnancy, syncytiotrophoblasts secrete chorionic gonadotropin, a glycoprotein hormone that is essential for the maintenance of the corpus luteum and thus the pregnancy itself. This hormone is composed of an α subunit, which is identical to the α subunit of the pituitary hormone, and a β subunit (β-hCG), which is unique to trophoblastic tissue and confers its specific biologic activity. The hormone becomes detectable 8 days after ovulation, and its level doubles every 2 to 4 days, reaching its peak at 10 to 12 weeks of gestation followed by a steady decline. Because all trophoblastic tumors secrete β-hCG, its level serves as an excellent biomarker for tumor activity in nonpregnant patients.[6,53]

In a normal pregnancy, hCG is hyperglycosylated with both subunits in the first trimester. However, in GTD, hCG can exist in a variety of forms, such as a free β-subunit, nicked free β-subunit, c-terminal peptide, β-core, or hyperglycosylated form.[54] Because the assay used to detect and monitor hCG levels in the setting of GTD must recognize all these possible forms, home pregnancy tests are not recommended; instead, commercial assays should be used.[3,6] Even so, some commercial assays may only detect pregnancy-related hCG and thus are unreliable for detecting GTD-related isoforms, leading to false-negative readings. Alternatively, assays may be ineffective if they cross-react with heterophile antibodies, leading to false-positive results.[3,6] Of note, heterophile antibodies are large and filtered in the renal glomerulus and thus not able to pass through into the urine. As a result, urine pregnancy tests may be useful to exclude a false-positive test result from heterophile antibodies.

Overall, a patient's hCG level correlates with burden of disease in both hydatidiform moles as well as GTN. Because of this, the diagnosis of postmolar GTN is determined by β-hCG levels. Based on the International Federation of Gynecology and Obstetrics (FIGO) criteria, the diagnosis of postmolar GTN based on hCG levels occurs when[55–57]

- Weekly hCG levels plateau (remain within 10% of the previous result) over a 3-week period
- hCG levels increase more than 10% across three values recorded over a 2-week duration

This in turn assists in determining the need for additional therapy. Of note, elevations in hCG levels should also prompt an evaluation and work-up to rule out a new pregnancy. After initiating chemotherapy, monitoring of serial β-hCG levels is mandatory throughout treatment to ensure adequate therapy. Because the level of β-hCG is considered proportional to the tumor burden, it is a direct measurement of how efficacious the current therapy is.

Other biomarkers may be helpful for correlation of tumor burden as well. Previously, the ratio of β-hCG in the serum compared with that in the cerebrospinal fluid was used to detect brain metastases in GTD, with a ratio of less than 10:1 considered a positive predictor for brain metastases.[58] However, now with the availability of MRI, this is rarely used.

In the setting of GTD, other laboratory tests may be used during evaluation and treatment. CA-125 may have a role as a marker for GTD, particularly with its elevation in the development of persistent GTD.[59] Human placental growth hormone is also detected in variants of GTD and has been postulated as a potential biomarker for diagnosis.[25] The complete blood count is helpful to determine anemia and thrombocytopenia because bleeding is a common symptom. DIC is an uncommon presentation but may occur in patients with excessive blood loss. With DIC, clotting times may be prolonged, and coagulation factors may be consumed. Hepatic and renal impairment is rare. Thyroid function studies should be performed in patients with a clinical history or physical examination concerning

for hyperthyroidism. Thyrotoxicosis, although rare, can occur in patients with very high β-hCG levels (<100,000 IU/L) and if present can make surgery risky. If the patient is to undergo surgical management and thyrotoxicosis is present, prompt coordination with anesthesia before any procedure is important, including a dilation and curettage.[60]

PHANTOM HUMAN CHORIONIC GONADOTROPIN SYNDROME

Phantom hCG syndrome, otherwise known as phantom choriocarcinoma syndrome or pseudohypergonadotropinemia, is a persistent mild elevation of hCG when no true hCG or trophoblastic tissue exists. This is because of the presence of heterophile antibodies that interfere with the detection assay. Phantom hCG syndrome is clinically significant because it may lead to unnecessary treatment after primary evacuation or after successful chemotherapy for GTN.

Heterophile antibodies cause false-positive test results because they are able to mimic hCG immunoactivity in the sandwich enzyme-linked immunosorbent assay. They bind both the capture and tracing antibody, thereby causing a false-positive result. Because large heterophile antibodies are filtered at the level of the glomerulus, the urine hCG test is negative in the setting of a heterophile antibody. Thus, urine pregnancy tests should be used to rule out false-positive assay results and aid in the diagnosis of phantom hCG.

Aside from urine pregnancy tests, serial dilutions may also be used to determine phantom hCG syndrome. Nonlinearity in serial dilutions suggests the presence of heterophile antibodies and interference in the assay. Other differential diagnoses for elevated hCG may be considered, which include all forms of GTD, germ cell tumors, any cancer that has undergone trophoblastic differentiation (including epithelial cancers), and very rarely, familial elevated hCG.[13] If both urine and serum hCG test results are positive, then real hCG is present, and occult malignant GTD must be excluded.

STAGING AND PROGNOSIS

There are many staging and prognostic systems used to characterize GTD. These systems determine prognostic groups to direct optimal therapy options to ensure the highest possible cure rate. More specifically, it predicts the potential for development of resistance to single-agent chemotherapy with methotrexate or dactinomycin. Patients are classified based on individual risk factors such as histologic subtype, extent of disease, hCG titer before treatment, duration of disease, nature of antecedent pregnancy, and extent of prior treatment. The most commonly used system is the FIGO 2000 staging system (Table 42–4), which was developed from the World Health Organization (WHO) scoring system (Table 42–5). A score of 0 to 6 suggests low-risk disease or low risk of resistance to single-agent chemotherapy, and thus treatment with single-agent chemotherapy is most likely appropriate.[55] Patients with a score greater than 6 have high-risk disease or a higher risk of developing resistance to monotherapy and are best treated using combination therapy.[6,55]

TABLE 42–4 International Federation of Gynecology and Obstetrics 2000 Staging System for Gestational Trophoblastic Disease[a]

Stage	Description
I	Tumor confined to the uterus
II	Tumor extends to other genital structures (ie, ovary, fallopian tube, vagina, broad ligaments) by metastasis or direct extension
III	GTN extends to the lungs with or without known genital metastases
IV	All other metastases

[a]Stage should be followed by World Health Organization score (eg, stage I:3 or stage IV:12).
GTN, gestational trophoblastic neoplasia.

More than 50% of patients with scores of 5 or 6 will fail single-agent therapy and require combination chemotherapy. Despite this, single-agent therapy is still used initially for these patients to spare patients who do respond to the more toxic effects of combination therapy.[61]

Other factors have also been identified that may assist in predicting drug resistance and prognosis. These include pulsatility index, which uses Doppler ultrasonography, measures uterine vascularity, and predicts methotrexate resistant disease.[61] Additionally, hCG regression nomograms and kinetics may assist in predicting early onset of resistance with a single-agent therapy.[62] None of these is as studied or widely accepted as the WHO criteria.

MANAGEMENT

Each patient is considered individually based on the FIGO 2000 scoring system. The following outlines the general diagnostic and therapeutic approaches used at the University of Texas MD Anderson Cancer Center.

TABLE 42–5 World Health Organization Prognostic Scoring for Gestational Trophoblastic Disease

WHO Score	0	1	2	4
Age (years)	**<40**	**≥40**	**—**	**—**
Antecedent pregnancy	Hydatidiform mole	Abortion	Term	
Interval months from index pregnancy	<4	4 to <7	7 to <13	≥13
Pretreatment serum hCG level (IU/mL)	$<10^3$	10^3 to $<10^4$	10^4 to $<10^5$	$\geq 10^5$
Largest tumor size (including uterus)	<3 cm	3 to <5 cm	≥5 cm	-
Site of metastases	Lung	Spleen, kidney	GI	Liver, brain
Number of metastases	—	1 to 4	5 to 8	>8
Previous failed chemotherapy	—	—	Single drug	Two or more drugs

Low risk ≤6; hgh risk ≥7.
This combination of the modified World Health Organization (WHO) risk factor scoring system with the International Federation of Gynecology and Obstetrics (FIGO) Cancer Staging and Nomenclature Committee in September 2000 and ratified in June 2002 with the FIGO announcement.
GI, gastrointestinal; β-hCG, β human chorionic gonadotropin.
Modified with permission from Kohorn EI. The new FIGO 2000 staging and risk factor scoring system for gestational trophoblastic disease: description and critical assessment. *Int J Gynecol Cancer.* 2001;11(1):73-77.

Molar Pregnancy

Primary Treatment

Hydatidiform mole is curable and treated with surgery. Suction evacuation and curettage, often performed under ultrasound guidance, is the preferred method of treatment to ensure removal of all molar tissue and avoid uterine perforation.[3] If the uterus is greater than 16 weeks in size, there is an increased risk of pulmonary embolization of molar tissue, and thus care at a referral center should be considered if possible.[6] Bleeding is variable, but the overall risk of hemorrhage increases with uterine size, so available blood products for transfusion should be available if the uterus is greater than 16 weeks.[12] The use of intravenous oxytocin infusion with the onset of the surgery may be considered to limit blood lost, but caution is necessary in patients with comorbidities because of the risk of hyponatremia and fluid overload.[63] Rh-negative patients with partial hydatidiform moles should be appropriately given anti-D immunoglobulin prophylaxis.

If the patient has completed childbearing and no longer desires future fertility, hysterectomy to remove the uterus with the mole intact is reasonable (Fig. 42–4). The ovaries should be preserved, even if theca lutein cysts are present. Removal of the uterus allows for permanent sterilization while also decreasing the possible need of subsequent chemotherapy because of persistent disease.[45]

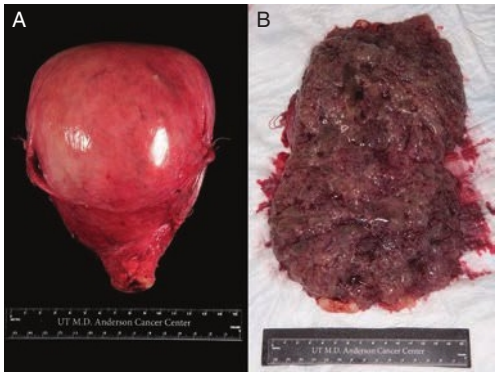


FIGURE 42–4 Gross specimen of complete molar pregnancy removed with hysterectomy. A. Enlarged uterus. B. Uterus opened demonstrating diffuse trophoblastic tissue within the cavity.

Postsurgical Care and Indications for Chemotherapy

After primary surgical treatment, weekly serum β-hCG levels should be obtained until three consecutive weekly assays are normal. This typically occurs within 8 weeks, but roughly 20% of patients continue to have elevated β-hCG levels for 14 to 16 weeks after surgical evacuation. Patients with complete molar pregnancies and normalization of β-hCG levels should continue to be monitored with monthly serum β-hCG levels for 6 months. Because of the risk of subsequent GTN is

much lower in those with partial molar pregnancies (0.5%-1%) and because when hCG normalizes, this risk falls to 1 in 3000, most centers follow-up women with partial hydatidiform moles that normalize without chemotherapy with serial hCG levels until they have two normal values.[6,44,61]

Although historically, guidelines recommended use of contraception to avoid pregnancy for 12 months after normalization of hCG levels, more recent data have demonstrated that there is no increased risk of recurrent molar pregnancy between 6 and 12 months.[13] Thus, most experts recommend only 6 months of contraception.[6] There is a relative contraindication to intrauterine devices because of the potential risk of uterine perforation.[64,65] Oral contraceptive pills are considered the contraception of choice because they are also helpful to suppress luteinizing hormone, which may interfere with the detection of low levels of hCG. Currently, there is no evidence in regard to use of etonogestrel implants or Depo-Provera injection for contraception in this patient population.

The majority of patients after surgical evacuation do not need any further therapy, but 20% will develop malignant disease requiring further management.[66–68] Pathology from these patients include complete hydatidiform mole (78%), partial hydatidiform mole (9%), and choriocarcinoma (8%).[67] Most of these patients (81%) have low-risk disease based on FIGO 2000 criteria (see Table 42–5), 18% have high-risk disease, and 1% have PSTT. Malignant disease requiring further therapy is based on the following criteria[6,44,55–57]:

- Weekly hCG levels plateau (remain within 10% of the previous result) over a 3-week period
- hCG levels increase more than 10% across three values recorded over a 2-week duration
- Persistence of detectable serum hCG for more than 6 months after a molar evacuation
- Tissue diagnosis of choriocarcinoma
- Evidence of metastatic disease
- Elevation of β-hCG level after a normal result
- Postevacuation bleeding not caused by retained tissues

Of note, an elevated but downtrending hCG level 6 months after molar evaluation does not mandate chemotherapy because hCG levels often spontaneously normalize in these patients,[69] but restaging with imaging and close monitoring is important. However, a level greater than 20,000 IU/L for more than 4 weeks after evacuation does prompt use of chemotherapy because the risk for uterine perforation and hemorrhage is high.[3,6] It is imperative to use effective contraception and to exclude any new pregnancy during this surveillance period rather than assume development of GTN.

Prophylactic Chemotherapy

Prophylactic adjuvant chemotherapy after molar evacuation is controversial and not recommended because the risk outweighs the benefit, except in rare occasions when follow-up compliance is not possible in low-resource settings.[6,70] Overall, surveillance is mandatory for all patients, and unnecessary chemotherapy exposes many women to medication toxicity and may induce drug resistance.[71,72]

Malignant Gestational Trophoblastic Disease

After diagnosis of malignant disease, patients should be appropriately evaluated to determine staging and scoring. For patients diagnosed via hCG monitoring, examination should include history, physical examination, serum hCG level, pelvic ultrasonography (to exclude pregnancy, measure uterine size, and exclude any pelvic metastasis), and chest radiography. If disease is seen on chest x-ray imaging to suggest pulmonary metastasis, chest CT should be obtained, but only lesions seen on chest radiography should be used for scoring.[6,55] If possible, especially in high-resource settings, initial radiologic evaluation should probably be with CT of the chest, abdomen, and pelvis. As stated earlier, though, pulmonary nodules smaller than 1 cm in size should not be counted in staging and scoring purposes. Routine brain imaging is probably not necessary, but if there is evidence of pulmonary metastasis, brain imaging with CT or MRI (MRI preferred) is necessary.

For patients diagnosed with malignant diseased based on pathology demonstrating choriocarcinoma or suspected GTN after a nonmolar pregnancy, full-body imaging should be obtained because of the potential for aggressive disease. This should include CT of the chest and abdomen, MRI of the brain and pelvis, and pelvic ultrasound.[6]

After evaluation, patients are stratified and staged based on the FIGO 2000 staging incorporating the modified WHO scoring system (see Tables 42–4 and 42–5). This determines the patient's initial treatment plan. Patients are stratified to the low-risk group, or a score of 0 to 6, who have a low risk of developing resistance to single-agent chemotherapy, or they are stratified to a high-risk group, or score of greater than 6, indicating a high risk of resistance to single-agent chemotherapy requiring use of combination therapy.

Low-Risk Disease

The overall prognosis for patients with low-risk disease is exceptional because current therapies result in a cure rate close to 100%, despite the presence of metastatic disease or resistance to first- or second-line therapy.[61] For patients who no longer desire fertility,

hysterectomy can be the primary treatment, although this may not eliminate the need for additional chemotherapy. However, most patients are of reproductive age and desire future fertility and thus should receive chemotherapy as first-line therapy for low-risk disease. Because of a low WHO score, these patients are suitable for single-agent chemotherapy (Table 42–6).

Both methotrexate, with or without folinic acid, and dactinomycin are suitable single-agent therapies for patients with low-risk disease (see Table 42–6). Several studies have evaluated various schedules for these therapies, with a variety of inclusion criteria, which makes them difficult to compare for a superior regimen.

One randomized trial was completed comparing low-dose, weekly methotrexate (30 mg/m^2) with 14-day dactinomycin. This study found that dactinomycin was superior with a complete response rate of 53.3% compared with 69.7%, respectively.[73] The major flaw of this study is the use of a known inferior methotrexate regimen. Despite these results, many still favor the use of methotrexate, possibly because of a better side effect profile, with no alopecia, less nausea and vomiting, and less myelosuppression compared with dactinomycin use.[13] There are a lot of retrospective as well as registry data that show high efficacy for other methotrexate regimens. These multidose regimens use folinic acid rescue and have efficacy rates that equal single-agent dactinomycin. On the other hand, dactinomycin arguably has superior efficacy with a less frequent dosing schedule.[6] To add, efficacy of these regimens may also differ within this low-risk disease group depending on WHO score. In the Gynecologic Oncology Group study mentioned earlier, weekly intramuscular methotrexate is successful in 70% of patients with WHO scores of 0 or 1,[73] but this drops to 40% in patients with WHO scores of 2 to 4 and then 12% in patients with WHO scores of 5 or 6.[74] As a result, many do not recommend or use weekly methotrexate regimens or, at best, suggest that weekly methotrexate should be reserved for patients with WHO scores of 2 or less, and biweekly pulsed dactinomycin or multiday methotrexate regimens should be the preferred treatment for women with WHO scores of 5 or 6.

Treatment of patients with low-risk disease confined to the uterus may also consider a second suction curettage. One prospective study found that 38% of patients treated with a second curettage instead of a single-agent chemotherapy demonstrated normalization of hCG levels without significant morbidity.[75] Routine use of second curettage should be avoided. In patients who wish to avoid chemotherapy and have low WHO scores, it can be considered with careful counseling about the high likelihood of needing chemotherapy anyway as well as the fact that the course of treatment might be prolonged.

During treatment, patients should be monitored with every 1- to 2-week serum hCG levels to determine response. If a persistent elevation over 3 consecutive weeks is demonstrated or an increase over 2 consecutive weeks lasting more than 2 weeks, resistance to first-line therapy is demonstrated.[6] However, if levels are low, phantom hCG syndrome should be ruled out.

Rescoring of patients who develop resistance to primary chemotherapy is not always necessary unless levels remain persistently elevated over a long period of time and PSTT or ETT is suspected.[61] Restaging imaging can also be considered in patients with low-risk disease who have plateaued or rising β-hCG levels to determine if they have now become high-risk and require multiagent therapy or can switch to another single-agent regimen. Hysterectomy is offered if disease is confined to the uterus; however, if the patient wishes to retain fertility, alternative chemotherapy is recommended. Patients initially treated with methotrexate with low hCG levels may consider

TABLE 42–6 Chemotherapy Regimens for Low-Risk[a] Gestational Trophoblastic Disease

Drug	Administration	Cycle[b] (days)
Methotrexate and folinic acid	50 mg IM on days 1, 3, 5, and7 15 mg PO on days 2, 4, 6, and 8	14
Methotrexate and folinic acid	1 mg/kg (≤70 mg) IM or IV on days 1, 3, 5, and 7 0. 1 mg/kg IM or IV on days 2, 4, 6, and 8	14
Methotrexate	0.4 mg/kg IM or IV daily for 5 days	14
Methotrexate	30–50 mg/m^2 IM	7
Dactinomycin	10 μg/kg (maximum, 0.5mg) IV daily for 5 days	14
Dactinomycin	1.25 mg/m^2	14

[a]Therapy based on World Health Organization risk criteria.
[b]Withhold treatment for marrow recovery if necessary.
IM, intramuscular; IV, intravenous; PO, oral.

dactinomycin if hCG level is less than 300 IU/L.[61,76] Patients who fail initial single-agent therapy with higher levels of hCG should be treated with combination etoposide, methotrexate, and dactinomycin alternating weekly with cyclophosphamide and vincristine (EMA-CO) chemotherapy.[61]

When hCG levels have normalized (<5 IU/L), three additional treatments of chemotherapy past normal are recommended to minimize the potential for recurrence.[6,77] Two additional cycles may be adequate in low-risk patients.

High-Risk Disease

High-risk disease is unlikely to be cured with single-agent chemotherapy. Additionally, these patients are at highest risk of treatment failure. Instead, these patients should be treated with combination therapy, first-line regimen being EMA-CO[78] (Table 42–7). The survival rate for patients with high-risk choriocarcinoma using this regimen is 83%.[79] It is generally well tolerated with toxicity including alopecia, mild anemia, neutropenia, and stomatitis. Reproductive function is preserved in 75% of patients. As for patients with significant tumor burden, rapid tumor necrosis may result in hemorrhage, and thus consideration may be given to a lower dose induction therapy first. After normalization of hCG, three additional consolidation cycles (6 weeks) of EMA-CO are administered.

EMA-CO is considered first-line therapy for high-risk disease (see Table 42–7). Other regimens such as EMA-EP (etoposide, methotrexate, dactinomycin, cisplatin) or the ACE regimen (dactinomycin, cisplatin, and etoposide) appear to be effective but are usually used only in special circumstances or as salvage therapy after failing EMA-CO.[80] Patients should be treated until β-hCG normalizes and then given three postnormalization consolidative cycles of chemotherapy.

Metastases Requiring Special Care

For patients with advanced metastatic disease, certain considerations may need to be taken. For patients with significant vaginal bleeding, resuscitation with blood products may be required until resolution of bleeding may occur, typically within 3 or 4 days. Other temporizing measures to consider may include embolization, hysterectomy, and arterial ligation.[81] Overall, though, death is rare with appropriate resuscitation and management.

Patients with widely metastatic disease, sometimes referred to as being at ultra-high risk, as noted with a WHO score greater than 12, may be at significant risk for pulmonary, intraperitoneal, and intracranial hemorrhage (Fig. 42–5). Therefore, lower dose induction chemotherapy should be considered first followed by full-dose combination chemotherapy to decrease morbidity and mortality. This includes use of induction low-dose etoposide 100 mg/m^2 and cisplatin 20 mg/m^2 (EP; days 1 and 2, every 7 days) to reduce early deaths before starting EMA-CO. In one study, EP induction was given to 23.1% of high-risk patients (33 of 140)

TABLE 42–7 EMA-CO: Preferred First-Line Chemotherapy Regimen for High-Risk[a] Gestational Trophoblastic Disease

Drug Regimen		Administration
Course I (EMA)		
Day 1	Etoposide	100 mg/m^2 IV over 30 minutes
	Methotrexate	300 mg/m^2 IV over 12 hours
	Dactinomycin	0.5 mg IV bolus
Day 2	Etoposide	100 mg/m^2 IV over 30 minutes
	Folinic Acid	15 mg IV/IM/PO every 6 hours for four doses, beginning 24 hours after start of methotrexate
	Dactinomycin	0.5 mg IV bolus
Course II (CO)		
	Cyclophosphamide	600 mg/m^2 IV over 30 minutes
	Vincristine	0.8 mg/m^2 (up to 2 mg) IV bolus
Repeat each regimen in sequence every 14 days as toxicity permits.		

[a]Therapy based on the World Health Organization risk criteria.
[b]In case of central nervous system metastases, the dose of infused methotrexate is increased to 1000 mg/m^2 IV over 12 hours after alkalization of the urine. Increase the number of folinic acid doses to eight given every 6 hours. This regimen is called "high-dose methotrexate EMA-CO."
IV, intravenous; PO, oral.

with large disease burden for one to four cycles, and the early death rate was reduced to only 0.7% compared with 7.2% before its use.[82]

Pulmonary metastases can be extensive and concerning for respiratory failure and death.[83] Some factors associated with respiratory compromise or early death include cyanosis, pulmonary hypertension, dyspnea, anemia, tachycardia, extensive (>50%) lung opacification, mediastinal involvement, bilateral pleural effusion, and an elevated WHO prognostic score.[84] For patients with extensive pulmonary disease, induction chemotherapy, as described earlier, has been suggested to decrease the risk of respiratory failure, although this strategy may not protect against pulmonary failure and death.[84]

Patients with CNS metastasis require additional unique considerations (see Fig. 42–5). These patients may need neurosurgical intervention acutely to manage any bleeding or concern for increased intracranial pressure. Whole-brain radiotherapy may be considered (3000 cGY or radiotherapy over 10 fractions), but this is controversial because no evidence currently exists to support improved long-term outcomes, and instead this may increase risk of memory impairment and secondary cancers.[13] Other centers recommend initiating induction EP repeated weekly for 1 to 3 weeks until stabilized followed by a high-dose methotrexate EMA-CO chemotherapy unless the WHO score is 13 or greater or if other poor prognostic factors are present.[85] In this regimen, the methotrexate dose is increased to 1 mg/m.^{2} Alternatively, intrathecal methotrexate 12.5 mg may be considered with CO, but this should not be concurrently administered with whole-brain radiotherapy because of the risk of multifocal leukoencephalopathy.[86] Intrathecal methotrexate should only be given in a multidisciplinary setting at centers experienced with intrathecal chemotherapy.

For patients with WHO scores of 13 or greater, EP-EMA should be considered instead of EMA-CO with increased methotrexate dose.[82,87] Intrathecal methotrexate may also be given with EP.[86]

At the end of chemotherapy, stereotactic radiotherapy or gamma-knife treatment may be considered to treat any residual unresectable lesions.[61] The overall survival rate in patients with CNS metastasis is as low as 67% with the use of whole-brain radiotherapy combined with chemotherapy,[85] but a cure rate of 88% has been reported with use of chemotherapy alone.[88] Again, patients with CNS metastases should be ideally managed in a multidisciplinary manner at a high-volume center.

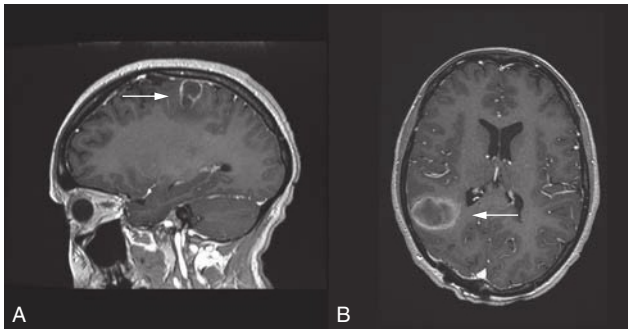


FIGURE 42–5 Magnetic resonance imaging scan of the brain of a patient with metastatic choriocarcinoma. A. Sagittal section of the brain. B. Horizontal section of the brain. *Arrows* demonstrate a metastatic lesion.

Patients in First Remission

Patients in first remission with high risk of recurrence are monitored closely with serum β-hCG levels and posttreatment baseline radiologic imaging. Patients with lung metastases should have a repeat high-resolution CT scan at the end of chemotherapy to serve as a baseline for follow-up. Often, these patients may have residual nodules seen on imaging indicating fibrous scar tissue. Similarly, patients with brain metastases should have MRI of the head obtained at the end of therapy, and patients with liver metastases should have a CT scan of the abdomen. If the uterus remains in place, a baseline MRI of the pelvis should also be considered. This is because modest increases in β-hCG levels signifying relapse may be accompanied by subtle changes in previously "sterile" lesions seen on initial posttreatment images. In certain situations, these solitary or oligometastatic "resistant" lesions may be amenable to surgical resection. If the imaging obtained after chemotherapy reveals suspicious nodules or masses while β-hCG levels are normal, a positron emission tomograph (PET)–CT scan may be warranted to serve as a baseline.[89] If the β-hCG level rises during follow-up, PET-CT helps identify any active disease.[89]

Salvage Therapy

Although most patients with GTN re cured with standard therapy, 20% to 25% of patients with high-risk metastatic disease will have persistent or recurrent GTN. For these patients, surgical resection, alternative chemotherapy often with a platinum-based regimen (Table 42–8), and immunotherapy should be considered.

The most commonly used chemotherapy regimen is EP-EMA, with omission of day 2 etoposide and dactinomycin and alternating weekly with etoposide and cisplatin. This has a cure rate greater than 75% but is associated with significant toxicity[64,90] (see Table 42–8). Some evidence suggests that TE/TP (paclitaxel and etoposide alternating weekly with paclitaxel and cisplatin) may be equally as efficacious but with less toxicity.[6,91] Other therapies may include ACE; VIP (etoposide, ifosfamide, and cisplatin); BEP (bleomycin,

TABLE 42–8 Common Salvage Therapies for Gestational Trophoblastic Disease

Drug Regimen		Administration
EP/EMA		
Course 1 (EP)	Etoposide	150 mg/m² IV over 1 hour
	Cisplatin	25 mg/m² IV over 4 hours
	Cisplatin	25 mg/m² IV over 4 hours
	Cisplatin	25 mg/m² IV over 4 hours
Course 2 (EMA)	Dactinomycin	0.5 mg IV bolus
	Etoposide	100 mg/m² IV over 1 hour
	Methotrexate	300 mg/m² IV over 12 hours
	Folinic acid	15 mg PO/IV every 12 hours for four doses starting 24 hours after start of methotrexate
EP alternates with EMA every 7 days.		
TE/PT		
Course 1 (TE[a])	Paclitaxel	135 mg/m² IV over 3 hours
	Etoposide	150 mg/m² IV over 1 hour
Course 2 (PT[a])	Cisplatinum	60 mg/m² IV over 2 hours
	Paclitaxel	135 mg/m² IV over 3 hours
TE alternates with PT every 14 days.		

[a]Given with premedications dexamethasone 20 mg orally (PO) 12 hours before paclitaxel, dexamethasone 20 mg PO 3 to 6 hours before paclitaxel, ranitidine 50 mg intravenous (IV) bolus 30 to 60 minutes before paclitaxel, and chlorphenamine 10 mg IV bolus 30 to 60 minutes before paclitaxel.
Data from Newlands ES, Mulholland PJ, Holden L, et al: Etoposide and cisplatin/etoposide, methotrexate, and actinomycin D (EMA) chemotherapy for patients with high-risk gestational trophoblastic tumors refractory to EMA/cyclophosphamide and vincristine chemotherapy and patients presenting with metastatic placental site trophoblastic tumors, J Clin Oncol 2000 Feb;18(4):854-859 and Wang J, Short D, Sebire NJ, et al: Salvage chemotherapy of relapsed or high-risk gestational trophoblastic neoplasia (GTN) with paclitaxel/cisplatin alternating with paclitaxel/etoposide (TP/TE), *Ann Oncol* 2008 Sep;19(9):1578-1583.

etoposide, and cisplatin); cisplatin, vincristine, and methotrexate; PVB (cisplatin, vinblastine, and bleomycin); PEBA (cisplatin, etoposide, bleomycin, and doxorubicin); ICE (high-dose ifosfamide, carboplatin, and etoposide); and combinations with gemcitabine or capecitabine.[90] Outcomes vary, and response rates range from 20% to 75%.

PET-CT may be used to detect isolated metastases, which may benefit from surgical resection.[92] For example, in one study, 39% of patients underwent resection of resistance foci of disease with a long-term survival rate of 82%.[93]

Furthermore, immunotherapy is currently being investigated as a novel approach to treatment in patients with multidrug-resistant GTN. Programmed cell death ligand 1 (PD-L1) is a transmembrane protein that binds to programmed cell death protein 1 (PD-1), a checkpoint molecule that transmits an inhibitory signal to T-cells. Monoclonal antibodies against PD-L1 and PD-1, examples of checkpoint inhibitors, have demonstrated impressive clinical response in patients with a variety of cancer types. PD-L1 is strongly expressed in patients with GTN,[94–96] and thus use of checkpoint inhibitors has been investigated as a potential therapeutic for this malignancy.

This preclinical data are further supported by a small case series of four patients with drug-resistant GTN treated with an anti-PD-1 monoclonal antibody, in which three of the four demonstrated remission.[97] Currently, a multicenter phase II clinical trial, TROPHIMMUN (NCT03135769) is underway to evaluate the use of avelumab, an anti-PD-L1 monoclonal antibody in patients with GTN resistant to monochemotherapy or polychemotherapy. Preliminary results suggest that immunotherapy in this disease may be effective and better tolerated than standard chemotherapy.[98]

However, the risk of permanent fertility impairment caused by lasting antitrophoblast immunity is a concern that requires further investigation before immunotherapies can be recommended for patients with GTN, particularly as an earlier line therapy. A case report regarding a patient from the TROPHIMMUN trial presents the first report of a healthy baby born after use of this immunotherapy treatment for GTN, providing some promise for the use of immunotherapy in GTN while still preserving fertility.[99]

Placental Site Trophoblastic Tumor

PSTTs are rare tumors that often occur after a nonmolar gestation. Serum hCG is not uniformly helpful in

diagnosis, treatment, or follow-up.[100] PSTTs are often aggressive with a poor prognosis and generally thought to be less chemosensitive. They present with lung metastasis in 10% to 29% of cases, and an additional 10% will develop metastases during follow-up.[100] One study reported that the overall mortality rate for PSTT is roughly 16% to 21%[67]; however, advanced-stage disease may be more concerning because another study demonstrated that 88% of patients with early disease were disease free at 28 months after diagnosis compared with 11% of patients with advanced-stage disease.[37]

FIGO scoring is not helpful to determine treatment. Instead, treatment is dictated by the presence of metastatic disease and years since antecedent pregnancy. For patients with nonmetastatic disease who present less than 4 years after an antecedent pregnancy, the primary treatment is hysterectomy with ovarian conservation.[100] Routine lymphadenectomy is of limited utility, and only sampling and removal of suspicious lymph nodes is recommended.[37] For patients with metastatic disease who present less than 4 years after antecedent pregnancy, EP-EMA is recommended with subsequent surgical resection of residual disease and hysterectomy if there is demonstrated response.[90] Patients with unresectable recurrent disease may require radiation or combination chemotherapy with EMA-CO or TE/TP.[90]

Patients who present more than 4 years after a prior pregnancy have a worse prognosis, with a 100% mortality rate compared with 98% long-term survival of patients presenting within 4 years.[100] As a result, these patients should consider high-dose chemotherapy or clinical trials regardless of extent of disease.[100]

Epithelioid Trophoblastic Tumor

ETT is a rare disease and is generally more aggressive than PSTT and choriocarcinoma. It is also considered less chemosensitive than choriocarcinoma, and thus surgical treatment is incorporated into management. Patients are treated similar to those with PSTT.

CO-TWIN PREGNANCY

It is estimated that a healthy co-twin pregnancy developing alongside a complete or partial hydatidiform mole occurs in 1 in 20,000 to 100,000 pregnancies.[3] Co-twin pregnancies may typically be detected by pelvic ultrasound, but additional tests such as amniocentesis and chromosome analysis may be necessary. This has been demonstrated in both spontaneous as well as in vitro fertilization pregnancies. However, this may presumably increase with the increase use of ovulation induction agents.[101] Some suggest termination of the pregnancy because of the low probability of a successful outcome and possible increased risk of development of malignant disease.[102] However, recent studies have suggested that 38% to 57% of women delivery a healthy baby, without increase risk of malignant transformation of the hydatidiform mole.[103] Other potential risks associated with these pregnancies include severe complications such as preeclampsia, hemorrhage, and thyrotoxicosis, which typically occur in the second trimester.[104] Preterm delivery is also a concern. Overall, the decision on any therapy should be made after thorough discussion with the patient in conjunction with a perinatologist and gynecologic oncologist with careful risk assessment for both the mother and the fetus.

FUTURE CHILDBEARING AND SURVIVORSHIP

Women successfully treated for molar pregnancy have a 1% risk of future molar pregnancy.[41] Furthermore, women with complete moles have higher risk of recurrence compared with women with partial moles.[105] After 6 months of surveillance with no elevation in β-hCG levels, patients may consider conception. However, future pregnancies should be monitored closely because of the higher risk of repeat molar disease. For women who underwent chemotherapy, 83% are able to conceive despite prior therapy, and most patients are able to carry a pregnancy to term with a successful live birth.[41]

In terms of effects of chemotherapy, EMA-CO has been shown to induce menopause 3 years earlier than anticipated for women.[61] The evidence to support risk of secondary primary malignancy, such as acute myelogenous leukemia and thyroid carcinoma, is inconclusive.[3] Additionally, survivorship concerns center around issues of sexual dysfunction and reproductive quality of life and disproportionately affect socially disadvantaged patients.[6,106]

CONCLUSION

GTD represents a wide spectrum of neoplastic disease that arises from placental trophoblastic tissue after abnormal fertilization. Patients are stratified into prognostic groups based on the FIGO 2000 staging system incorporating the modified WHO scoring system. This integrates factors such as tumor histologic subtype, extent of disease, hCG titer level, duration of disease, nature of antecedent pregnancy, and extent of prior treatment. Each patient should receive individualized treatment after careful stratification under the care of a multidisciplinary team. Surgery and chemotherapy play important roles in effective management of these patients. Additionally, careful follow-up with regular laboratory tests of β-hCG levels is essential to success.

MD ANDERSON PRACTICE TIPS

- Hydatidiform moles are curable and treated with surgery. Suction evacuation and curettage under ultrasound guidance is recommended; patients who have completed childbearing may undergo a hysterectomy.
- Patients with low-risk GTN (score 0–6) may be treated with single-agent therapy such as methotrexate or dactinomycin.
- Patients with high-risk GTN (score >6) are recommended to undergo combination therapy, most often with EMA-CO as first-line treatment. If at all possible, these patients should be cared for either at or in conjunction with a referral center with experience with GTN.
- Patients with widely metastatic disease at risk of significant risk of pulmonary, intraperitoneal, or intracranial hemorrhage should be considered for induction chemotherapy (etoposide and cisplatin) followed by full-dose combination chemotherapy.
- For the 20% to 25% of patients with persistent or recurrent GTN, a variety of salvage therapy options are available, including surgical resection, alternative platinum-based chemotherapy regimens, and immunotherapy.
- Patients with GTD should use reliable contraception throughout surveillance, during treatment, and for 6 to 12 months after normalization of hCG levels.

REFERENCES

1. Ober WB, Fass RO. The early history of choriocarcinoma. *J Hist Med Allied Sci*. 1961;16:49-73.
2. Lurain JR. Gestational trophoblastic disease I: epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole. *Am J Obstet Gynecol*. 2010;203(6):531-539.
3. Seckl MJ, Sebire NJ, Berkowitz RS. Gestational trophoblastic disease. *Lancet*. 2010;376(9742):717-729.
4. American Cancer Society. What are the key statistics about gestational trophoblastic disease? https://www.cancer.org/cancer/gestational-trophoblastic-disease/about/key-statistics.html
5. Berkowitz RS, Goldstein DP. Clinical practice. Molar pregnancy. *N Engl J Med*. 2009;360(16):1639-1645.
6. Mangili G, Lorusso D, Brown J, et al. Trophoblastic disease review for diagnosis and management: a joint report from the International Society for the Study of Trophoblastic Disease, European Organisation for the Treatment of Trophoblastic Disease, and the Gynecologic Cancer InterGroup. *Int J Gynecol Cancer*. 2014;24(9 suppl 3):S109-S116.
7. Soares PD, Maestá I, Costa OL, et al. Geographical distribution and demographic characteristics of gestational trophoblastic disease. *J Reprod Med*. 2010;55(7-8):305-310.
8. Berkowitz RS, Cramer DW, Bernstein MR, et al. Risk factors for complete molar pregnancy from a case-control study. *Am J Obstet Gynecol*. 1985;152(8):1016-1020.
9. Parazzini F, La Vecchia C, Mangili G, et al. Dietary factors and risk of trophoblastic disease. *Am J Obstet Gynecol*. 1988;158(1):93-99.
10. Berkowitz RS, Bernstein MR, Harlow BL, et al. Case-control study of risk factors for partial molar pregnancy. *Am J Obstet Gynecol*. 1995;173(3 pt 1):788-794.
11. Sebire NJ, Foskett M, Fisher RA, et al. Risk of partial and complete hydatidiform molar pregnancy in relation to maternal age. *BJOG*. 2002;109(1):99-102.
12. Ngan HYS, Seckl MJ, Berkowitz RS, et al. Update on the diagnosis and management of gestational trophoblastic disease. *Int J Gynecol Obstet*. 2018;143:79-85.
13. Brown J, Naumann RW, Seckl MJ, Schink J. 15 years of progress in gestational trophoblastic disease: scoring, standardization, and salvage. *Gynecol Oncol*. 2017;144(1):200-207.
14. Hoffner L, Surti U. The genetics of gestational trophoblastic disease: a rare complication of pregnancy. *Cancer Genet*. 2012;205(3):63-77.
15. Ohama K, Kajii T, Okamoto E, et al. Dispermic origin of XY hydatidiform moles. *Nature*. 1981;292(5823):551-552.
16. Wallace DC, Surti U, Adams CW, Szulman AE. Complete moles have paternal chromosomes but maternal mitochondrial DNA. *Hum Genet*. 1982;61(2):145-147.
17. Yamashita K, Wake N, Araki T, et al. Human lymphocyte antigen expression in hydatidiform mole: androgenesis following fertilization by a haploid sperm. *Am J Obstet Gynecol*. 1979;135(5):597-600.
18. Savage J, Adams E, Veras E, et al. Choriocarcinoma in women: analysis of a case series with genotyping. *Am J Surg Pathol*. 2017;41(12):1593-1606.
19. Davis JR, Surwit EA, Garay JP, Fortier KJ. Sex assignment in gestational trophoblastic neoplasia. *Am J Obstet Gynecol*. 1984;148(6):722-725.
20. Chiu PM, Liu VW, Ngan HY, et al. Detection of mitochondrial DNA mutations in gestational trophoblastic disease. *Hum Mutat*. 2003;22(2):177.
21. Steller MA, Mok SC, Yeh J, et al. Effects of cytokines on epidermal growth factor receptor expression by malignant trophoblast cells in vitro. *J Reprod Med*. 1994;39(3):209-216.
22. Li HW, Tsao SW, Cheung AN. Current understandings of the molecular genetics of gestational trophoblastic diseases. *Placenta*. 2002;23(1):20-31.
23. Fulop V, Mok SC, Genest DR, et al. c-myc, c-erbB-2, c-fms and bcl-2 oncoproteins. Expression in normal placenta, partial and complete mole, and choriocarcinoma. *J Reprod Med*. 1998;43(2):101-110.
24. Cheung AN, Srivastava G, Pittaluga S, et al. Expression of c-myc and c-fms oncogenes in trophoblastic cells in hydatidiform mole and normal human placenta. *J Clin Pathol*. 1993;46(3):204-207.
25. Hübener C, Bidlingmaier M, Wu Z, et al. Human placental growth hormone: a potential new biomarker in gestational trophoblastic disease. *Gynecol Oncol*. 2015;136(2):264-268.
26. Fulop V, Mok SC, Genest DR, et al. p53, p21, Rb and mdm2 oncoproteins. Expression in normal placenta, partial and complete mole, and choriocarcinoma. *J Reprod Med*. 1998;43(2):119-127.
27. Halperin R, Peller S, Sandbank J, et al. Expression of the p53 gene and apoptosis in gestational trophoblastic disease. *Placenta*. 2000;21(1):58-62.
28. Parry DA, Logan CV, Hayward BE, et al. Mutations causing familial biparental hydatidiform mole implicate c6orf221 as a possible regulator of genomic imprinting in the human oocyte. *Am J Hum Genet*. 2011;89(3):451-458.
29. Deveault C, Qian JH, Chebaro W, et al. NLRP7 mutations in women with diploid androgenetic and triploid moles: a proposed mechanism for mole formation. *Hum Mol Genet*. 2009;18(5):888-897.
30. Fisher RA, Hodges MD, Newlands ES. Familial recurrent hydatidiform mole: a review. *J Reprod Med*. 2004;49(8):595-601.
31. Sebire NJ, Fisher RA, Rees HC. Histopathological diagnosis of partial and complete hydatidiform mole in the first trimester of pregnancy. *Pediatr Dev Pathol*. 2003;6(1):69-77.
32. Fisher RA, Lavery SA, Carby A, et al. What a difference an egg makes. *Lancet*. 2011;378(9807):1974.
33. Hoffner L, Dunn J, Esposito N, et al. P57KIP2 immunostaining and molecular cytogenetics: combined approach aids in diagnosis of morphologically challenging cases with molar phenotype and in detecting androgenetic cell lines in mosaic/chimeric conceptions. *Hum Pathol*. 2008;39(1):63-72.
34. Lurain JR, Brewer JI. Invasive mole. *Semin Oncol*. 1982;9(2):174-180.
35. Schmid P, Nagai Y, Agarwal R, et al. Prognostic markers and long-term outcome of placental-site trophoblastic tumours: a retrospective observational study. *Lancet*. 2009;374(9683):48-55.
36. Baergen RN, Rutgers JL, Young RH, et al. Placental site trophoblastic tumor: a study of 55 cases and review of the literature emphasizing factors of prognostic significance. *Gynecol Oncol*. 2006;100(3):511-520.
37. Hyman DM, Bakios L, Gualtiere G, et al. Placental site trophoblastic tumor: analysis of presentation, treatment, and outcome. *Gynecol Oncol*. 2013;129(1):58-62.
38. Heller DS. Update on the pathology of gestational trophoblastic disease. *APMIS*. 2018;126(7):647-654.
39. Shih IM, Kurman RJ. Epithelioid trophoblastic tumor: a neoplasm distinct from choriocarcinoma and placental site trophoblastic tumor simulating carcinoma. *Am J Surg Pathol*. 1998;22(11):1393-1403.
40. Allison KH, Love JE, Garcia RL. Epithelioid trophoblastic tumor: review of a rare neoplasm of the chorionic-type intermediate trophoblast. *Arch Pathol Lab Med*. 2006;130(12):1875-1877.
41. Berkowitz RS, Tuncer ZS, Bernstein MR, Goldstein DP. Management of gestational trophoblastic diseases: subsequent pregnancy experience. *Semin Oncol*. 2000;27(6):678-685.
42. Goldstein DP, Berkowitz RS. Current management of gestational trophoblastic neoplasia. *Hematol Oncol Clin North Am*. 2012;26(1):111-131.

43. Amir SM, Osathanondh R, Berkowitz RS, Goldstein DP. Human chorionic gonadotropin and thyroid function in patients with hydatidiform mole. *Am J Obstet Gynecol*. 1984;150(6):723-728.
44. Kohorn EI. Worldwide survey of the results of treating gestational trophoblastic disease. *J Reprod Med*. 2014;59(3-4):145-153.
45. Berkowitz RS, Goldstein DP. Current management of gestational trophoblastic diseases. *Gynecol Oncol*. 2009;112(3):654-662.
46. Kumar J, Ilancheran A, Ratnam SS. Pulmonary metastases in gestational trophoblastic disease: a review of 97 cases. *Br J Obstet Gynaecol*. 1988;95(1):70-74.
47. Berkowitz RS, Goldstein DP. Pathogenesis of gestational trophoblastic neoplasms. *Pathobiol Annu*. 1981;11:391-411.
48. Benson CB, Genest DR, Bernstein MR, et al. Sonographic appearance of first trimester complete hydatidiform moles. *Ultrasound Obstet Gynecol*. 2000;16(2):188-191.
49. Lin LH, Polizio R, Fushida K, Francisco RPV. Imaging in gestational trophoblastic disease. seminars in ultrasound, CT and MRI. *Semin Ultrasound CT MR*. 2019;40(4):332-349.
50. Jauniaux E. Ultrasound diagnosis and follow-up of gestational trophoblastic disease. *Ultrasound Obstet Gynecol*. 1998;11(5):367-377.
51. Darby S, Jolley I, Pennington S, Hancock BW. Does chest CT matter in the staging of GTN? *Gynecol Oncol*. 2009;112(1):155-160.
52. Price JM, Lo C, Abdi S, et al. The role of computed tomography scanning of the thorax in the initial assessment of gestational trophoblastic neoplasia. *Int J Gynecol Cancer*. 2015;25(9):1731-1736.
53. Pastorfide GB, Goldstein DP, Kosasa TS. The use of a radioimmunoassay specific for human chorionic gonadotropin in patients with molar pregnancy and gestational trophoblastic disease. *Am J Obstet Gynecol*. 1974;120(8):1025-1028.
54. Cole LA. hCG, its free subunits and its metabolites. Roles in pregnancy and trophoblastic disease. *J Reprod Med*. 1998;43(1):3-10.
55. Kohorn EI. The new FIGO 2000 staging and risk factor scoring system for gestational trophoblastic disease: description and critical assessment. *Int J Gynecol Cancer*. 2001;11(1):73-77.
56. Kohorn EI. Negotiating a staging and risk factor scoring system for gestational trophoblastic neoplasia. A progress report. *J Reprod Med*. 2002;47(6):445-450.
57. Ngan HY, Bender H, Benedet JL, et al. Gestational trophoblastic neoplasia, FIGO 2000 staging and classification. *Int J Gynaecol Obstet*. 2003;83(suppl 1):175-177.
58. Athanassiou A, Begent RH, Newlands ES, et al. Central nervous system metastases of choriocarcinoma. 23 years' experience at Charing Cross Hospital. *Cancer*. 1983;52(9):1728-1735.
59. Koonings PP, Schalerth JB. CA-125: a marker for persistent gestational trophoblastic disease? *Gynecol Oncol*. 1993;49(2):240-242.
60. Pereira JV, Lim T. Hyperthyroidism in gestational trophoblastic disease—a literature review. *Thyroid Res*. 2021;14(1):1.
61. Seckl MJ, Sebire NJ, Fisher RA, et al. Gestational trophoblastic disease: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013;24(suppl 6):vi39-vi50.
62. You B, Harvey R, Henin E, et al. Early prediction of treatment resistance in low-risk gestational trophoblastic neoplasia using population kinetic modelling of hCG measurements. *Br J Cancer*. 2013;108(9):1810-1816.
63. Hancock BW, Tidy JA. Current management of molar pregnancy. *J Reprod Med*. 2002;47(5):347-354.
64. Medical Eligibility Criteria for Contraceptive Use; 2015.
65. Gaffield ME, Kapp N, Curtis KM. Combined oral contraceptive and intrauterine device use among women with gestational trophoblastic disease. *Contraception*. 2009;80(4):363-371.
66. Lurain JR, Brewer JI, Torok EE, Halpern B. Natural history of hydatidiform mole after primary evacuation. *Am J Obstet Gynecol*. 1983;145(5):591-595.
67. Braga A, Uberti EM, Fajardo Mdo C, et al. Epidemiological report on the treatment of patients with gestational trophoblastic disease in 10 Brazilian referral centers: results after 12 years since international FIGO 2000 consensus. *J Reprod Med*. 2014;59(3):241-247.
68. Soper JT. Surgical therapy for gestational trophoblastic disease. *J Reprod Med*. 1994;39(3):168-174.
69. Agarwal R, Teoh S, Short D, et al. Chemotherapy and human chorionic gonadotropin concentrations 6 months after uterine evacuation of molar pregnancy: a retrospective cohort study. *Lancet*. 2012;379(9811):130-135.
70. Fu J, Fang F, Xie L, et al. Prophylactic chemotherapy for hydatidiform mole to prevent gestational trophoblastic neoplasia. *Cochrane Database Syst Rev*. 2012;10:CD007289.
71. Goldstein DP. Prevention of gestational trophoblastic disease by use of actinomycin D in molar pregnancies. *Obstet Gynecol*. 1974;43(4):475-479.
72. Kim DS, Moon H, Kim KT, et al. Effects of prophylactic chemotherapy for persistent trophoblastic disease in patients with complete hydatidiform mole. *Obstet Gynecol*. 1986;67(5):690-694.
73. Osborne RJ, Filiaci V, Schink JC, et al. Phase III trial of weekly methotrexate or pulsed dactinomycin for low-risk gestational trophoblastic neoplasia: a Gynecologic Oncology Group study. *J Clin Oncol*. 2011;29(7):825-831.
74. Sita-Lumsden A, Short D, Lindsay I, et al. Treatment outcomes for 618 women with gestational trophoblastic tumours following a molar pregnancy at the Charing Cross Hospital, 2000-2009. *Br J Cancer*. 2012;107(11):1810-1814.
75. Osborne RJ, Filiaci VL, Schink JC, et al. Second curettage for low-risk nonmetastatic gestational trophoblastic neoplasia. *Obstet Gynecol*. 2016;128(3):535-542.
76. McNeish IA, Strickland S, Holden L, et al. Low-risk persistent gestational trophoblastic disease: outcome after initial treatment with low-dose methotrexate and folinic acid from 1992 to 2000. *J Clin Oncol*. 2002;20(7):1838-1844.
77. Lybol C, Sweep FC, Harvey R, et al. Relapse rates after two versus three consolidation courses of methotrexate in the treatment of low-risk gestational trophoblastic neoplasia. *Gynecol Oncol*. 2012;125(3):576-579.
78. Lurain JR. Advances in management of high-risk gestational trophoblastic tumors. *J Reprod Med*. 2002;47(6):451-459.
79. Bagshawe KD. Treatment of high-risk choriocarcinoma. *J Reprod Med*. 1984;29(11):813-820.
80. Even C, Pautier P, Duvillard P, et al. Actinomycin D, cisplatin, and etoposide regimen is associated with almost universal cure in patients with high-risk gestational trophoblastic neoplasia. *Eur J Cancer*. 2014;50(12):2082-2089.
81. Tse KY, Chan KK, Tam KF, Ngan HY. 20-year experience of managing profuse bleeding in gestational trophoblastic disease. *J Reprod Med*. 2007;52(5):397-401.
82. Alifrangis C, Agarwal R, Short D, et al. EMA/CO for high-risk gestational trophoblastic neoplasia: good outcomes with induction low-dose etoposide-cisplatin and genetic analysis. *J Clin Oncol*. 2013;31(2):280-286.
83. DuBeshter B, Berkowitz RS, Goldstein DP, Bernstein MR. Analysis of treatment failure in high-risk metastatic gestational trophoblastic disease. *Gynecol Oncol*. 1988;29(2):199-207.
84. Bakri YN, Berkowitz RS, Khan J, et al. Pulmonary metastases of gestational trophoblastic tumor. Risk factors for early respiratory failure. *J Reprod Med*. 1994;39(3):175-178.
85. Altintaş A, Vardar MA. Central nervous system involvement in gestational trophoblastic neoplasia. *Eur J Gynaecol Oncol*. 2001;22(2):154-156.
86. Neubauer NL, Latif N, Kalakota K, et al. Brain metastasis in gestational trophoblastic neoplasia: an update. *J Reprod Med*. 2012;57(4):288-292.

87. Bolze PA, Riedl C, Massardier J, et al. Mortality rate of gestational trophoblastic neoplasia with a FIGO score of ≥13. *Am J Obstet Gynecol*. 2016;214(3):390.e1-8.
88. Savage P, Kelpanides I, Tuthill M, et al. Brain metastases in gestational trophoblast neoplasia: an update on incidence, management and outcome. *Gynecol Oncol*. 2015;137(1):73-76.
89. Chang TC, Yen TC, Li YT, et al. The role of 18F-fluorodeoxyglucose positron emission tomography in gestational trophoblastic tumours: a pilot study. *Eur J Nucl Med Mol Imaging*. 2006;33(2):156-163.
90. Newlands ES, Mulholland PJ, Holden L, et al. Etoposide and cisplatin/etoposide, methotrexate, and actinomycin D (EMA) chemotherapy for patients with high-risk gestational trophoblastic tumors refractory to EMA/cyclophosphamide and vincristine chemotherapy and patients presenting with metastatic placental site trophoblastic tumors. *J Clin Oncol*. 2000;18(4):854-859.
91. Wang J, Short D, Sebire NJ, et al. Salvage chemotherapy of relapsed or high-risk gestational trophoblastic neoplasia (GTN) with paclitaxel/cisplatin alternating with paclitaxel/etoposide (TP/TE). *Ann Oncol*. 2008;19(9):1578-1583.
92. Mapelli P, Mangili G, Picchio M, et al. Role of 18F-FDG PET in the management of gestational trophoblastic neoplasia. *Eur J Nucl Med Mol Imaging*. 2013;40(4):505-513.
93. Lurain JR, Schink JC. Importance of salvage therapy in the management of high-risk gestational trophoblastic neoplasia. *J Reprod Med*. 2012;57(5-6):219-224.
94. Veras E, Kurman RJ, Wang TL, Shih IM. PD-L1 expression in human placentas and gestational trophoblastic diseases. *Int J Gynecol Cancer*. 2017;36(2):146-153.
95. Bolze PA, Patrier S, Massardier J, et al. PD-L1 expression in premalignant and malignant trophoblasts from gestational trophoblastic diseases is ubiquitous and independent of clinical outcomes. *Int J Gynecol Cancer*. 2017;27(3):554-561.
96. Inaguma S, Wang Z, Lasota J, et al. Comprehensive immunohistochemical study of programmed cell death ligand 1 (PD-L1): analysis in 5536 cases revealed consistent expression in trophoblastic tumors. *Am J Surg Pathol*. 2016;40(8):1133-1142.
97. Ghorani E, Kaur B, Fisher RA, et al. Pembrolizumab is effective for drug-resistant gestational trophoblastic neoplasia. *Lancet*. 2017;390(10110):2343-2345.
98. You BM, Bolze PA, Lotz J-P, et al. TROPHIMMUN, a 2 cohort phase II trial of the anti-PD-L1 monoclonal antibody avelumab in chemo-resistant gestational trophoblastic neoplasia (GTN) patients: preliminary outcomes in cohort A. *Ann Oncol*. 2018;29:viii727-viii728.
99. Bolze PA, You B, Lotz JP, et al. Successful pregnancy in a cancer patient previously cured of a gestational trophoblastic tumor by immunotherapy. *Ann Oncol*. 2020;31(6):823-825.
100. Papadopoulos AJ, Foskett M, Seckl MJ, et al. Twenty-five years' clinical experience with placental site trophoblastic tumors. *J Reprod Med*. 2002;47(6):460-464.
101. Shazly SA, Ali MK, Abdel Badee AY, et al. Twin pregnancy with complete hydatidiform mole and coexisting fetus following ovulation induction with a non-prescribed clomiphene citrate regimen: a case report. *J Med Case Rep*. 2012;6:95.
102. Matsui H, Sekiya S, Hando T, et al. Hydatidiform mole coexistent with a twin live fetus: a national collaborative study in Japan. *Hum Reprod*. 2000;15(3):608-611.
103. Sebire NJ, Foskett M, Paradinas FJ, et al. Outcome of twin pregnancies with complete hydatidiform mole and healthy cotwin. *Lancet*. 2002;359(9324):2165-2166.
104. Vejerslev LO. Clinical management and diagnostic possibilities in hydatidiform mole with coexistent fetus. *Obstet Gynecol Surv*. 1991;46(9):577-588.
105. Eagles N, Sebire NJ, Short D, et al. Risk of recurrent molar pregnancies following complete and partial hydatidiform moles. *Hum Reprod*. 2016;31(6):1379.
106. Stafford L, McNally OM, Gibson P, Judd F. Long-term psychological morbidity, sexual functioning, and relationship outcomes in women with gestational trophoblastic disease. *Int J Gynecol Cancer*. 2011;21(7):1256-1263.

Section IX Genitourinary Malignancies

Section Editor: Nizar M. Tannir

43 Renal Cell Carcinoma

44 Bladder Cancer

45 Prostate Cancer

46 Penile Cancer

47 Germ Cell Tumors

This page intentionally left blank

43 Renal Cell Carcinoma

Andrew W. Hahn
Jose A. Karam
Christopher G. Wood
Nizar M. Tannir

KEY CONCEPTS

- The International Metastatic RCC Database Consortium (IMDC) and Memorial Sloan Kettering risk scores have become important tools to aid in the selection of first-line treatment of patients with metastatic clear cell renal cell carcinoma (RCC). The IMDC risk score includes the following risk factors: elevated serum corrected calcium level, anemia, Karnofsky performance score less than 80, systemic treatment for metastatic disease within 1 year, absolute neutrophil count greater than the upper limit of normal (ULN), and platelet count greater than the ULN.
- As of 2020, contemporary first-line treatment options for metastatic RCC (mRCC) include nivolumab plus ipilimumab, pembrolizumab plus axitinib, avelumab plus axitinib, and cabozantinib. The only first-line treatments to demonstrate improved overall survival (OS) compared with sunitinib are nivolumab plus ipilimumab (CheckMate 214) and pembrolizumab plus axitinib (KEYNOTE-426).
- Contemporary second-line or later treatment options for mRCC include cabozantinib, nivolumab, lenvatinib plus everolimus, and axitinib. There is limited prospective evidence for treatment sequencing after contemporary first-line therapies, which presents a challenge for clinicians.
- Patients with metastatic non–clear cell RCC have inferior outcomes compared with patients with metastatic clear cell RCC, and treatment outcomes vary by histologic subgroup of non–clear cell RCC. In general, patients with metastatic non–clear cell RCC should be referred to a tertiary cancer center for enrollment in clinical trials.
- Adjuvant treatment for locally advanced RCC is not currently standard of care. Adjuvant treatment with vascular endothelial growth factor (VEGF)–targeted therapy has not consistently improved OS. Adjuvant treatment with checkpoint inhibitors is currently being evaluated in prospective clinical trials.
- The efficacy and timing of cytoreductive nephrectomy (CN) for patients with intermediate- or poor-risk mRCC receiving VEGF-targeted therapy were called into question by the CARMENA and SURTIME trials. At MD Anderson Cancer Center, CN is not recommended for patients with poor-risk disease, and in most patients with intermediate-risk disease, we begin with systemic therapy and reserve CN for patients with a response to treatment and good performance status.

INCIDENCE AND DIAGNOSIS

According to the World Health Organization Global Cancer Observatory (GLOBOCAN) database, there were estimated to be 60,336 new cases of kidney cancer in the United States in 2018, and 15,333 patients were projected to die as a consequence of disease progression.[1] Renal cell carcinoma (RCC) is the most common histology found in kidney tumors, with clear cell RCC (ccRCC) being the most common histologic subtype (Fig. 43–1). Non–clear cell RCC (nccRCC) subtypes include chromophobe, papillary, oncocytoma, collecting duct carcinoma, renal medullary carcinoma (RMC), translocation, and unclassified RCC.

In a 2015 analysis of multiple international databases, the incidence of RCC varied significantly worldwide, and in general, the incidence of RCC has steadily increased for several decades, including in the United States.[2] In contrast, the mortality rate for RCC has steadily declined since the 1990s in high-resource countries, such as those in North America, Europe, and Australia. In the United States, the rising incidence of RCC is largely attributed to increased detection of localized tumors. In an analysis of the Surveillance,

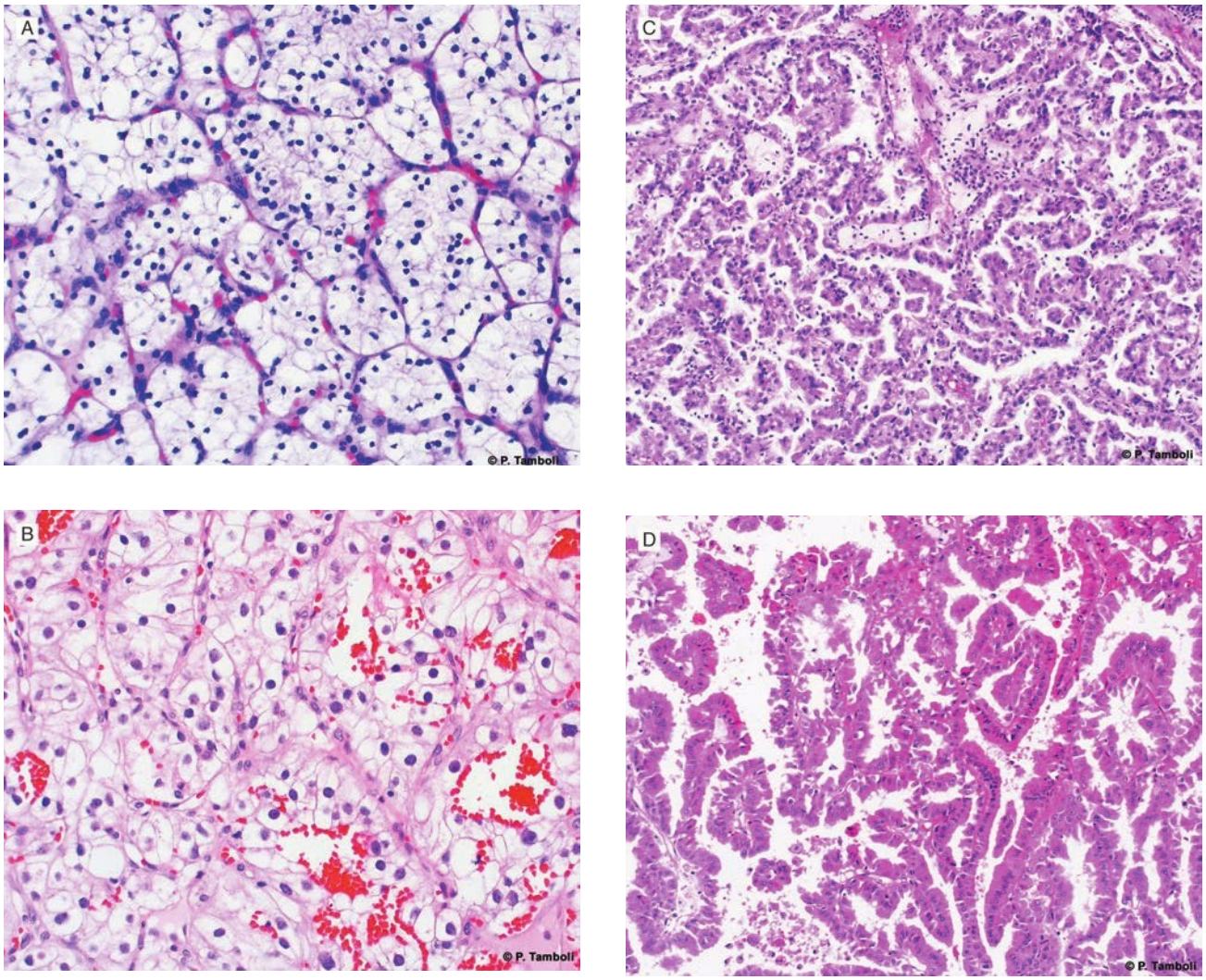


FIGURE 43–1 Photomicrographs of clear cell (conventional) renal cell carcinoma (RCC) with low-grade (A) and high-grade (B) nuclear features. Photomicrographs of a type 1 papillary RCC (C) showing papillae lined by short cuboidal cells and a type 2 papillary RCC (D) showing papillae lined by tall columnar cells, with eosinophilic cytoplasm and high-grade nuclear features. (Used with permission from Pheroze Tamboli, MD.)

Epidemiology, and End Results database from 1988 to 2006, whereas the incidence of localized RCC has increased rapidly, the incidence of distant RCC has declined.[3] Many have speculated that increased use of computed tomography (CT) imaging may be contributing to this finding.

STAGING, GENETIC AND CLINICAL RISK FACTORS

The eighth American Joint Commission on Cancer (AJCC) Tumor, Node, Metastasis staging system for RCC was updated in 2017.[4] In this staging schema, T1 and T2 tumors are limited to the kidney, T3 tumors extend into major veins or perinephric tissue, and T4 tumors invade beyond Gerota's fascia. N and M stage refer to the presence of regional lymph nodes or distant metastatic disease, respectively. Major staging categories are as follows: stage 1 is a T1N0 cancer, stage 2 is a T2N0 cancer, stage 3 can be T3N0-1 or T1-2N1 cancer, and stage 4 refers to any T4 or M1 cancer.

The link between germline genetic mutations and the development of RCC is well established and applies to a small but biologically important subset of RCC cases.[5] Known hereditary kidney cancer syndromes include hereditary papillary renal cancer (*c-MET* gene), hereditary leiomyomatosis and RCC syndrome (*fumarate hydratase [FH]* gene), Birt-Hogg-Dube syndrome (*FLCN* gene), tuberous sclerosis complex (*TSC1* and *TSC2* genes), von Hippel-Lindau

disease (*VHL* gene), and hereditary BAP-1-associated RCC (*BAP1* gene).[6] Although these genomic alterations play an important role in the biology of RCC in both familial and sporadic cases, environmental factors also contribute to the risk of developing a renal neoplasm. Smoking is associated with an increased risk of developing RCC. In a meta-analysis of 24 studies, current smokers had a relative risk (RR) of RCC incidence of 1.36, and the RR was lower but still elevated for former smokers (1.16).[7]

Obesity or increased body mass index (BMI) has also been linked to increased risk of developing RCC. Several studies have demonstrated a higher incidence of obesity or increased BMI in patients with RCC, suggesting an epidemiologic linkage.[8,9] However, studies have also shown that patients with high BMIs have a more favorable prognosis after surgery and improved survival in patients with metastatic disease who are treated with angiogenesis-targeted therapy, coined "the obesity paradox."[10,11] Additional possible risk factors for RCC include hypertension, diabetes mellitus, acquired polycystic kidney disease in dialysis patients, and occupational exposures (eg, cadmium, petroleum byproducts, asbestos).

RISK ASSESSMENT AND MOLECULAR BIOMARKERS

The natural history of RCC widely ranges depending on both tumor genetic factors and clinical prognostic factors. For patients who present with localized disease, nephrectomy can be curable, but a subset of patients who undergo a nephrectomy with curative intent will go on to develop metastatic disease. Additionally, some patients with RCC present with metastatic disease, and mRCC generally carries a poor prognosis. The traditional measures of performance status, tumor stage, and tumor grade each demonstrate good correlation with clinical outcome.[8] A variety of additional clinical, pathologic, and molecular features are associated with prognosis (Table 43–1).[9,10] In the localized setting, several nomograms incorporate histopathologic factors to predict the risk of recurrence, such as the Memorial Sloan Kettering (MSKCC) postoperative nomogram; the stage, size, grade, and necrosis (SSIGN) score for RCC; and the UCLA Integrated Staging System for RCC.[12–14] Furthermore, multigene panels have been developed to assist in prognostication of localized RCC at the time of surgery, including ClearCode 34 and the 16-gene recurrence score.[15,16]

Prognostic Models for Risk Assessment in Metastatic Renal Cell Carcinoma

In 1999, Motzer et al[17] identified five risk factors (elevated serum corrected calcium level, anemia, lactate dehydrogenase >1.5 times the upper limit of normal [ULN], Karnofsky performance score [KPS] <80, and primary tumor in place) that segregated patients into three risk groups (good, zero factors; intermediate, one or two factors; and poor, three or more factors).[17] In 2002, an updated version, now referred to as the MSKCC risk criteria (also referred to as the "Motzer criteria"), was published with the original four risk factors, with the fifth being treatment with interferon within 1 year of diagnosis.[18] For clinical trial purposes, the fifth factor is often considered time to initiation of systemic therapy within 1 year from initial diagnosis of RCC. With the introduction of targeted therapy, the

TABLE 43–1 Prognostic Factors in Metastatic Renal Cell Carcinoma

Patient- or Treatment-Related Factors	Laboratory Studies	Tumor-Related Factors	Molecular Markers
Performance status	Lactate dehydrogenase	Site or number of metastatic sites	*ClearCode 34, cell cycle progression score, 16-gene RS*
Age, gender, race	Alkaline phosphatase	Disease-free interval	*BAP1, SETD1,* and *PBRM1* mutations
Symptoms: weight loss, fatigue, pain, loss of appetite, fever	Calcium	Metastasis-free interval	Carbonic anhydrase IX expression
Overweight	Albumin	Tumor burden	p53 overexpression
Prior nephrectomy	Liver dysfunction	Histologic type	IMP3 expression
Prior therapy	Anemia, neutrophilia	Sarcomatoid dedifferentiation	
	Thrombocytosis	Ploidy	

International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) was formed, and a modified prognostic scoring system was put forth in 2009 and externally validated in 2013.[19,20] The IMDC prognostic scoring system (also referred to as the "Heng score") has six risk factors (elevated serum corrected calcium level, anemia, KPS <80, systemic treatment for metastatic disease within 1 year, absolute neutrophil count >ULN, and platelet count >ULN). Similar to the MSKCC scoring system, good risk is defined as zero risk factors, intermediate risk as one to two risk factors, and poor risk as three or more risk factors. Although other systems have been proposed, the MSKCC and IMDC remain the most widely used (Table 43–2).

Molecular Pathogenesis and Biomarkers

ccRCC is characterized by early loss of *VHL,* a tumor suppressor gene that encodes a protein responsible for ubiquitination and proteasomal degradation of hypoxia-inducible factor (HIF). When there is a loss-of-function alteration to *VHL,* accumulation of HIF results in increased expression of vascular endothelial growth factor (VEGF), platelet-derived growth factor subunit B, and other proteins that mediate glucose transport, proliferation, and angiogenesis.[21] In The Cancer Genome Atlas (TCGA) study of patients with ccRCC, the most common genomic alterations were found in *VHL* (55%), *PBRM1* (38%), *SETD2* (13%), *KDM5C* (7%), *BAP1* (11%), and *PTEN* (5%).[22] Of note, *VHL*, *SETD2* (a histone methyltransferase), *BAP1* (histone deubiquitinase), and *PBRM1* (part of chromatin remodeling complex) all lie on chromosome 3p.

Interest in predictive and prognostic genomic biomarkers for RCC has grown as next-generation sequencing technology has become widely available; however, genomic biomarkers are not routinely used to guide treatment selection for patients with mRCC and remain an area of active research. *PBRM1*, *TP53*, and *BAP1* consistently appear to be prognostic across studies of single-gene biomarkers for RCC. In a study of 145 patients with localized RCC, mutations in *BAP1* were associated with poor survival (median overall survival [OS], 4.6 years), bit mutations in *PBRM1* were associated with improved OS (median OS, 10.6 years).[23] In a separate TCGA study of 538 patients with ccRCC, *BAP1*, *TP53*, and *CDKN2A* were associated with inferior OS.[22] Finally, in a retrospective analysis of the COMPARZ and RECORD-3 trials, mutations in TP53 or BAP1 and absence of mutation in PBRM1 were prognostic of inferior OS.[24] Single-gene alterations have not been shown to predict response to treatment in patients with mRCC. However, gene expression signatures of angiogenesis have shown promise in predicting response to VEGF-targeted therapy in three separate studies.[25–27] Programmed cell death ligand 1 (PD-L1) expression does not appear to predict response to immune checkpoint inhibitors in patients with mRCC.

MANAGEMENT OF NONMETASTATIC RENAL CELL CARCINOMA

With the introduction of improved cross-sectional imaging, the detection of renal masses has increased substantially. At present, the majority of renal masses

TABLE 43–2 The Memorial Sloan Kettering Cancer Center (MSKCC) Modified Risk Score for Metastatic Renal Cell Carcinoma and the International Metastatic Renal Cell Database Consortium (IMDC) Risk Score with Survival by Risk Stratification

MSKCC 2002 Factors (1 point each)	Risk Group (points)	Overall Survival (months)	IMDC Risk Score (1 point each)	Risk Group (points)	Overall Survival (months)
Anemia	Good (0)	30	Anemia	Good (0)	43
Elevated calcium			Elevated calcium		
KPS <80	Intermediate (1–2)	14	KPS <80	Intermediate (1–2)	22.5
Metastatic treatment within 1 year of diagnosis			Metastatic treatment within 1 year		
LDH >1.5× ULN	Poor (3–5)	5	Platelet count >ULN	Poor (3–6)	7.8
			Neutrophil count >ULN		

KPS, Karnofsky performance score; LDH, lactate dehydrogenase; ULN, upper limit of normal.

are detected incidentally and not through the classic triad of palpable mass, hematuria, and flank pain. When evaluating a patient with a renal mass, cross-sectional imaging with a CT renal mass protocol is most useful to delineate anatomical nuances that could help determine the surgical approach in appropriate patients. Magnetic resonance imaging is not routinely used but is particularly helpful in evaluating patients with indeterminate renal cystic lesions, in patients with limited renal function when no contrast can used, and in patients with renal mass and inferior vena cava (IVC) tumor thrombus.

By definition, a small renal mass (SRM) is any mass in the kidney that is 4 cm or smaller in size (cT1a). These SRMs could represent benign renal tumors (~20%), malignant renal tumors, metastatic tumors to the kidney, and rarely an infectious process. Management of patients with a SRM depends on a multitude of patient and tumor factors, including age, comorbidities, concurrent malignancies, renal function, size of the mass, rate of growth of the mass (if known), and biopsy results (if known). Most patients do not require a renal mass biopsy (RMB). For patients with SRM, an RMB (multiple core biopsies, not fine-needle aspiration) is generally performed when the results of such an intervention could result in a change in patient management. RMB has an acceptable very low complication rate and a good diagnostic rate (~90%).[28] In the setting of patients with concurrent malignancies, it is important to carefully review the imaging because tumors metastatic to the kidney generally have a different appearance than RCC, especially when small in size. Metastases to the kidney are generally ill-defined and more infiltrative and mainly occur in the presence of metastases to other organs as well. If indicated, an RMB can be done in this setting, especially when the renal mass is isolated without other evidence of disease.

Active surveillance is now an established approach for managing well-selected patients with SRM. Generally, these are patients with multiple comorbidities and concurrent active malignancies receiving systemic therapy. Several retrospective series, meta-analyses, and prospective cohort studies note that the rate of developing metastatic RCC while on active surveillance is encouragingly low (<2%).[29–32] These patients can be followed every 3 to 6 months initially for the first 2 years, with imaging tailored for individual patient situations. For patients with concurrent active malignancies, the imaging for active surveillance of the SRM can be combined with the primary tumor imaging, granted that IV contrast is needed, because noncontrast CT (eg, in positron emission tomography–CT) is not helpful for the purposes of active surveillance.

Percutaneous thermal ablation—with radiofrequency ablation, cryoablation, and more recently microwave ablation—is another treatment modality for select patients with SRM. Traditionally, thermal ablation has been used in patients who are older and with comorbidities, but more recent results from centers of excellence with longer follow-up period are expanding the use of this treatment modality beyond this population. In a retrospective cohort of more than 1400 patients with SRMs, local recurrence-free survival was similar among partial nephrectomy, cryoablation, and radiofrequency ablation, but metastases-free survival was better with partial nephrectomy or cryoablation compared with radiofrequency ablation. Not surprisingly, patients treated with partial nephrectomy were younger and healthier compared with those treated with thermal ablation, and their OS was higher.[33] Generally, the smaller the tumor, the higher the likelihood of success of thermal ablation techniques.[34] The main advantages of thermal ablation are the low rate of serious adverse events, the short recovery period after the procedure, and preservation of renal function. The main disadvantages include need for long-term follow-up and potential need for repeat biopsy if a recurrence is suspected on imaging. In addition, if a local recurrence is detected and repeat ablation is not deemed feasible, salvage surgery (partial or radical nephrectomy) is generally difficult because of postablation desmoplastic reaction.

Partial nephrectomy is still the gold standard for treating the majority of patients with SRM. It provides an accurate diagnosis, ascertains a complete resection, preserves renal function, and can provide the best curative potential in the majority of patients (>95%). Partial nephrectomy is mainly done with robotic-assisted laparoscopic approach at present, although it can also be done using a traditional open surgical approach or pure laparoscopic approach in selected patients. The robotic-assisted laparoscopic approach has the advantage of lower blood loss, lower postoperative complications, shorter hospital stay, and quicker recovery and return to normal activity compared with the open approach, although the vast majority of studies to date are retrospective and subject to selection bias.[35–37] An ongoing clinical trial (the OpeRa trial) is currently comparing these two partial nephrectomy approaches, with an expected study completion date of 2022 (NCT03849820).

Radical nephrectomy is generally considered for patients with SRM in rare cases when partial nephrectomy is deemed technically not feasible even with expert centers or urologic oncologists.[38]

For most patients with cT1b masses and for almost all patients with cT2 and higher tumors, radical nephrectomy is generally indicated, with some exceptions. Radical nephrectomy is generally performed with a minimally invasive approach (robotic-assisted laparoscopic or pure laparoscopic), with open radical nephrectomy reserved for patients with very large tumors or locally advanced tumors involving the IVC or adjacent organs. Patients with IVC tumor thrombus (cT3b and cT3c)

without evidence of metastatic disease should undergo prompt surgical resection by an experienced urologic oncologist with the assistance of vascular or thoracic surgery as needed. These patients should generally not undergo biopsy (as to not delay care), not receive any neoadjuvant systemic therapy (unless on a clinical trial or if the patient is not a surgical candidate after review in a multidisciplinary setting), and not undergo preoperative renal artery embolization. Patients with cT4 disease are rare (~1% of patients undergoing radical nephrectomy) and generally have poor prognosis, although some patients can be cured with multidisciplinary care and aggressive surgical resection.[39] If these patients are suspected to have sarcomatoid dedifferentiation based on imaging features, a biopsy should be obtained, and consideration should be given for neoadjuvant immunotherapy given the poor outcomes of patients with cT4 and sarcomatoid dedifferentiation.

Generally, ipsilateral adrenalectomy is performed when there is radiographic evidence of tumor involvement and not as a routine part of radical nephrectomy.[40] Similarly, lymph node dissection is generally performed when there is suspicion for lymph node involvement on preoperative imaging or intraoperatively because the rate of positive lymph nodes (pN1) is low in the setting of cN0.[41]

Patients with local recurrence after definitive therapy with thermal ablation, partial nephrectomy, or radical nephrectomy can still be potentially cured in the absence of concurrent metastatic disease by repeat thermal ablation, salvage partial nephrectomy or radical nephrectomy, or salvage surgical resection of local recurrence in appropriate surgical candidates.[42–44]

Adjuvant Treatment for High-Risk Localized or Locally Advanced Renal Cell Carcinoma

Because of the poor prognosis of mRCC, four clinical trials have assessed adjuvant VEGF-targeted therapy in patients with locally advanced RCC, and four trials are currently investigating adjuvant immunotherapy. The S-TRAC, ASSURE, PROTECT, and ATLAS trials have produced mixed results in regard to disease-free survival (DFS), but none has significantly improved OS. S-TRAC was a phase III clinical trial that randomized 615 patients with high-risk RCC to adjuvant sunitinib or placebo for 1 year or until disease recurrence.[45] High-risk RCC was defined as T stage 3 or greater, regional lymph node involvement, or both. Adjuvant sunitinib improved DFS by 24% (6.8 vs 5.6 years; hazard ratio [HR], 0.75; 95% confidence interval [CI], 0.59–0.98), but OS did not significantly differ between the two arms (HR, 0.92; 95% CI, 0.66–1.28).[45] Furthermore, grade 3 or higher adverse events were more frequently reported in patients who received adjuvant sunitinib (63.4% vs 21.7%).

In the phase III ASSURE trial, 1943 patients with pathologic T stage 1b or greater were randomized 1:1:1 to sunitinib, sorafenib, or placebo.[46] No significant differences in DFS or OS were observed between sunitinib and placebo (DFS HR, 1.02; 95% CI, 0.85–1.23; OS HR, 1.17; 95% CI, 0.90–1.52) or sorafenib and placebo (DFS HR, 0.97; 95% CI, 0.80–1.17; OS HR, 0.98; 95% CI, 0.75–1.28). In a subgroup analysis of high-risk patients using the definition established in the S-TRAC trial, there remained no difference in DFS or OS between sunitinib or sorafenib versus placebo.[47]

PROTECT was a phase III trial that evaluated pazopanib versus placebo in 1538 patients with high-risk locally advanced RCC.[48] Pazopanib did not significantly improve DFS compared with placebo (HR, 0.86; 95% CI, 0.70–1.06), and it caused frequent alanine aminotransferase and aspartate aminotransferase elevations.

Finally, 724 patients with pathologic T stage 2 or greater or node-positive disease were randomized to axitinib or placebo for 1 to 3 years in the phase III ATLAS trial. The trial was discontinued because of futility at a preplanned interim analysis (DFS HR, 0.87; 95% CI, 0.66–1.15).[49] In a pooled meta-analysis of the S-TRAC, ASSURE, and PROTECT trials, adjuvant VEGF-targeted therapy was not significantly associated with improved DFS or OS, and it significantly increased the odds of grade 3 to 4 adverse events.[50]

Four clinical trials are currently evaluating immune checkpoint inhibitors as adjuvant therapy for high-risk localized or locally advanced RCC. KEYNOTE-564 and IMmotion010 are randomizing patients to pembrolizumab and atezolizumab, respectively, or placebo for 1 year after nephrectomy or metastasectomy. In CheckMate 914, 800 patients with high-risk localized RCC are being randomized to nivolumab plus ipilimumab or placebo for 6 months after nephrectomy. Finally, PROSPER RCC is assigning 805 patients with high-risk localized RCC to nivolumab or placebo, and patients will receive two doses as neoadjuvant treatment proceed to nephrectomy and then finish 1 year of adjuvant therapy. At MD Anderson Cancer Center (MDACC), we do not routinely use adjuvant VEGF-targeted therapy for patients with high-risk localized RCC, and we await the results of ongoing clinical trials before using adjuvant immunotherapy.

METASTATIC DISEASE WITH CLEAR CELL HISTOLOGY

Role of Cytoreductive Nephrectomy in Metastatic Disease

Surgical resection of the primary tumor, cytoreductive nephrectomy (CN), has been shown to improve OS in select patients with mRCC. In the cytokine era

of high-dose interleukin-2 (HDIL-2) and interferon-α (IFN-α), two phase III clinical trials, SWOG 949 and EORTC (European Organization for Research and Treatment of Cancer) 30947, found that IFN-α plus CN improved OS compared with IFN-α alone.[51,52] A pooled analysis of these two trials demonstrated an improvement in median OS from 7.8 months to 13.6 months with IFN-α plus CN.[53] Questions regarding the benefit of CN reemerged after the introduction of targeted therapies for mRCC. In a retrospective analysis of the IMDC database, patients treated in the targeted-therapy era appeared to benefit from CN if they had three or fewer IMDC prognostic risk factors, whereas those with four or more factors did not appear to benefit.[54] In a systematic review of 10 observational studies that evaluated CN in the targeted-therapy era, all of the point estimates for OS favored CN.[55]

CARMENA is the only randomized clinical trial to compare CN followed by sunitinib with sunitinib alone in patients with MSKCC intermediate or poor-risk mRCC, and it was designed as a noninferiority trial.[56] In CARMENA, sunitinib alone was noninferior to nephrectomy followed by sunitinib for OS, and survival was longer in the sunitinib alone group. Although CARMENA is the only level I evidence available for CN in the targeted-therapy era, the trial has several limitations. CARMENA planned to enroll 576 patients, but it only accrued 450 patients over an 8-year period, resulting in an underpowered study. There was also high crossover in both directions between the two treatment arms. Finally, guidelines do not recommend CN for patients with poor-risk mRCC, yet CARMENA enrolled a high percentage of patients with MSKCC poor-risk disease (43%). SURTIME is a phase III clinical trial performed during the targeted-therapy era that sought to evaluate whether a period of sunitinib before nephrectomy improved outcomes compared with immediate CN followed by sunitinib.[57] Deferred CN did not improve the primary endpoint of progression-free rate, but deferred CN significantly improved OS (32 vs 15 months). The improved OS seen with deferred CN may be due to the higher percentage of patients who received sunitinib in the deferred arm (98% vs 80%). At MDACC, CN is not recommended for patients with IMDC poor-risk disease, and in most patients with IMDC intermediate-risk disease, we begin with systemic therapy and reserve CN for select patients with a response to treatment and good performance status.

Role of Metastasectomy

In carefully selected patients, metastasectomy plays an important role in the multidisciplinary treatment of patients with mRCC. Retrospective series have found survival benefit in resecting oligometastatic disease from multiple sites. Interpretation of these results is limited because of the highly selected and retrospective nature of these studies. In a pooled analysis of 56 retrospective studies, metastasectomy was associated with a significantly lower risk of death compared with patients who did not receive a metastasectomy.[58] Prognostic factors for OS after metastasectomy included complete resection of metastases, DFS after nephrectomy, primary tumor characteristics, number of metastases, and performance status. Lung metastasectomy was associated with the best survival benefit compared with other anatomic locations. Patients with no measurable disease after metastasectomy are at an increased risk of recurrence. Eastern Cooperative Oncology Group (ECOG)-American College of Radiology Imaging Network (ACRIN) 2810 (NCT01575548) compared 1 year of pazopanib 800 mg with placebo in patients with no evidence of disease after metastasectomy.[59] Pazopanib did not improve the primary endpoint, DFS, compared with placebo, and there was a statistically significant trend toward inferior OS with pazopanib compared with placebo. At MDACC, we strongly believe in a multidisciplinary approach to optimally manage patients with oligometastatic disease, and we do not use systemic therapy for patients without evidence of measurable disease after metastasectomy.

An algorithm to select candidates for metastasectomy and for the approach to postmetastasectomy systemic treatment is shown in Figure 43–2.

SYSTEMIC THERAPY FOR METASTATIC CLEAR CELL RENAL CELL CARCINOMA

Historical Overview

Over the past 15 years, systemic treatment of patients with metastatic ccRCC has evolved from nonspecific cytokine therapies to molecularly targeted therapies and now includes immune checkpoint inhibitors. Beginning in the 1990s until 2005, treatment of patients with mRCC was limited to nonspecific cytokine therapies, IFN-α and HDIL-2. Cytokine therapy, specifically HDIL-2, has the potential to produce durable complete responses (CRs) in a small percentage of patients, but it is limited by the potential of severe toxicity and lack of clinical benefit for the majority of patients who received it.[60] Then from 2005 through 2012, seven targeted therapies were approved to treat patients with mRCC, five against the VEGF pathway (sorafenib, sunitinib, bevacizumab, pazopanib, and axitinib) and two inhibitors of mammalian target of rapamycin

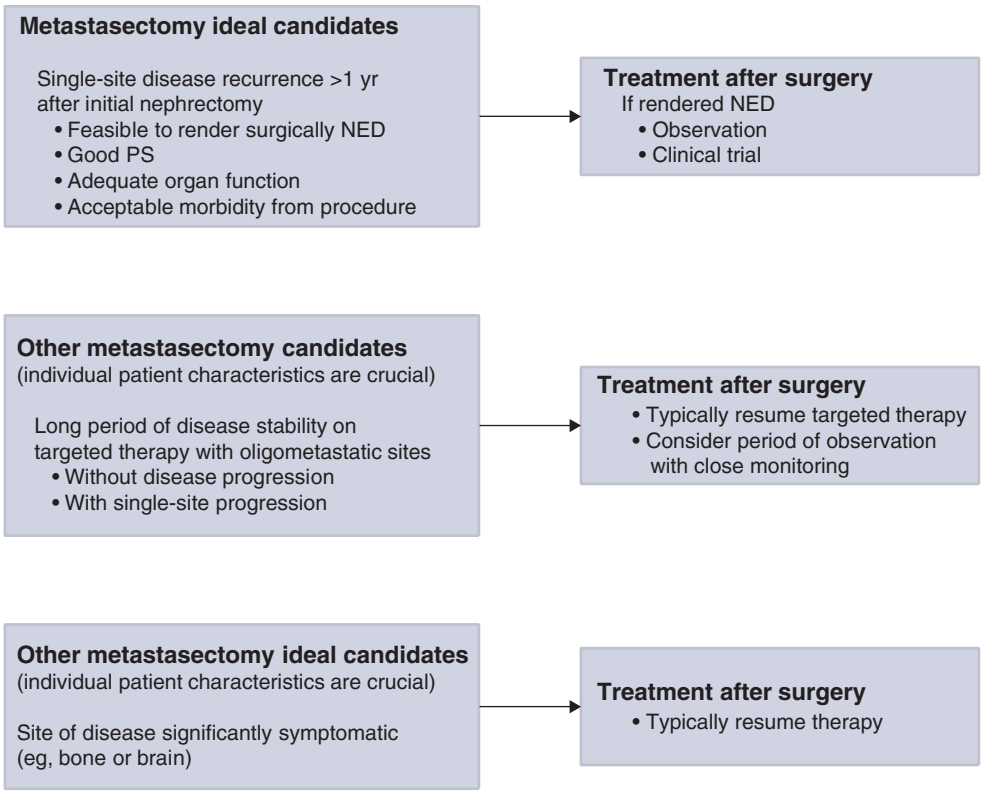


FIGURE 43–2 **Metastasectomy candidates and treatment after procedure. NED, no evidence of disease; PS, performance status.**

(mTOR (mammalian target of rapamycin), temsirolimus, and everolimus).[61–65] Most recently, the introduction of immune checkpoint inhibitors, multitargeted tyrosine kinase inhibitors (TKIs), and incorporation of the MSKCC and IMDC risk scores into clinical decision making has significantly improved outcomes for patients with mRCC.

First-Line Treatment of Metastatic Renal Cell Carcinoma

Nivolumab plus ipilimumab and pembrolizumab plus axitinib are the only first-line therapies to significantly improve OS compared with sunitinib. Nivolumab and pembrolizumab are immune checkpoint inhibitor antibodies against programmed death 1 (PD-1), and ipilimumab is an antibody against anti–cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). Nivolumab plus ipilimumab was approved as first-line treatment on the basis of CheckMate 214, a phase III clinical trial that randomized patients to nivolumab plus ipilimumab or sunitinib.[66] At 30 months of follow-up, nivolumab plus ipilimumab significantly improved OS (Not reached [NR] vs 26.6 months; HR, 0.66), progression-free survival (PFS; 8.2 months vs 8.3 months; HR, 0.77) and overall response rate (ORR) (42 vs 29%) in the primary cohort of patients with IMDC intermediate- or poor-risk disease (Table 43–3).[67] Notably, 11% of intermediate- or poor-risk patients achieved a CR with nivolumab plus ipilimumab compared with 1% with sunitinib. In the intention-to-treat population, nivolumab plus ipilimumab also significantly improved OS (NR vs 37.9 months; HR, 0.71), PFS (9.7 months vs 9.7 months; HR, 0.85), and ORR (41 vs 34%). However, sunitinib resulted in numerically longer OS (NR vs NR; HR, 1.22), PFS (13.9 months vs 19.9 months), and higher ORR (39 vs 50%) in a subgroup analysis of patients with IMDC favorable-risk disease. In regard to toxicity, nivolumab plus ipilimumab resulted in fewer grade 3/4 adverse effects compared with sunitinib, yet more patients had to discontinue treatment because of adverse events with nivolumab plus ipilimumab, which is likely attributable to the unique toxicity profile of immune checkpoint inhibitors. Also, 29% of patients treated with nivolumab plus ipilimumab required at least 40 mg of prednisone to manage immune-mediated adverse events.

Pembrolizumab plus axitinib was approved as first-line treatment for patients with mRCC on the basis of the KEYNOTE-426 trial.[68] KEYNOTE-426 was a phase III clinical trial that randomized patients to pembrolizumab plus axitinib or sunitinib, and in contrast to CheckMate-214, all IMDC risk cohorts were included in the primary efficacy cohort. At first interim analysis,

TABLE 43–3 Pivotal Trials for First-Line Treatment of Metastatic Renal Cell Carcinoma

Agent(s)	Trial Design	Primary Efficacy Cohort	Patients (*n*)	Median PFS[a] (HR, 95% CI)	Median OS[a] (HR, 95% CI)
Nivolumab + ipilimumab	Nivolumab + ipilimumab vs sunitinib	IMDC intermediate- or poor-risk groups	847	8.2 vs 8.3 (0.77, 0.65–0.90)	NR vs 26.6 (0.66, 0.54–0.80)
Pembrolizumab + axitinib	Pembrolizumab + axitinib vs sunitinib	All IMDC risk groups and PD-L1 status	861	15.1 vs 11.1 (0.69, 0.57–0.84)	NR vs NR (0.53, 0.38–0.74)
Cabozantinib	Cabozantinib vs sunitinib	IMDC intermediate- or poor-risk groups	157	8.6 vs 5.3 (0.48, 0.31–0.74)	26.6 vs 21.2 (0.80, 0.53–1.21)
Avelumab + axitinib	Avelumab + axitinib vs sunitinib	All IMDC risk groups, PD-L1 positive	886	13.8 vs 7.2 (0.61, 0.47–0.79)	N/A (0.78, 0.55–1.08)
Sunitinib	Sunitinib vs IFN-α	All IMDC risk groups	750	11 vs 5 (0.42, 0.32–0.54)	26 vs 22 (0.82, 0.67–1.0)
Pazopanib	Pazopanib vs placebo	All IMDC risk groups	435	9.2 vs 4.2 (0.46, 0.34–0.62)	23 vs 21 (0.91, 0.71–1.16)

[a]All progression-free survival (PFS) and overall survival (OS) values listed are in months.
CI, confidence interval; HR, hazard ratio; mRCC, metastatic renal cell carcinoma.

pembrolizumab plus axitinib significantly improved OS (NR vs NR; HR, 0.53), PFS (15.1 months vs 11.1 months; HR, 0.69), and ORR (59 vs 36%). The benefit of pembrolizumab plus axitinib over sunitinib was observed across all IMDC subgroups and irrespective of PD-L1 expression. The incidence of grade 3/4 adverse events was similar between the two treatment arms (76 vs 71%), as was treatment discontinuation (11% vs 14%).

Cabozantinib, avelumab plus axitinib, sunitinib, and pazopanib have improved PFS but not OS as first-line treatment of mRCC, so these agents may have a role for defined patient populations. CABOSUN was a phase II clinical trial that randomized 157 patients with IMDC intermediate- or poor-risk mRCC to cabozantinib versus sunitinib.[69] Cabozantinib is a multitarget TKI that inhibits VEGF, Mesenchymal Epithelial Transition (MET), and AXL. At 34.5 months of follow-up, cabozantinib significantly improved PFS (8.6 vs 5.3; HR, 0.48) and ORR (20 vs 9%) compared with sunitinib, but the improvement in OS was not statistically significant (26.6 months vs 21.2 months; HR, 0.80).[70] The rate of grade 3/4 adverse events and treatment discontinuation because adverse events was similar between treatment arms. At MDACC, we reserve first-line cabozantinib for patients with IMDC intermediate- or poor-risk disease who are ineligible for immune checkpoint inhibitors.

Avelumab is an immune checkpoint inhibitor antibody against PD-L1. Avelumab plus axitinib was studied against sunitinib in the phase III JAVELIN Renal 101 trial.[71] In contrast to CheckMate 214 and KEYNOTE-426, the primary endpoint was evaluated in patients who were PD-L1 positive, which was defined as 1% or greater expression on immune cells. At first interim analysis, avelumab plus axitinib significantly improved PFS in the PD-L1 positive cohort (13.8 months vs 7.2 months; HR, 0.61) and the intention-to-treat (ITT) cohort (13.8 months vs 8.4 months; HR, 0.69) when compared to sunitinib. OS data were immature at the reported interim analysis, and OS was numerically higher with avelumab plus axitinib but not statistically significant. Avelumab plus axitinib also significantly improved ORR compared with sunitinib in the PD-L1–positive cohort (55% vs 26%) and the ITT cohort (51% vs 26%). However, the CR rate with avelumab plus axitinib was lower than was seen with nivolumab plus ipilimumab (3.4% in ITT cohort). Finally, avelumab plus axitinib was well tolerated with similar grade 3/4 adverse events (71% vs 71%) and treatment discontinuation (7% vs 13%) compared with sunitinib. At MDACC, we do not routinely use first-line avelumab plus axitinib because it has not shown a significant improvement in OS, whereas pembrolizumab plus axitinib and nivolumab plus ipilimumab have. This would likely change if future analyses demonstrate a significant improvement in OS with this combination.

Although the first-line therapies that we have discussed demonstrated superiority in the ITT populations, sunitinib and pazopanib still play a role in the first-line treatment of favorable-risk mRCC, specifically in patients ineligible for immune checkpoint inhibitors. Sunitinib was

approved as first-line treatment on the basis of a phase III trial that randomized patients to sunitinib and IFN-α. In that trial, median PFS was significantly improved with sunitinib (11 months vs 5 months), but median OS did not significantly differ between the two groups (26 months vs 22 months).[72,73] The insignificant difference in OS between the two groups was thought to be secondary to crossover from IFN to sunitinib and salvage therapy after protocol. Pazopanib was another VEGF TKI approved on the basis of a phase III clinical trial that compared pazopanib with placebo in patients who previously received nonspecific cytokine therapy but no other systemic treatment.[74] In that study, pazopanib significantly improved PFS (9.2 months vs 4.2 months; HR, 0.46), but OS was not significantly improved with pazopanib (23 months vs 21 months; HR, 0.91). In a similar fashion to the sunitinib trial, there was high crossover from the placebo arm to pazopanib, which confounded the OS data.[75]

Second-Line or Later Treatment of Metastatic Renal Cell Carcinoma

For patients with progressive disease, contemporary second-line or later treatment consists of nivolumab, cabozantinib, lenvatinib plus everolimus, axitinib, or previously unused combinations of immune checkpoint inhibitors (Table 43–4). Second-line or later nivolumab monotherapy was approved in 2015 on the basis of CheckMate 025, which was a phase III trial comparing nivolumab with everolimus.[76] In CheckMate 025, nivolumab significantly improved OS (25 months vs 20 months; HR, 0.73) and ORR compared with everolimus (25% vs 5%). There was no significant difference in PFS between nivolumab and everolimus (4.6 months vs 4.4 months; HR, 0.88). Nivolumab was well tolerated with less grade 3/4 adverse events (19% vs 37%) and treatment discontinuation because of adverse events (8% vs 13%) than everolimus. The efficacy of nivolumab after prior PD-1 axis inhibition is unclear because CheckMate 025 did not include patients who received first-line immune checkpoint inhibitors, so at MDACC, we generally use second-line nivolumab for patients who received first-line VEGF TKI monotherapy.

The METEOR trial was a phase III clinical trial that compared cabozantinib with everolimus after progression on prior VEGF TKI.[77] Cabozantinib significantly improved the primary endpoint of PFS (7 months vs 4 months; HR, 0.51), as well as OS (21 months vs 17 months; HR, 0.66) and ORR (17% vs 3%) compared with everolimus.[78] In a subgroup analysis of efficacy by prior treatment received, cabozantinib improved survival across all prior treatments, including sunitinib, pazopanib, or immune checkpoint inhibitor.[79] In another subgroup analysis, the efficacy of cabozantinib was maintained in patients who had bone metastases at enrollment.[80] Accordingly, we commonly use second-line or later cabozantinib for our patients with bone metastases at MDACC.

Lenvatinib is a multitarget TKI that inhibits VEGFR, fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR), rearranged during transfection (RET), and KIT, and it is approved in combination with everolimus for second-line or later treatment of mRCC. Lenvatinib plus everolimus was evaluated in a phase II trial that randomized 153 patients to lenvatinib, everolimus, or lenvatinib plus everolimus.[81] In that trial, lenvatinib plus everolimus significantly improved PFS (14.6 months vs 5.5 months; HR, 0.40) and ORR (43% vs 6%) compared to everolimus. At the time of primary analysis, lenvatinib plus everolimus did not significantly improve OS compared with everolimus, but a post-hoc analysis performed 6 months later found that lenvatinib plus everolimus significantly improved OS compared with everolimus (26 months vs 15 months; HR, 0.51). Lenvatinib plus everolimus produced more grade 3/4 adverse events than everolimus (71% vs 50%), and the most common grade 3/4 adverse events were diarrhea, fatigue, hypertension, and anemia.

Axitinib is a VEGF TKI that is now primarily used in combination with pembrolizumab or avelumab, yet it is also approved as monotherapy for second-line or later treatment of mRCC on the basis of the AXIS trial, which was a phase III trial that compared second-line axitinib with sorafenib.[63] In AXIS, axitinib significantly improved median PFS (7 months vs 5 months; HR, 0.67) and ORR (19% vs 9%) compared with sorafenib. Median OS was not statistically different between the two groups (20 months vs 19 months; HR, 0.97).[82]

Treatment Selection for Patients with Metastatic Renal Cell Carcinoma

Optimal treatment selection and sequencing has become increasingly complicated because of the rapid development of novel therapies for patients with mRCC. To date, only one trial has directly compared contemporary first-line treatments, the COMPARZ trial.[83] Furthermore, the different primary efficacy cohorts used in CheckMate 214 (IMDC intermediate or poor risk), KEYNOTE-426 (all IMDC risk groups), and JAVELIN Renal 101 (≥1% PD-L1 expression in all IMDC risk groups) limits the value of network meta-analyses to indirectly compare treatments.[84] At MDACC, we use IMDC risk group, sites of metastasis, and burden of metastasis to tailor treatment selection and sequencing for patients with mRCC. Furthermore, we offer clinical trial enrollment to all eligible patients.

For patients with IMDC intermediate- or poor-risk disease, we often use the following agents: first-line nivolumab plus ipilimumab, first-line pembrolizumab plus axitinib, second-line or later cabozantinib, and

TABLE 43–4 Pivotal Trials for Second-Line or Later Treatment of Metastatic Renal Cell Carcinoma

Agent(s)	Trial Design	Prior Treatment	Patients (*n*)	Median PFS[a] (HR, 95% CI)	Median OS[a] (HR, 95% CI)
Nivolumab	Nivolumab vs everolimus	1–2 antiangiogenic treatments	821	4.6 vs 4.4 (0.88, 0.75–1.03)	25.0 vs 19.6 (0.73, 0.57–0.93)
Cabozantinib	Cabozantinib vs everolimus	≥1 antiangiogenic treatment	658	7.4 vs. 3.9 (0.51, 0.41–0.62)	21.4 vs 16.5 (0.66, 0.53–0.83)
Lenvatinib + everolimus	Lenvatinib + everolimus vs lenvatinib vs everolimus	≥1 antiangiogenic treatment	153	14.6 vs 5.5 (0.40, 0.24–0.68)	25.5 vs 17.5 (0.55, 0.30–1.01)
Axitinib	Axitinib vs sorafenib	≥1 approved treatment	723	6.7 vs 4.7 (0.67, 0.54–0.81)	20.1 vs 19.2 (0.97, 0.80–1.17)

[a]All progression-free survival (PFS) and overall survival (OS) values listed are in months.
CI, confidence interval; HR, hazard ratio; mRCC, metastatic renal cell carcinoma.

second-line or later lenvatinib plus everolimus. We prefer to begin with first-line nivolumab plus ipilimumab for most patients with IMDC intermediate- or poor-risk disease because it produced higher CR rates, and retrospective data show higher ORRs with VEGF-targeted therapy after nivolumab plus ipilimumab.[85] If a patient needs a response to upfront treatment because of high-volume disease or a high-risk site of metastasis, we begin with pembrolizumab plus axitinib because of its higher ORR. For second-line or later treatment, cabozantinib remains a viable treatment option after progression on axitinib because it also targets MET and AXL. Nivolumab plus ipilimumab and pembrolizumab plus axitinib have not been studied as second-line treatments, but both are listed on the current National Comprehensive Cancer Network guidelines as second-line treatment options.[86] Furthermore, a retrospective study evaluated second-line or later combinations of immune checkpoint inhibition and VEGF-targeted therapy in 36 patients with mRCC and demonstrated an ORR of 35%.[87]

In patients with IMDC favorable-risk disease and a low volume of metastases, we generally consider the following agents in sequential order: sunitinib–pazopanib, nivolumab with or without ipilimumab, cabozantinib, and lenvatinib plus everolimus. In this population, we begin with sunitinib or pazopanib based on the efficacy findings for favorable-risk disease reported in CheckMate 214.[66] Physician preference can guide selection between sunitinib and pazopanib because the COMPARZ trial showed that pazopanib was noninferior to sunitinib for PFS and OS.[83] In patients with IMDC favorable-risk disease and a high volume of metastases, we often begin with pembrolizumab plus axitinib, instead of sunitinib–pazopanib, and then proceed to cabozantinib and lenvatinib plus everolimus. The treatment algorithms discussed earlier should be tailored to individual patients, and a summary can be found in Figure 43–3.

Management of Adverse Events by Drug Class

Blockade of VEGF results in class adverse effects, which include hypertension, fatigue, proteinuria, increased risk of bleeding, wound dehiscence, and thromboembolic events (Table 43–5). All of the VEGF-targeted therapies cause these side effects to varying degrees. Sunitinib, pazopanib, cabozantinib, and lenvatinib are also inhibitors of other receptor tyrosine kinases and thus commonly induce hand–foot syndrome, diarrhea, dysgeusia, and hypothyroidism. In some cases, sunitinib can also result in cardiomyopathy with decreased ejection fraction.[88–90]

Adverse events caused by VEGF-targeted therapies can often be managed with a combination of supportive care, dose reductions or interruptions, and alternative dosing schedules. Table 43–6 summarizes the standard dose-reduction algorithms used in the registration trials of VEGF-targeted therapies. In addition to dose interruptions and dose reductions, a change in schedule may be beneficial for some patients receiving sunitinib. In registration trials, sunitinib was administered as 4 weeks on, 2 weeks off, but a phase II trial evaluated an alternative schedule of 2 weeks on, 1 week off (2/1) in 77 patients with mRCC.[91] Although the trial did not meet its primary endpoint of decreased grade 3 adverse events, it did show that sunitinib 2/1 was associated with fewer grade 4 adverse events and treatment discontinuation.

Symptom control is also essential for patients receiving VEGF-targeted therapies, and Table 43–7 outlines

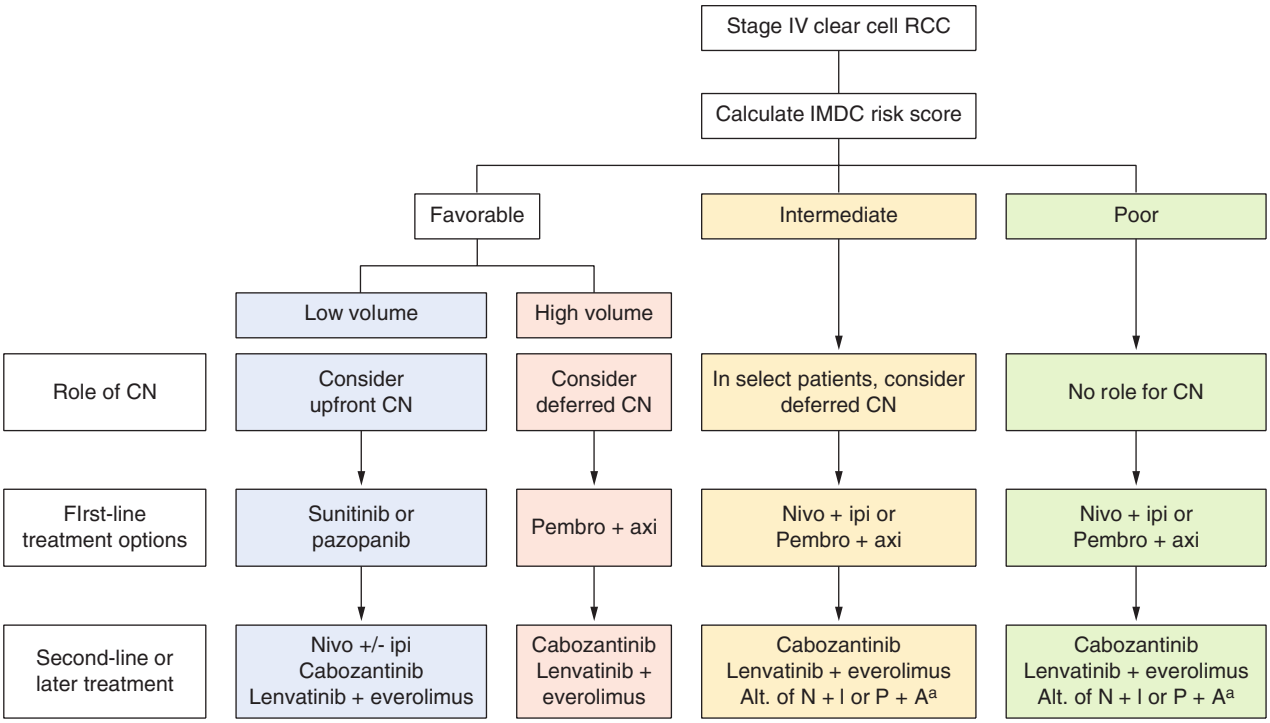


FIGURE 43–3 General approach to management of metastatic clear cell RCC, including the role of systemic therapy and cytoreductive nephrectomy (CN), in June 2020. [a]There are no prospective data to support second-line or later pembrolizumab plus axitinib, but it is currently listed in the National Comprehensive Cancer Network guidelines. alt., alternative; axi, axitinib; ipi, ipilimumab; IMDC, International Metastatic RCC Database Consortium; N + I, nivolumab plus ipilimumab; nivo, nivolumab; P + A, pembrolizumab plus axitinib; pembro, pembrolizumab.

TABLE 43–5 Summary of Side Effects of Vascular Endothelial Growth Factor–Targeted Therapy in Renal Cell Carcinoma[a]

Agent	Sunitinib	Pazopanib	Axitinib	Sorafenib
Hypertension	XX/–	XX/X	XX/X	X/X
Fatigue	XXX/X	X/X	XX/X	XX/X
Hand–foot skin reaction	XX/X	XX/X	XX/X	XX/X
Diarrhea	XX	XXX/X	XXX/X	XX/X
Dysgeusia	XX/X	X/		X/–
Stomatitis	X/X		X/X	X/X
Cardiac toxicity	X/X	X/X		X/X
Nausea	XX/X		XX/X	X/X
Asthenia	X/X		X/X	XX/X
Pulmonary toxicity				X/X
Hepatotoxicity	XX/X	XXX/XX		
Hypertriglyceridemia				
Rash	X/X		X/X	XX/X
Hyperglycemia		XX/X		
Hypothyroidism	X/0	X/–	X/X	X/–
Proteinuria	X/X	X/X		X/X
Cytopenias	XXX/X	XX/X	XX/X	X/X
Increased creatinine	XXX/X	XX/X	X/0	X/X

[a]X, XX, and XXX = low (0%–25%); intermediate (25%–50%); and high incidence (>50%), all grades or grade 3 or higher.

TABLE 43–6 Dose Reduction Algorithm Used in Pivotal Trials of Vascular Endothelial Growth Factor–Targeted Therapies

Agent	Standard Dose	Dose-Reduction Schema
Sunitinib	50 mg PO daily 4 weeks on followed by 2 weeks off	Dose level 1: 37.5 mg PO daily, 4 weeks on, 2 weeks off
		Dose level 2: 25 mg PO daily, 4 weeks on, 2 weeks off
		Alternate[b]: schedule change to 50 mg PO 14 days on and 7 days off
Pazopanib	800 mg PO daily	600 mg/day (dose level 1); 400 mg/day (dose level 2)
Axitinib	5 mg PO bid	3 mg PO bid (dose level 1); 2 mg PO bid (dose level 2)
Cabozantinib	60 mg PO daily	40 mg/day (dose level 1); 20 mg/day (dose level 2)
Lenvatinib		
Sorafenib	400 mg PO bid	Dose level 1: 400 mg PO daily
		Dose level 2: 400 mg PO every other day
		Alternate[b]: dose reduction to 600 mg PO daily

[a]After patients are on therapy, there are several ways to mitigate side effects. The package inserts of each agent outline the standard algorithm for dose reduction. This table summarizes the standard dose-reduction algorithms used in clinical trials of these agents.
[b]Not prospectively validated but used empirically with good effect.
bid, twice a day; IFN, interferon; IV, intravenous; MU, million units; PO, oral; SC, subcutaneous; TIW, three times a week.

supportive care measures that can mitigate or prevent specific side effects. It is essential that the patient and health care team maintain an ongoing dialogue during each cycle of therapy to ensure that patients proactively and appropriately manage these adverse events. Successful adverse event management translates into higher drug compliance and a greater probability of achieving a successful outcome.

Immune checkpoint inhibitors, including nivolumab, pembrolizumab, and ipilimumab, are associated with unique class adverse events, which are referred to as immune-related adverse events (irAEs). irAEs are thought to be secondary to nonspecific immune system activation, and irAEs can affect any organ system. Some of the more common irAEs include rash, colitis, hepatitis, pneumonitis, endocrine involvement (thyroid, hypophysitis, adrenal insufficiency, type 1 diabetes mellitus), and arthralgias.[92] For detailed recommendations on management of irAEs, refer to the American Society of Clinical Oncology practice guideline.[93] In sum, management of irAEs varies by grade of toxicity and organ involvement. For grade 1 irAEs, immune checkpoint inhibitor should be continued, except for neurologic or cardiac toxicity. Grade 2 irAEs warrant holding the immune checkpoint inhibitor, and corticosteroids may be administered depending on the clinical scenario. Grade 3 or 4 irAEs require treatment with high-dose corticosteroids while holding the immune checkpoint inhibitor, and in the setting of grade 4 irAEs, the immune checkpoint inhibitor should be permanently discontinued. Overall, irAEs can present with a wide range of clinical manifestations at any time during treatment, so clinicians must remain vigilant for irAEs in all patients treated with immune checkpoint inhibitors.

Emerging Therapies

Novel therapies are needed for second-line or later treatment of mRCC because combinations of immune checkpoint inhibitors and VEGF-targeted therapy are now standard first-line options. Therapies targeting glutamine metabolism, HIF, and manipulation of the immune response to cancer are currently in development for patients with mRCC. RCC cells depend on glutamine metabolism, and glutaminase plays an essential role by converting glutamine into glutamate.[94] Telaglenastat is a glutaminase inhibitor that has been studied in combination with everolimus and is currently being evaluated with cabozantinib. ENTRATA was a phase II trial that compared telaglenastat plus everolimus versus placebo plus everolimus in patients who had previously progressed on at least two lines of therapy. In this trial, telaglenastat plus everolimus significantly improved PFS (3.8 months vs 1.9 months; HR, 0.64).[95] Currently, a phase II trial, CANTATA, is evaluating telaglenastat plus cabozantinib versus telaglenastat plus placebo in patients who have progressed on one or two prior treatments (NCT03428217). Primary analysis of CANTATA was anticipated in September 2020.

There is an accumulation of HIF-2α in patients with ccRCC cause of inactivation of VHL, which results in cell proliferation and angiogenesis.[21] MK-6482 (previously PT2977) is an oral HIF-2α inhibitor that was studied in a single-arm phase I/II trial of 55 patients with mRCC who progressed on at least one prior systemic therapy. In that trial, MK-6482 was well tolerated and demonstrated antitumor activity with an ORR of 24%.[96] A phase III trial is currently evaluating

TABLE 43–7 Management Recommendations for Commonly Experienced Toxicities with Vascular Endothelial Growth Factor–Targeted Therapies

Side Effect	Preventive Measures	Supportive Care Measures		
Diarrhea	In patients with prior history of diarrhea on agent, consider loperamide once daily in morning	Loperamide 1–2 tabs after diarrhea	Diphenoxylate plus atropine	1 scoop of psyllium with 1 oz of water daily
Hand–foot syndrome	Heavy emollients applied to hands and feet bid and prn	As in preventive measures, plus urea-based callus creams		
Fatigue	Regular physical activity	Consider modafinil or methylphenidate	Check thyroid function	Short naps Regular exercise Regularized diet
Hypertension		Maintain BP below 140/90 mm Hg using 1. Calcium channel blockers (amlodipine okay but not diltiazem) 2. ACE inhibitors 3. Beta-blockers		
Hypothyroidism		Levothyroxine		
Dysgeusia	Salt and soda mouthwash four times a day	Avoidance of hot and spicy foods Salt and soda mouthwash	Carafate	
Mouth sores	Salt and soda mouthwash four times a day	Xylocaine-based mouthwash		
Hyperglycemia	Scrupulous glycemic control	Scrupulous glycemic control		
Rash (sorafenib)		Dose adjustment		
		Aveeno baths		
Rash (temsirolimus and everolimus)		Topical steroids		
Noninfectious pneumonitis (temsirolimus and everolimus)		Corticosteroids		

ACE, angiotensin-converting enzyme; bid, twice a day; BP, blood pressure; prn, as needed.

MK-6482 monotherapy against everolimus as second- or third-line treatment for patients with mRCC after prior PD-1 or PD-L1 checkpoint inhibitor and VEGF-targeted therapy (NCT04195750). Finally, RCC is an immunogenic tumor with a history of responses to HDIL-2, but HDIL-2 is no longer routinely used because of high rates of toxicity, low ORR rates, and the development of immune checkpoint inhibitors. Bempegaldesleukin (NKTR-214) is a human recombinant IL-2 attached to releasable polyethylene glycol chains that is currently being studied in patients with mRCC. In a phase I trial of 28 patients with advanced malignancies, bempegaldesleukin was well tolerated and demonstrated antitumor activity in some of the patients with mRCC, so there is interest in combining bempegaldesleukin with immune checkpoint inhibitors to potentiate their activity.[97] Bempegaldesleukin is currently being evaluated in a phase III trial comparing nivolumab plus bempegaldesleukin versus investigator's choice

of cabozantinib or sunitinib in patients with treatment-naïve mRCC (NCT03729245).

NON–CLEAR CELL RENAL CELL CARCINOMA

Metastatic nccRCC comprises 25% to 30% of RCCs and is associated with a worse prognosis than ccRCC. Patients with metastatic nccRCC were excluded from registration trials, so their outcomes with approved treatments differ from reported clinical trial experiences. Furthermore, survival differs by histologic subtype in patients with metastatic nccRCC. To date, four clinical trials have evaluated systemic therapy across all histologies of metastatic nccRCC.[98–101] At MDACC, we conducted a phase II single-arm study of sunitinib in patients with metastatic nccRCC who had received up to two previous lines of treatment and reported a median PFS of 2.7 months and an ORR of 5%.[100] The ESPN trial was a multicenter, phase II trial that randomized patients with metastatic nccRCC to sunitinib or everolimus.[99] The primary endpoint was PFS after first-line treatment. The trial was stopped early because of futility of satisfying the primary endpoint, with a median PFS of 4.1 months with everolimus compared with 6.1 months with sunitinib. Everolimus and sunitinib were also compared in the phase II ASPEN trial, which randomized patients with untreated, metastatic papillary, chromophobe, or unclassified nccRCC.[98] In ASPEN, sunitinib significantly improved PFS compared with everolimus (8.3 months vs 5.6 months; HR, 1.41) These trials demonstrated that sunitinib and everolimus have modest activity in patients with metastatic nccRCC, and attention has now moved to PD-1 inhibition and multitargeted TKIs for patients with metastatic nccRCC. In KEYNOTE-427 cohort B, 165 patients were treated with pembrolizumab, and the ORR was 24.8%.[101] Multiple retrospective cohort studies have also shown that nivolumab (ORR, 19%–21%) and cabozantinib (ORR, 14%–27%) have antitumor activity in patients with metastatic nccRCC.[102–106]

Papillary Renal Cell Carcinoma

Papillary RCC (pRCC) is the most prevalent nccRCC histology, comprising 40% of patients with nccRCC. Conventionally, pRCC is split into two groups, type 1 and 2, based on light microscopy findings. Papillary type 2 carries a worse prognosis and is associated with hereditary leiomyomatosis and RCC syndrome (HLRCC), which is an autosomal dominant syndrome characterized by alterations to the *FH* gene.[107] More recently, a study from TCGA of 161 patients with pRCC showed that type 1 pRCC is associated with *MET* alterations (81%), and type 2 pRCC is associated with *CDKN2A* silencing, *SETD2* mutations, *TFE3* fusions, and increased expression of the NRF2-antioxidant response element pathway.[108] These findings suggest that the conventional groups of pRCC do not clearly delineate the underlying biology of pRCC. Because of the high prevalence of *MET* alterations in pRCC, multiple clinical trials have evaluated TKIs that target MET, including erlotinib, foretinib, crizotinib, and savolitinib.[109] However, these TKIs have demonstrated modest activity at best, so clinical development of these agents was discontinued. A single-arm, phase II trial demonstrated that axitinib has activity as first-line treatment of metastatic pRCC with an ORR of 28.6%, median PFS of 6.6 months, and median OS of 18.9 months.[110] Two clinical trials are currently evaluating cabozantinib versus sunitinib in patients with pRCC (SWOG 1500; NCT02761057), and in all patients with nccRCC (CABOSUN II; NCT03541902), which is a trial led by MDACC.

Sarcomatoid Renal Cell Carcinoma

RCC with sarcomatoid dedifferentiation (sRCC) is not a distinct histologic subtype of RCC because any RCC histology can also have sarcomatoid dedifferentiation present, and approximately 5% of all patients with RCC demonstrate sarcomatoid dedifferentiation in their tumors.[111] Varying percentages of sarcomatoid involvement can be seen, and it is difficult to determine the underlying histologic background in cases in which there is a predominance of sarcomatoid cells. Genomic analyses have shown that sRCC has increased alterations in *TP53*, *CDKN2A*, and *NF2* as well as upregulation of transforming growth factor β signaling.[112,113] Immune checkpoint inhibitors have shown promising activity in patients with metastatic sRCC. In a post-hoc analysis of CheckMate-214, patients with sRCC had significantly improved OS, PFS, and ORR with nivolumab plus ipilimumab compared with sunitinib, and it resulted in a noteworthy CR rate of 18.3%.[114] Similarly, pembrolizumab plus axitinib significantly improved all efficacy endpoints in patients with sRCC in a post-hoc analysis of KEYNOTE-426, and the CR rate was 11.6%.[101] These post-hoc analyses suggest that patients with sRCC should be offered first-line treatment with nivolumab plus ipilimumab or pembrolizumab plus axitinib because of improved survival and potential for a CR.

Collecting Duct Carcinoma

Tumors arising from the collecting duct epithelium are located in the medulla or center portion of the kidney, in contrast to RCC tumors, which arise from tubules in the cortex.[115] The diagnosis of CDC is

based on both clinical and histologic features. Sarcomatoid dedifferentiation is common, and patterns of metastasis are similar to those of a high-grade, rapidly progressive RCC. There is no established effective systemic therapy for metastatic CDC, although marginal benefit is occasionally seen with chemotherapy regimens developed for urothelial carcinoma.[116]

Renal Medullary Carcinoma

Renal medullary carcinoma (RMC) is a rare and particularly aggressive malignancy that is found in young patients with sickle cell hemoglobinopathies, usually sickle cell trait, and is associated with the loss of a tumor suppressor gene, *SMARCB1*.[117,118] Comprehensive genomic and transcriptomic profiling of RMC has shown that it is characterized by high DNA replication stress and a high number of focal chromosomal alterations.[119] RMC has a poor prognosis with a median OS of 13 months and fewer than 5% of patients living beyond 3 years in the largest retrospective cohort to date.[120] RMC is generally refractory to VEGF-targeted therapy, and the most commonly used systemic treatment is cytotoxic chemotherapy with a platinum-based regimen.[120,121] Accordingly, patients with RMC should be referred to a high-volume center for enrollment in a clinical trial specific to RMC. Currently, there are at least four clinical trials specific to patients with RMC, including trials evaluating immunotherapy (NCT03274258, NCT02496208, NCT02721732) and a proteasome inhibitor, ixazomib, in combination with cytotoxic chemotherapy (NCT03587662). In regard to nephrectomy, an expert panel led by oncologists from MDACC recommends upfront systemic therapy for all patients with RMC, even if they present with localized disease.[117]

Chromophobe Renal Cell Carcinoma

Chromophobe RCC comprises approximately 5% to 10% of all RCC cases, making it the second most common non–clear cell histology. By stage, chromophobe RCC has a better prognosis than ccRCC.[122] Chromophobe RCC is characterized by chromosome loss in chromosomes 1, 2, 6, 10, 13, 17, and 21.[123,124] In a TCGA study of 66 patients with chromophobe RCC, the authors found that mitochondrial alterations play a role in disease biology and identified unique *TERT* promoter rearrangements.[125] In the same study, the most commonly mutated genes in chromophobe RCC were *TP53* (32%) and *PTEN* (9%). Both VEGF-targeted therapy and mTOR inhibitors have antitumor activity in patients with metastatic chromophobe RCC.[98,99,126] In a subgroup analysis of the ASPEN trial, everolimus was associated with longer PFS than sunitinib in patients with metastatic chromophobe RCC (11.4 months vs 5.5 months).[98] In the small, retrospective studies currently available, nivolumab has not resulted in a partial or CR among patients with metastatic chromophobe RCC.[102–104]

Xp11.2 Translocation Carcinoma

Xp11.2 translocation carcinoma is a rare disease entity that is proportionally more common in children but can also occur in young adults.[127] A strong female predominance is observed. The *TFE3* gene located at Xp11.2 has a number of potential translocation partners leading to fusion of a novel gene. An analysis of 16 patients with translocation RCC found significant genomic heterogeneity, with 17q gain, 9p loss, 3p loss, and 17p loss being the most common findings.[128] Histologically, these tumors may resemble ccRCC or show mixed clear and papillary features. These histologic findings in a young adult should prompt further histologic and molecular characterization of the tumor. Staining for *TFE3* permits relatively specific identification of this disease entity, but if it is highly suspected, a break-apart fluorescent in situ hybridization assay should be used to increase sensitivity.[129,130] In the limited retrospective data available, Xp11.2 translocation carcinoma carries a poor prognosis, and VEGF-targeted therapy appears to have some activity. In a retrospective review of 15 adults with translocation carcinoma treated at four centers in the United States, VEGF-targeted therapy produced an ORR of 20%, with a median PFS of 7.1 months and median OS of 14.3 months.[131] Additionally, a French study of 21 patients with adult translocation carcinoma treated with VEGF-targeted therapy or mTOR inhibitors reported an ORR of 33% with median PFS of 8.2 months in first-line treatment and OS of 27 months.[132]

CONCLUSION

For patients with mRCC, immune checkpoint inhibitors and multitargeted TKIs have significantly improved survival and response to treatment. Individualized treatment selection and sequencing remains challenging in mRCC because of the lack of trials directly comparing contemporary therapies and a paucity of predictive biomarkers. In the metastatic setting, patients with nccRCC continue to have a poor prognosis, and these patients should be referred to high-volume centers where clinical trials are available. Finally, in recent years, clinical trials have demonstrated limited benefit with adjuvant TKIs after nephrectomy and questioned the role of CN for IMDC intermediate and poor-risk RCC.

MD ANDERSON PRACTICE TIPS

- Currently, molecular biomarkers are not predictive of response to treatment for patients with mRCC. For prognostication, PBRM1 is associated with a favorable prognosis, and BAP1 is associated with a poor prognosis.
- Despite the approval of adjuvant sunitinib, there is no role for adjuvant VEGF-targeted therapy for patients with locally advanced RCC. Clinical trials evaluating adjuvant immune checkpoint inhibitors are ongoing.
- The efficacy and timing of CN for patients with intermediate- or poor-risk mRCC receiving VEGF-targeted therapy were called into question by the CARMENA and SURTIME trials. At MDACC, CN is not recommended for patients with poor-risk disease, and in most patients with intermediate-risk disease, we begin with systemic therapy and reserve CN for patients with a response to treatment and good performance status.
- The IMDC risk score should be used to guide first-line treatment selection for patients with metastatic ccRCC. To date, only nivolumab plus ipilimumab and pembrolizumab plus axitinib have improved OS as first-line treatment of patients with mRCC.
- Contemporary second-line or later treatment options include cabozantinib, lenvatinib plus everolimus, nivolumab, axitinib, and referral to a clinical trial. Treatment selection depends on the prior lines of therapy received and the characteristics of a patient's disease.
- In the metastatic setting, patients with nccRCC continue to have a poor prognosis, and these patients should be referred to high-volume centers where clinical trials are available.

REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer*. 2019;144:1941-1953.
2. Znaor A, Lortet-Tieulent J, Laversanne M, et al. International variations and trends in renal cell carcinoma incidence and mortality. *Eur Urol*. 2015;67:519-530.
3. Sun M, Thuret R, Abdollah F, et al. Age-adjusted incidence, mortality, and survival rates of stage-specific renal cell carcinoma in North America: a trend analysis. *Eur Urol*. 2011;59:135-141.
4. Amin M, Edge S, Greene F. *AJCC Cancer Staging Manual*. 8th edition. Springer; 2017.
5. Linehan WM, Walther MM, Zbar B. The genetic basis of cancer of the kidney. *J Urol*. 2003;170:2163-2172.
6. Shuch B, Zhang J. Genetic predisposition to renal cell carcinoma: implications for counseling, testing, screening, and management. *J Clin Oncol*. 2018:Jco2018792523.
7. Cumberbatch MG, Rota M, Catto JW, La Vecchia C. The role of tobacco smoke in bladder and kidney carcinogenesis: a comparison of exposures and meta-analysis of incidence and mortality risks. *Eur Urol*. 2016;70:458-466.
8. Chow WH, Gridley G, Fraumeni JF Jr, Jarvholm B. Obesity, hypertension, and the risk of kidney cancer in men. *N Engl J Med*. 2000;343:1305-1311.
9. Adams KF, Leitzmann MF, Albanes D, et al. Body size and renal cell cancer incidence in a large US cohort study. *Am J Epidemiol*. 2008;168:268-277.
10. Kamat AM, Shock RP, Naya Y, et al. Prognostic value of body mass index in patients undergoing nephrectomy for localized renal tumors. *Urology*. 2004;63:46-50.
11. Albiges L, Hakimi AA, Xie W, et al. Body mass index and metastatic renal cell carcinoma: clinical and biological correlations. *J Clin Oncol*. 2016;34:3655-3663.
12. Sorbellini M, Kattan MW, Snyder ME, et al. A postoperative prognostic nomogram predicting recurrence for patients with conventional clear cell renal cell carcinoma. *J Urol*. 2005;173:48-51.
13. Parker WP, Cheville JC, Frank I, et al. Application of the stage, size, grade, and necrosis (SSIGN) score for clear cell renal cell carcinoma in contemporary patients. *Eur Urol*. 2017;71:665-673.
14. Zisman A, Pantuck AJ, Dorey F, et al. Improved prognostication of renal cell carcinoma using an integrated staging system. *J Clin Oncol*. 2001;19:1649-1657.
15. Brooks SA, Brannon AR, Parker JS, et al. ClearCode34: a prognostic risk predictor for localized clear cell renal cell carcinoma. *Eur Urol*. 2014;66:77-84.
16. Rini BI, Escudier B, Martini JF, et al. Validation of the 16-gene recurrence score in patients with locoregional, high-risk renal cell carcinoma from a phase III trial of adjuvant sunitinib. *Clin Cancer Res*. 2018;24:4407-4415.
17. Motzer RJ, Mazumdar M, Bacik J, et al. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol*. 1999;17:2530-2540.
18. Motzer RJ, Bacik J, Murphy BA, et al. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. *J Clin Oncol*. 2002;20:289-296.
19. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *J Clin Oncol*. 2009;27:5794-5799.
20. Heng DY, Xie W, Regan MM, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. *Lancet Oncol*. 2013;14:141-148.
21. Kim WY, Kaelin WG. Role of VHL gene mutation in human cancer. *J Clin Oncol*. 2004;22:4991-5004.
22. Ricketts CJ, De Cubas AA, Fan H, et al. The Cancer Genome Atlas comprehensive molecular characterization of renal cell carcinoma. *Cell Rep*. 2018;23:313-326.e5.
23. Kapur P, Pena-Llopis S, Christie A, et al. Effects on survival of BAP1 and PBRM1 mutations in sporadic clear-cell renal-cell carcinoma: a retrospective analysis with independent validation. *Lancet Oncol*. 2013;14:159-167.
24. Voss MH, Reising A, Cheng Y, et al. Genomically annotated risk model for advanced renal-cell carcinoma: a retrospective cohort study. *Lancet Oncol*. 2018;19:1688-1698.
25. McDermott DF, Huseni MA, Atkins MB, et al. Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma. *Nat Med*. 2018;24:749-757.
26. Hakimi AA, Voss MH, Kuo F, et al. Transcriptomic profiling of the tumor microenvironment reveals distinct subgroups of clear cell renal cell cancer: data from a randomized phase III trial. *Cancer Discov*. 2019;9:510-525.
27. Choueiri TK, Albiges L, Haanen JBAG, et al. Biomarker analyses from JAVELIN Renal 101: avelumab + axitinib (A+Ax) versus sunitinib (S) in advanced renal cell carcinoma (aRCC). *J Clin Oncol*. 2019;37:101.
28. Marconi L, Dabestani S, Lam TB, et al. Systematic review and meta-analysis of diagnostic accuracy of percutaneous renal tumour biopsy. *Eur Urol*. 2016;69:660-673.
29. Kunkle DA, Egleston BL, Uzzo RG. Excise, ablate or observe: the small renal mass dilemma—a meta-analysis and review. *J Urol*. 2008;179:1227-1233; discussion 1233-1234.
30. Smaldone MC, Kutikov A, Egleston BL, et al. Small renal masses progressing to metastases under active surveillance: a systematic review and pooled analysis. *Cancer*. 2012;118:997-1006.
31. Jewett MA, Mattar K, Basiuk J, et al. Active surveillance of small renal masses: progression patterns of early stage kidney cancer. *Eur Urol*. 2011;60:39-44.
32. Pierorazio PM, Johnson MH, Ball MW, et al. Five-year analysis of a multi-institutional prospective clinical trial of delayed intervention and surveillance for small renal masses: the DISSRM registry. *Eur Urol*. 2015;68:408-415.
33. Thompson RH, Atwell T, Schmit G, et al. Comparison of partial nephrectomy and percutaneous ablation for cT1 renal masses. *Eur Urol*. 2015;67:252-259.
34. Johnson BA, Sorokin I, Cadeddu JA. Ten-year outcomes of renal tumor radio frequency ablation. *J Urol*. 2019;201:251-258.
35. Tsai SH, Tseng PT, Sherer BA, et al. Open versus robotic partial nephrectomy: systematic review and meta-analysis of contemporary studies. *Int J Med Robot*. 2019;15:e1963.
36. Wu Z, Li M, Liu B, et al. Robotic versus open partial nephrectomy: a systematic review and meta-analysis. *PLoS One*. 2014;9:e94878.
37. Shen Z, Xie L, Xie W, et al. The comparison of perioperative outcomes of robot-assisted and open partial nephrectomy: a systematic review and meta-analysis. *World J Surg Oncol*. 2016;14:220.
38. Campbell S, Uzzo RG, Allaf ME, et al. Renal mass and localized renal cancer: AUA guideline. *J Urol*. 2017;198:520-529.
39. Borregales LD, Kim DY, Staller AL, et al. Prognosticators and outcomes of patients with renal cell carcinoma and adjacent organ invasion treated with radical nephrectomy. *Urol Oncol*. 2016;34:237.e19-26.
40. Weight CJ, Kim SP, Lohse CM, et al. Routine adrenalectomy in patients with locally advanced renal cell cancer does not offer oncologic benefit and places a significant portion of patients at risk for an asynchronous metastasis in a solitary adrenal gland. *Eur Urol*. 2011;60:458-464.
41. Babaian KN, Kim DY, Kenney PA, et al. Preoperative predictors of pathological lymph node metastasis in patients with renal

cell carcinoma undergoing retroperitoneal lymph node dissection. *J Urol*. 2015;193:1101-1107.
42. Karam JA, Wood CG, Compton ZR, et al. Salvage surgery after energy ablation for renal masses. *BJU Int*. 2015;115:74-80.
43. Thomas AZ, Adibi M, Borregales LD, et al. Surgical management of local retroperitoneal recurrence of renal cell carcinoma after radical nephrectomy. *J Urol*. 2015;194:316-322.
44. Wood EL, Adibi M, Qiao W, et al. Local tumor bed recurrence following partial nephrectomy in patients with small renal masses. *J Urol*. 2018;199:393-400.
45. Ravaud A, Motzer RJ, Pandha HS, et al. Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. *N Engl J Med*. 2016;375:2246-2254.
46. Haas NB, Manola J, Uzzo RG, et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. *Lancet*. 2016;387:2008-2016.
47. Haas NB, Manola J, Dutcher JP, et al. Adjuvant treatment for high-risk clear cell renal cancer: updated results of a high-risk subset of the ASSURE randomized trial. *JAMA Oncol*. 2017;3:1249-1252.
48. Motzer RJ, Haas NB, Donskov F, et al. Randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with localized or locally advanced renal cell carcinoma. *J Clin Oncol*. 2017;35:3916-3923.
49. Gross-Goupil M, Kwon TG, Eto M, et al. Axitinib versus placebo as an adjuvant treatment of renal cell carcinoma: results from the phase III, randomized ATLAS trial. *Ann Oncol*. 2018;29:2371-2378.
50. Sun M, Marconi L, Eisen T, et al. Adjuvant vascular endothelial growth factor-targeted therapy in renal cell carcinoma: a systematic review and pooled analysis. *Eur Urol*. 2018;74:611-620.
51. Mickisch GH, Garin A, van Poppel H, et al. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. *Lancet*. 2001;358:966-970.
52. Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med*. 2001;345:1655-1659.
53. Flanigan RC, Mickisch G, Sylvester R, Tangen C, et al. Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. *J Urol*. 2004;171:1071-1076.
54. Heng DY, Wells JC, Rini BI, et al. Cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma: results from the International Metastatic Renal Cell Carcinoma Database Consortium. *Eur Urol*. 2014;66:704-710.
55. Bhindi B, Abel EJ, Albiges L, et al. Systematic review of the role of cytoreductive nephrectomy in the targeted therapy era and beyond: an individualized approach to metastatic renal cell carcinoma. *Eur Urol*. 2019;75:111-128.
56. Mejean A, Ravaud A, Thezenas S, et al. Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. *N Engl J Med*. 2018;379:417-427.
57. Bex A, Mulders P, Jewett M, et al. Comparison of immediate vs deferred cytoreductive nephrectomy in patients with synchronous metastatic renal cell carcinoma receiving sunitinib: the SURTIME randomized clinical trial. *JAMA Oncol*. 2019;5:164-170.
58. Ouzaid I, Capitanio U, Staehler M, et al. Surgical metastasectomy in renal cell carcinoma: a systematic review. *Eur Urol Oncol*. 2019;2:141-149.
59. Appleman LJ, Puligandla M, Pal SK, et al. Randomized, double-blind phase III study of pazopanib versus placebo in patients with metastatic renal cell carcinoma who have no evidence of disease following metastasectomy: a trial of the ECOG-ACRIN cancer research group (E2810). *J Clin Oncol*. 2019;37:4502.
60. McDermott DF, Regan MM, Clark JI, et al. Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2005;23:133-141.
61. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med*. 2007;356:125-134.
62. Escudier B, Pluzanska A, Koralewski P, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet*. 2007;370:2103-2111.
63. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet*. 2011;378:1931-1939.
64. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med*. 2007;356:2271-2281.
65. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet*. 2008;372:449-456.
66. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med*. 2018;378:1277-1290.
67. Motzer RJ, Rini BI, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2019;20:1370-1385.
68. Rini B, Plimack E, Stus V, et al. Pembrolizumab (pembro) plus axitinib (axi) versus sunitinib as first-line therapy for metastatic renal cell carcinoma (mRCC): outcomes in the combined IMDC intermediate/poor risk and sarcomatoid subgroups of the phase 3 KEYNOTE-426 study. *J Clin Oncol*. 2019;37:4500.
69. Choueiri TK, Halabi S, Sanford BL, et al. Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: the alliance A031203 CABOSUN trial. *J Clin Oncol*. 2017;35:591-597.
70. Choueiri TK, Hessel C, Halabi S, et al. Cabozantinib versus sunitinib as initial therapy for metastatic renal cell carcinoma of intermediate or poor risk (Alliance A031203 CABOSUN randomised trial): progression-free survival by independent review and overall survival update. *Eur J Cancer*. 2018;94:115-125.
71. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2019;380:1103-1115.
72. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med*. 2007;356:115-124.
73. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2009;27:3584-3590.
74. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol*. 2010;28:1061-1068.
75. Sternberg CN, Hawkins RE, Wagstaff J, et al. A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update. *Eur J Cancer*. 2013;49:1287-1296.
76. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373:1803-1813.
77. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373:1814-1823.
78. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR):

final results from a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2016;17:917-927.
79. Powles T, Motzer RJ, Escudier B, et al. Outcomes based on prior therapy in the phase 3 METEOR trial of cabozantinib versus everolimus in advanced renal cell carcinoma. *Br J Cancer*. 2018;119:663-669.
80. Escudier B, Powles T, Motzer RJ, et al. Cabozantinib, a new standard of care for patients with advanced renal cell carcinoma and bone metastases? subgroup analysis of the METEOR trial. *J Clin Oncol*. 2018:Jco2017747352.
81. Motzer RJ, Hutson TE, Glen H, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. *Lancet Oncol*. 2015;16:1473-1482.
82. Motzer RJ, Escudier B, Tomczak P, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. *Lancet Oncol*. 2013;14:552-562.
83. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med*. 2013;369:722-731.
84. Hahn AW, Klaassen Z, Agarwal N, et al. First-line treatment of metastatic renal cell carcinoma: a systematic review and network meta-analysis. *Eur Urol Oncol*. 2019;2(6):708-715.
85. Dudani S, Graham J, Wells JC, et al. First-line immuno-oncology combination therapies in metastatic renal-cell carcinoma: results from the International Metastatic Renal-cell Carcinoma Database Consortium. *Eur Urol*. 2019;76(6):861-867.
86. Motzer RJ, Jonasch E, Agarwal N, et al. Kidney cancer, version 2.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2017;15:804-834.
87. Laccetti AL, Economides MP, Venkatesan AM, et al. Combination anti-angiogenic tyrosine kinase inhibition and anti-PD1 immunotherapy in metastatic renal cell carcinoma: a retrospective analysis of safety, tolerance, and clinical outcomes. *J Clin Oncol*. 2019;37:630.
88. Schmidinger M, Zielinski CC, Vogl UM, et al. Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2008;26:5204-5212.
89. Khakoo AY, Kassiotis CM, Tannir N, et al. Heart failure associated with sunitinib malate: a multitargeted receptor tyrosine kinase inhibitor. *Cancer*. 2008;112:2500-2508.
90. Hall PS, Harshman LC, Srinivas S, Witteles RM. The frequency and severity of cardiovascular toxicity from targeted therapy in advanced renal cell carcinoma patients. *JACC Heart Fail*. 2013;1:72-78.
91. Jonasch E, Slack RS, Geynisman DM, et al. Phase II study of two weeks on, one week off sunitinib scheduling in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2018;36:1588-1593.
92. Hahn AW, Gill DM, Agarwal N, Maughan BL. PD-1 checkpoint inhibition: toxicities and management. *Urol Oncol*. 2017;35:701-707.
93. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of Immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2018;36:1714-1768.
94. Gameiro PA, Yang J, Metelo AM, et al. In vivo HIF-mediated reductive carboxylation is regulated by citrate levels and sensitizes VHL-deficient cells to glutamine deprivation. *Cell Metab*. 2013;17:372-385.
95. Motzer RJ, Lee CH, Emamekhoo H, et al. ENTRATA: randomized, double-blind, phase II study of telaglenastat (tela; CB-839) + everolimus (E) vs placebo (pbo) + E in patients (pts) with advanced/metastatic renal cell carcinoma (mRCC). *Ann Oncol*. 2019;30(5):889-890.
96. Jonasch E, Plimack ER, Bauer T, et al. First-in-human phase I/II trial of the oral HIF-2a inhibitor PT2977 in patients with advanced RCC. *Ann Oncol*. 2019;30(5):361-362.
97. Bentebibel SE, Hurwitz ME, Bernatchez C, et al. A first-in-human study and biomarker analysis of NKTR-214, a novel IL2Rbetagamma-biased cytokine, in patients with advanced or metastatic solid tumors. *Cancer Discov*. 2019;9:711-721.
98. Armstrong AJ, Halabi S, Eisen T, et al. Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial. *Lancet Oncol*. 2016;17:378-388.
99. Tannir NM, Jonasch E, Albiges L, et al. Everolimus versus sunitinib prospective evaluation in metastatic non-clear cell renal cell carcinoma (ESPN): a randomized multicenter phase 2 trial. *Eur Urol*. 2016;69:866-874.
100. Tannir NM, Plimack E, Ng C, et al. A phase 2 trial of sunitinib in patients with advanced non-clear cell renal cell carcinoma. *Eur Urol*. 2012;62:1013-1019.
101. Lee J, Ziobro M, Gafanov R, et al. KEYNOTE-427 cohort B: first-line pembrolizumab (pembro) monotherapy for advanced non–clear cell renal cell carcinoma (NCC-RCC). *J Clin Oncol*. 2019;37:4569.
102. McKay RR, Bosse D, Xie W, et al. The clinical activity of PD-1/PD-L1 inhibitors in metastatic non-clear cell renal cell carcinoma. *Cancer Immunol Res*. 2018;6:758-765.
103. Koshkin VS, Barata PC, Zhang T, et al. Clinical activity of nivolumab in patients with non-clear cell renal cell carcinoma. *J Immunother Cancer*. 2018;6:9.
104. Chahoud J, Msaouel P, Campbell MT, et al. Nivolumab for the Treatment of Patients with Metastatic Non-Clear Cell Renal Cell Carcinoma (nccRCC): a single-institutional experience and literature meta-analysis. *Oncologist*. 2020;25(3):252-258.
105. Campbell MT, Bilen MA, Shah AY, et al. Cabozantinib for the treatment of patients with metastatic non-clear cell renal cell carcinoma: a retrospective analysis. *Eur J Cancer*. 2018;104:188-194.
106. Martinez Chanza N, Xie W, Asim Bilen M, et al. Cabozantinib in advanced non-clear-cell renal cell carcinoma: a multicentre, retrospective, cohort study. *Lancet Oncol*. 2019;20:581-590.
107. Alam NA, Bevan S, Churchman M, et al. Localization of a gene (MCUL1) for multiple cutaneous leiomyomata and uterine fibroids to chromosome 1q42.3-q43. *Am J Hum Genet*. 2001;68:1264-1269.
108. Linehan WM, Spellman PT, Ricketts CJ, et al. Comprehensive molecular characterization of papillary renal-cell carcinoma. *N Engl J Med*. 2016;374:135-145.
109. Shuch B, Hahn AW, Agarwal N. Current treatment landscape of advanced papillary renal cancer. *J Clin Oncol*. 2017;35:2981-2983.
110. Negrier S, Rioux-Leclercq N, Ferlay C, et al. Axitinib in first-line for patients with metastatic papillary renal cell carcinoma: results of the multicentre, open-label, single-arm, phase II AXIPAP trial. *Eur J Cancer*. 2020;129:107-116.
111. Cheville JC, Lohse CM, Zincke H, et al. Sarcomatoid renal cell carcinoma: an examination of underlying histologic subtype and an analysis of associations with patient outcome. *Am J Surg Pathol*. 2004;28:435-441.
112. Malouf GG, Ali SM, Wang K, et al. Genomic characterization of renal cell carcinoma with sarcomatoid dedifferentiation pinpoints recurrent genomic alterations. *Eur Urol*. 2016;70:348-357.
113. Wang Z, Kim TB, Peng B, et al. Sarcomatoid renal cell carcinoma has a distinct molecular pathogenesis, driver mutation profile, and transcriptional landscape. *Clin Cancer Res*. 2017;23:6686-6696.
114. McDermott DF, Choueiri TK, Motzer RJ, et al. CheckMate 214 post-hoc analyses of nivolumab plus ipilimumab or sunitinib in IMDC intermediate/poor-risk patients with previously untreated advanced renal cell carcinoma with sarcomatoid features. *J Clin Oncol*. 2019;37:4513.

115. Peyromaure M, Thiounn N, Scotte F, et al. Collecting duct carcinoma of the kidney: a clinicopathological study of 9 cases. *J Urol*. 2003;170:1138-1140.
116. Oudard S, Banu E, Vieillefond A, et al. Prospective multicenter phase II study of gemcitabine plus platinum salt for metastatic collecting duct carcinoma: results of a GETUG (Groupe d'Etudes des Tumeurs Uro-Genitales) study. *J Urol*. 2007;177:1698-1702.
117. Msaouel P, Hong AL, Mullen EA, et al. Updated recommendations on the diagnosis, management, and clinical trial eligibility criteria for patients with renal medullary carcinoma. *Clin Genitourin Cancer*. 2019;17:1-6.
118. Cheng JX, Tretiakova M, Gong C, et al. Renal medullary carcinoma: rhabdoid features and the absence of INI1 expression as markers of aggressive behavior. *Mod Pathol*. 2008;21:647-652.
119. Msaouel P, Malouf GG, Su X, et al. Comprehensive molecular characterization identifies distinct genomic and immune hallmarks of renal medullary carcinoma. *Cancer Cell*. 2020;37:720-734.e13.
120. Shah AY, Karam JA, Malouf GG, et al. Management and outcomes of patients with renal medullary carcinoma: a multicentre collaborative study. *BJU Int*. 2017;120:782-792.
121. Carlo MI, Chaim J, Patil S, et al. Genomic characterization of renal medullary carcinoma and treatment outcomes. *Clin Genitourin Cancer*. 2017;15:e987-e994.
122. Signoretti S, Flaifel A, Chen YB, Reuter VE. Renal cell carcinoma in the era of precision medicine: from molecular pathology to tissue-based biomarkers. *J Clin Oncol*. 2018:Jco2018792259.
123. Kovacs A, Kovacs G. Low chromosome number in chromophobe renal cell carcinomas. *Genes Chromosomes Cancer*. 1992;4:267-268.
124. Speicher MR, Schoell B, du Manoir S, et al. Specific loss of chromosomes 1, 2, 6, 10, 13, 17, and 21 in chromophobe renal cell carcinomas revealed by comparative genomic hybridization. *Am J Pathol*. 1994;145:356-364.
125. Davis CF, Ricketts CJ, Wang M, et al. The somatic genomic landscape of chromophobe renal cell carcinoma. *Cancer Cell*. 2014;26:319-330.
126. Choueiri TK, Plantade A, Elson P, et al. Efficacy of sunitinib and sorafenib in metastatic papillary and chromophobe renal cell carcinoma. *J Clin Oncol*. 2008;26:127-131.
127. Argani P, Olgac S, Tickoo SK, et al. Xp11 translocation renal cell carcinoma in adults: expanded clinical, pathologic, and genetic spectrum. *Am J Surg Pathol*. 2007;31:1149-1160.
128. Malouf GG, Monzon FA, Couturier J, et al. Genomic heterogeneity of translocation renal cell carcinoma. *Clin Cancer Res*. 2013;19:4673-4684.
129. Rao Q, Williamson SR, Zhang S, et al. TFE3 break-apart FISH has a higher sensitivity for Xp11.2 translocation-associated renal cell carcinoma compared with TFE3 or cathepsin K immunohistochemical staining alone: expanding the morphologic spectrum. *Am J Surg Pathol*. 2013;37:804-815.
130. Argani P, Lal P, Hutchinson B, et al. Aberrant nuclear immunoreactivity for TFE3 in neoplasms with TFE3 gene fusions: a sensitive and specific immunohistochemical assay. *Am J Surg Pathol*. 2003;27:750-761.
131. Choueiri TK, Lim ZD, Hirsch MS, et al. Vascular endothelial growth factor-targeted therapy for the treatment of adult metastatic Xp11.2 translocation renal cell carcinoma. *Cancer*. 2010;116:5219-5225.
132. Malouf GG, Camparo P, Oudard S, et al. Targeted agents in metastatic Xp11 translocation/TFE3 gene fusion renal cell carcinoma (RCC): a report from the Juvenile RCC Network. *Ann Oncol*. 2010;21:1834-1838.

This page intentionally left blank

44 Bladder Cancer

Alexander Y. Andreev-Drakhlin
Ashish M. Kamat
Arlene O. Siefker-Radtke

KEY CONCEPTS

- Pembrolizumab has recently been approved for patients with Bacillus Calmette-Guerin (BCG)-unresponsive non–muscle-invasive urothelial cancer based on responses observed in a cohort of patients with carcinoma in situ in their bladders.
- Neoadjuvant cisplatin-based chemotherapy remains the standard of care treatment for muscle-invasive bladder cancer. Dose-dense MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) has largely supplanted traditional MVAC because of its improved toxicity profile and shorter time to surgery.
- Immune checkpoint inhibitors have been approved frontline treatment for patients with metastatic urothelial cancer who are not eligible for cisplatin-based chemotherapy. Programmed cell death ligand 1 (PD-L1) expression is required in this setting.
- Immune checkpoint inhibitors are also approved after chemotherapy with level 1 evidence showing a survival benefit with pembrolizumab in the second-line setting and with avelumab in the maintenance setting in patients with stable disease or better for frontline chemotherapy. At the moment, there is no definitive evidence as to whether maintenance checkpoint inhibition or checkpoint inhibition at progression is the optimal treatment strategy. PD-L1 expression is not needed in the postchemotherapy setting.
- In April 2019, the Food and Drug Administration (FDA) granted accelerated approval to erdafitinib, the first-in-class fibroblast growth factor receptor 3 (FGFR3) inhibitor based on efficacy in the second-line setting. FGFR3 mutations or fusions are required for treatment.
- In December 2019, the FDA granted accelerated approval to enfortumab vedotin, the first antibody–drug conjugate approved for urothelial cancer based on efficacy in the third-line setting (postchemotherapy, postimmunotherapy). This antibody targets nectin-4, which is highly expressed in urothelial cancer, so expression levels are not necessary.

The recent approvals of checkpoint inhibitors, the first biomarker targeted therapy for fibroblast growth factor receptor 3 (FGFR3) mutations, and the first antibody–drug conjugate have reinvigorated the field of urothelial cancer. Clinical trial programs in this field are rapidly evolving, with combinations of checkpoint inhibitors with these and other novel agents showing clinical activity that appears on par with what was initially achieved with MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) in the 1980s. Urothelial cancer is no longer just one disease. Additional developments in genomic medicine highlight the complexity and heterogeneity of urothelial cancer, providing the biologic framework for developing innovative precision therapy.

OVERVIEW

The urinary tract conveys urine from the confluence of urinary tubules in the renal papillae to the outside world. A specialized epithelial surface known as the urothelium lines this entire path and is composed primarily of transitional cells, extending from the renal pelvis through the ureters, bladder, and urethra. In males, it also lines the terminal prostatic ducts and prostatic

urethra. Although tumors arising from the urothelium can involve any organ along this path, about 90% of these cancers arise in the urinary bladder.

EPIDEMIOLOGY

Urothelial cancer is the fifth most common cancer diagnosis in the United States and is associated with cigarette smoking. In 2020, we anticipated about 85,000 new cases, with about 81,000 arising in the bladder. Altogether, these cases account for approximately 19,000 deaths.[1] These incidence figures are somewhat misleading, however, because compared with other tumors, only in the bladder are histologically bland hyperplastic lesions counted as cancers. In other sites, such lesions count as benign or at most premalignant, and thus the incidence figures include many patients with lesions that do not meet the conventional definition of malignancy. Imagine what the incidence figures for colon cancer would be if every patient with a polyp was counted as a case of colon cancer! Many such lesions recur; however, few progress to true malignancy. Thus, it is critically important to separate risk models that are designed to predict recurrence from those that predict progression, which is far more biologically significant. Because of this anomaly of classification, the literature on "risk of bladder cancer," both for incidence and recurrence, should be interpreted very carefully.

In contrast to most other carcinomas, the majority of patients with urothelial cancer (even after excluding the low-grade papillary "cancers") have early-stage, potentially curable disease at presentation. Only about 20% of patients present with disease that invades into the muscle wall. Fewer than 5% of patients present with locally advanced (ie, clinically extravesical) disease, and another 5% or so present with clinically apparent metastatic disease. When clinically metastatic, urothelial cancer is remarkably aggressive, exhibiting a natural history reminiscent of small cell carcinoma of the lungs. If untreated, the survival is measured in weeks; it is markedly chemosensitive; responses are typically short lived; the brain is a typical "sanctuary" site of relapse after response to initial therapy; and cure of patients with distant metastases, although well documented, remains *uncommon*.

The ready accessibility of urine and the fact that the urothelium itself can be accessed via minimally invasive cystoscopy make urothelial cancer an important context for understanding the processes of carcinogenesis and clonal evolution.

The current state of the art is rather sobering:

- Although immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1) and PD-L1 result in durable treatment responses in some patients, the proportion of patients responding to the therapy remains low, with most trials demonstrating an approximately 20% objective response rate in the metastatic setting.
- There are currently no reliable biomarkers to identify patients with urothelial cancer who benefit from immune checkpoint therapies.
- Fibroblast growth factor receptor (FGFR) inhibition with erdafitinib, a pan-FGFR inhibitor, results in objective treatment response in 40% of patients with FGFR-mutated urothelial cancer. However, most patients develop resistance to FGFR inhibitors within the first 6 months of therapy.

However, there is optimism in that

- Recent advances in drug development with antibody–drug conjugates show great promise in the treatment of patients with urothelial cancer.
- Further molecular characterization of urothelial cancer may have utility in guiding clinical decisions, leading to a personalized approach to care.

CLASSICAL EPIDEMIOLOGY

Malignant transformation of the urothelium parallels observations with other epithelial tumors,[2] in that it is distinctly uncommon before age 40 years and has a peak incidence in the seventh decade of life. The male:female ratio is about 3:1; the reason for this disparity is currently not clear. Malignant transformation is the result of a multistep process involving multiple genes. The appearance of clinical cancer typically follows carcinogenic exposure by decades. Fluid intake is inversely associated with risk,[3] supporting the concept that contact time of excreted carcinogens with the urothelial surface contributes to carcinogenesis.

There is a striking correlation of urothelial cancer incidence with exposure to certain environmental toxins. About half of all cases relate to smoking. Industrial exposures, especially to petrochemicals, account for another 10% to 15%. Many occupations with "chemical" exposures are linked to an excess risk of urothelial cancer. An association with aniline dye exposure was noted more than a century ago, and many aromatic amines (prototypically β-naphthyl amine) have now been shown to be potent urothelial carcinogens. Cigarette smoke is rich in both aromatic amines and the highly reactive bladder toxin acrolein. Another source of acrolein, which is strongly linked to urothelial carcinogenesis, is the metabolism of cyclophosphamide and ifosfamide. In one report, prolonged exposure to oral cyclophosphamide (as was a common intervention for some forms of cancer and for autoimmune disease in the 1970s) increased the risk of bladder cancer by a factor of nine.[4] Also noteworthy are exposures to the analgesic phenacetin and to the plant-toxin–related "Balkan nephropathy" in which the risk of upper tract tumors is increased.[5,6]

As is generally true for epithelial carcinogenesis, chronic irritation and inflammation have also been associated with malignant transformation. This is seen prototypically in settings such as staghorn calculus and other cases of chronic urolithiasis, chronic bladder catheterization (a particularly distressing complication of spinal cord injury[7] or congenital malformations), and classically, chronic schistosomiasis in the Middle East. Urothelial cancers that arise in the context of chronic irritation typically show squamous differentiation.

MOLECULAR EPIDEMIOLOGY

Assessment of genomic variations, as well as functional assessment of certain metabolic pathways, is now integrated routinely with classical aspects of cancer risk assessment. As might have been anticipated from the classical epidemiologic studies of environmental exposures, polymorphisms of various genes involved in xenobiotic metabolism are correlated with the risk of developing bladder cancer. However, these pathways are complex, and the impact of genetic changes is of course context dependent. Some examples include genes involved in carcinogen metabolism, such as glutathione S-transferase Mu 1 (GSTM1), and N-acetyltransferase 2 (NAT2).[8] Furthermore, large genome-wide association studies validated known associations for the GSTM1 deletion and NAT2 slow acetylation variant and identified additional sequence variants that can increase bladder cancer risk.[9]

TUMOR BIOLOGY

Carcinogenesis

A dual-track model has been proposed in urothelial cancer carcinogenesis (Fig. 44–1).[10] The majority of urothelial cancers, approximately 80% to 85%, arise from a hyperplastic epithelium and most commonly present as low-grade non–muscle-invasive bladder cancers (NMIBCs). Although these tumors tend to recur, they are much less likely to evolve into a more aggressive form of urothelial cancer. FGFR3 receptor alterations also follow a similar pattern, with alterations noted in over 60% of low-grade low-stage urothelial tumors.[11] The rest are nonpapillary high-grade muscle-invasive bladder cancers (MIBCs) arising from carcinoma in situ, which have a propensity to metastasize. The apolipoprotein B mRNA-editing enzyme catalytic polypeptide (APOBEC) cytidine deaminases-mediated mutagenesis mutation signature is present in both NMIBC and MIBC. However, NMIBCs are characterized by a significantly lower mutational burden.[12] Moreover, whereas NMIBCs are commonly genomically stable, MIBCs are frequently aneuploid with multiple chromosomal alterations and copy number changes.[13] These high-level differences in the mutational profiles are accompanied by significant differences in the commonly mutated genes in these two bladder cancer types.

The most common copy number alteration in NMIBC is deletion of chromosome 9 observed in approximately 50% of low-grade tumors. Chromosome 9 harbors CDKN2A, which encodes two proteins, p16 and p14ARF. Both function as tumor suppressors affecting the retinoblastoma (RB) pathway and p53 pathway.[14] This is also the location of the interferon-γ (IFN-γ) gene signature; loss of this signature has been implicated in resistance to immune checkpoint inhibitors.[15] The majority of NMIBC also contain point mutations, translocations, or amplification of FGFR3. Increased FGFR signaling leads to activation of the mitogen-activated protein kinase, resulting in increased cell proliferation and oncogenesis.[16,17] Activating PIK3CA mutations frequently co-occur with FGFR3 alterations,[18] raising the question as to whether this could be a potential mechanism of resistance to FGFR3 inhibition. In contrast, gain-of-function mutations in RAS gene family members and ERBB2 found in some NMIBCs are mutually exclusive with FGFR3 alterations.[19,20] Inactivating mutations in the cohesion complex tumor suppressor gene STAG2 are also frequently identified in NMIBC.[21] Recent targeted exon sequencing study that included 105 patients with NMIBC showed that the most frequently altered genes in NMIBC were the TERT promoter (73%), FGFR3 (49%), KDM6A (38%), PIK3CA (26%), STAG2 (23%), ARID1A (21%), and TP53 (21%). Of note, alterations in chromatin modifying genes, including KDM6A and ARID1A, are highly prevalent in NMIBC, occurring in 69% of the tumors.[20]

Multiomics efforts by many groups have provided a deep, integrative analysis of MIBC with the goal of developing new therapeutic approaches.[12,22–25] Although many genes have been shown to be altered, the majority of cases are characterized by the loss of function of key tumor suppressors, including TP53 (48%–49%), CDKN2A (22%–47%), and RB1 (13%–17%). PTEN (phosphatase and tensin homolog) deletions and MDM2 amplifications are also identified. Alterations between CDKN2A and TP53, CDKN2A and RB1, and TP53 and MFM2 tend to be mutually exclusive. FGFR3 point mutations and fusions are less frequent in MIBC compared with NMIBC and are found in up to 15% of tumors. Similar to NMIBC, epigenetic changes are highly prevalent in MIBC. A 2014 the cancer genome atlas (TCGA) study of 131 MIBCs showed that 76% of the tumors harbored an inactivating mutation in one or more of the chromatin regulatory genes, and 41% had at least two such mutations.[12]

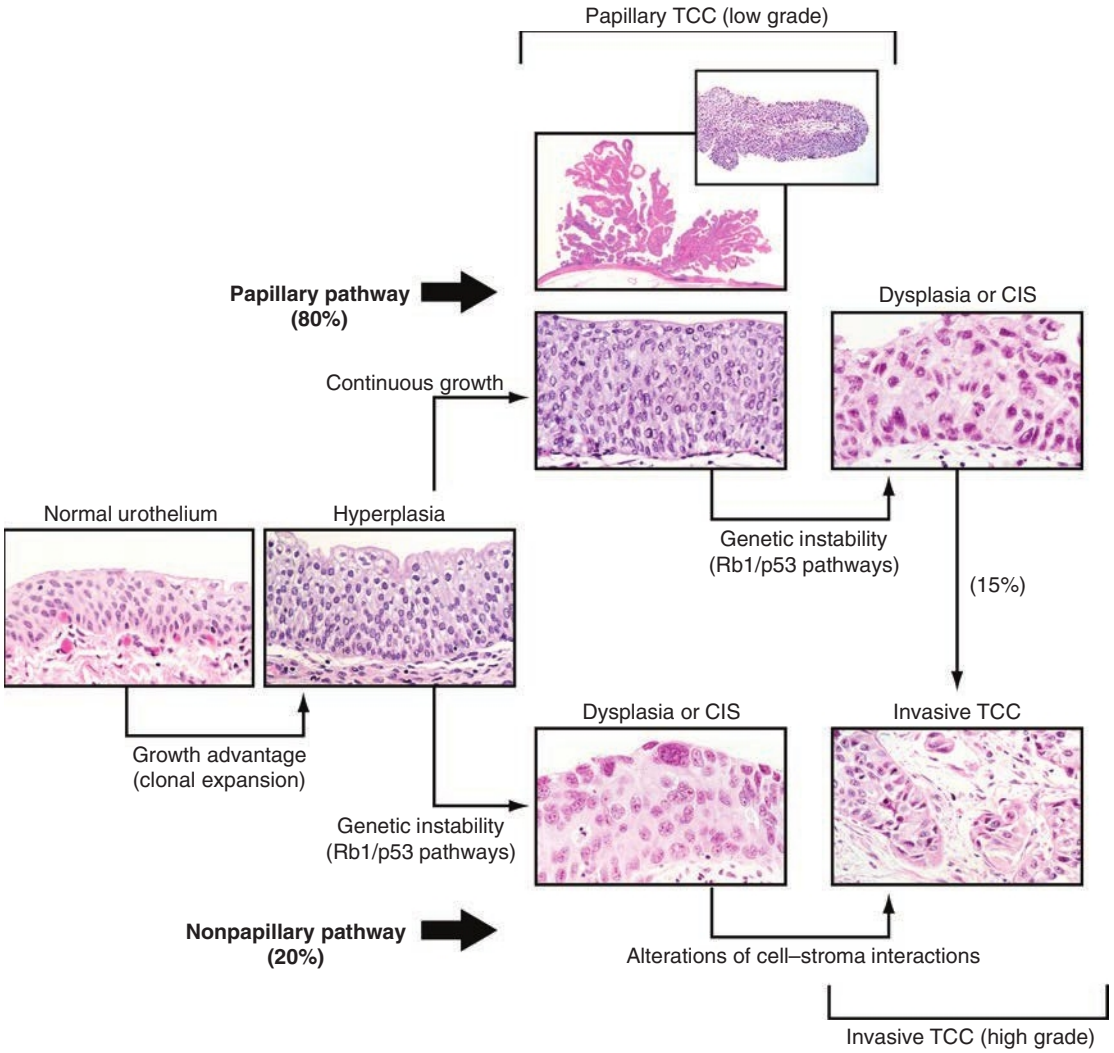


FIGURE 44–1 Dual-track pathway of urothelial cancer. CIS, carcinoma in situ; TCC, transitional cell carcinoma. (Reproduced with permission from Dinney CP, McConkey DJ, Millikan RE, et al: Focus on bladder cancer, *Cancer Cell* 2004 Aug;6(2):111-116.)

Multiple studies have focused on the molecular classification of bladder cancer. Although the Lund molecular taxonomy reported on mixed cohorts of MIBCs and NMIBCs,[25] subsequent efforts mostly focused on analyses of pure MIBC cohorts. The groups at University of North Carolina, MD Anderson Cancer Center (MDACC), and TCGA suggested several molecular classification systems of MIBC.[12,22,26] Although these studies defined different number of clusters, there was a high degree of concordance between the classifications with all tumors, at the highest level, being divided into basal and luminal subtypes. Notably, early evidence from a phase 2 clinical trial suggested that patients with the basal subtype had better outcomes when treated with platinum-based chemotherapy,[23] a finding also reported on additional retrospective tissue samples.[27] The 2017 update to the TCGA classification reevaluated the previously defined clusters and identified five subtypes that partially overlapped with the clusters defined in the prior study.[24]

A recent study analyzed the relationships between the published systems, based on 1750 MIBC transcriptomes.[28] The authors identified six consensus MIBC molecular classes with distinct oncogenic mechanisms, tumor microenvironments, and clinical associations: luminal papillary (LumP), luminal nonspecified (LumNS), luminal unstable (LumU), stroma rich, basal/squamous (Ba/Sq), and neuroendocrine-like (NE-like). LumP tumors were associated with the best survival, papillary morphology, frequent KDM6A mutations, and a strong activation of the FGFR3 signature. LumNS class tumors were enriched with older patients, micropapillary histology, and mutations in ELF3, which is a regulator of urothelial differentiation. LumU class was characterized by genomic instability, ERBB2 amplifications, mutations in TP53 and ERCC2, and the highest

tumor mutational burden. Stroma-rich tumors were associated with high levels of stromal and B-cell infiltration. Ba/Sq tumors overexpressed basal differentiation signature, had frequent TP53 and RB1 mutations, exhibited squamous histology, expressed immune checkpoint marker, and had high numbers of cytotoxic lymphocytes and natural killer cells, suggesting potential benefit from immune checkpoint inhibitors in this group of tumors. Finally, neuroendocrine (NE)-like group demonstrated neuroendocrine differentiation and strong enrichment of concurrent TP53 and RB1 inactivation and had the worst prognosis. There is a hope that this consensus classification will help the development of MIBC precision oncology by facilitating the translation of the molecular subtypes to clinical and research settings.

Novel Biologic Targets

Immune checkpoint inhibitors have transformed the world of cancer, including the field of urothelial cancer. However, the benefits are limited to a low percentage of patients with response rates at around 20%.[29–31] Attempts to select patients most likely to benefit from immunotherapy have been mostly unsuccessful. PD-L1 expression is the only biomarker currently in use in the frontline setting after a recent study suggested that patients with high–PD-L1 disease benefit from single-agent immunotherapy, and those with low–PD-L1 tumors benefitted more from frontline systemic chemotherapy.[31] Other factors, including tumor mutational burden, molecular subtype, and the IFN-γ signature, have not provided definitive benefit is selecting patients for immunotherapy.[15,29]

Approximately 20% of patients with advanced bladder cancer have activating mutations in FGFR.[24] Erdafitinib is the first-in-class FGFR inhibitor approved for the second-line treatment of patients with FGFR3-altered advanced urothelial cancer.[32] FGFR3 alterations are enriched in the immunologically cold, luminal-papillary subtype. However, there are conflicting reports on whether the FGFR3 altered urothelial tumor would benefit more from immunotherapy or FGFR3 targeted therapy.[32,33] An ongoing phase III trial, THOR, will answer this question by comparing erdafitinib with pembrolizumab in patients with FGFR3-mutated urothelial cancer. Other clinical trials, including NORSE, are investigating whether the addition of an immune checkpoint inhibitor to an FGFR inhibitor will enhance therapeutic responses in this patient population.[34]

Many other novel therapies are showing promise in the treatment of urothelial cancer. Nectin-4 is a cell adhesion molecule, which is highly expressed in more than 90% of bladder tumors. Enfortumab vedotin (EV), an antibody–drug conjugate targeting nectin-4, is the most recent addition to the treatment arsenal now approved for the treatment of metastatic bladder cancer.[35] Sacituzumab govitecan (SG) is a Trophoblast cell surface antigen-2 (trop-2)–directed antibody and topoisomerase inhibitor drug conjugate that has been granted the Food and Drug Administration (FDA) fast track designation for patients with urothelial carcinoma.[36] Sitravatinib, an oral tyrosine kinase inhibitor targeting the TAM (TYRO3, Axl, and Mer) family of receptor tyrosine kinases, is being studied in combination with nivolumab in patients previously treated with immunotherapy.[37] Bempegaldesleukin, a pegylated formulation of interleukin-2 (IL-2), has shown clinical activity in combination with nivolumab even in patients with low–PD-L1 tumors.[38]

HISTOLOGY

In the United States, approximately 90% of all urothelial malignancies are within the histologic spectrum of transitional cell carcinoma (TCC), which, in our view, merges without obvious demarcation with the "sarcomatoid" and "small cell" variants at the extreme of dedifferentiation. Most of the remainder exhibit squamous histology (especially prominent in the more distal urethra) or glandular differentiation (ie, adenocarcinoma). The finding of adenocarcinoma apart from the context of bladder exstrophy or a urachal tumor (see later) should prompt consideration of metastatic disease from some other primary site because bona fide primary adenocarcinomas originating from the urothelium are distinctly uncommon.

As noted earlier, primarily hyperplastic lesions, biologically akin to polyps in the gastrointestinal tract, account for a large portion of incident cases. In 1999, the World Health Organization (WHO) put forward a new classification of noninvasive papillary urothelial tumors in recognition of the fact that the malignant potential of these lesions varies widely[39]; even more recent updates reference these earlier recommendations.[40] The WHO terminology for these lesions, which together account for more than half of all new cases of urothelial neoplasia, is

- **Papillary urothelial neoplasm of low malignant potential.** This lesion is characterized by orderly progression of morphology within the urothelium and no cellular atypia. Recurrence occurs in about 25% of cases, but progression is rare.
- **Noninvasive papillary urothelial carcinoma, low grade.** This lesion shows some architectural variation and mild atypia. Such lesions commonly recur (in ≥50% of cases) but progression is seen in fewer than 7%.
- **Noninvasive papillary urothelial carcinoma, high grade.** This lesion shows predominantly disorganized architecture and moderate to marked

cytological atypia. Such lesions do not invade below the basement membrane, but they have substantial biologic potential, with progression to invasive, potentially life-threatening disease in up to 65% of cases. Note that in the WHO system, grades are collapsed to a two-tier system of low grade and high grade. In general, this would map to the older three-tier system as grade 1 = low grade, and grades 2 and 3 = high grade.

In contrast to these papillary cancers, some urothelial cancers exhibit dysplasia and chromosomal instability early on and constitute a "second pathway" of carcinogenesis,[10,41,42] and most of the cases with lethal potential are in this class (see Fig. 44–1). In contrast to the classic "mulberry" appearance, the nonpapillary lesions have a grossly flat or infiltrative appearance at cystoscopy. In older literature, such cancers have been known as *flat*, *sessile*, *solid*, or *tentacular*. Currently, the preferred nomenclature is simply "nonpapillary," although "flat" persists in the *AJCC Cancer Staging Manual*. These morphologic differences were noted long before an understanding of the genetic changes associated with cancer was appreciated. As expected for such distinct phenotypes, the characteristic genetic lesions have been found to be distinct.

In addition to papillary and nonpapillary variants, a *micropapillary* pattern is increasingly recognized.[43–46] The term *micropapillary* originally came from the recognition of morphologic resemblance to an aggressive variant of ovarian cancer. Indeed, this general histologic pattern has been reported in many epithelial malignancies and invariably identifies a more aggressive subset, as was first reported for bladder cancer in 1994. Gene expression profiling studies suggest these aggressive tumors are almost exclusively luminal, with enrichment of active peroxisome proliferator-activated receptor γ, suppression of p63 target genes, and activation of chromatin remodeling genes.[47] These tumors tend to be less sensitive to intravesical immunotherapy with BCG and should be treated with early extirpative surgery.[44] Thus, the biologic potential of urothelial neoplasia extends from relatively nonthreatening in papillary lesions, to potentially life threatening in nonpapillary lesions, to remarkably aggressive micropapillary lesions, all of which are recognizable as "transitional cell" cancer.

Depending on the series, about 30% (or more) of muscle-invasive urothelial cancers are found to have focal areas of squamous or glandular morphology when examined in detail. It is not clear that such "mixed" tumors have a different prognosis than "pure" TCC, and we do not consider this a meaningful subset at MDACC. Certainly, tumors with only focal areas of squamous or glandular differentiation do not exhibit the distinctive natural history of pure squamous cancers or pure adenocarcinomas. Primary nonepithelial cancers (eg, sarcomas, lymphomas, and melanomas) are exceedingly uncommon in the bladder. When they do occur, they do not appear to have a distinctive natural history or clinical management from what would be expected of similar tumors arising in more typical sites.

Urothelial cancers can dedifferentiate to include spindled ("sarcomatoid"), small cell, and plasmacytoid variants. In these cases, the clinical expression of the overall disease process is dominated by the aggressive component even if most of the primary cancer is well within the typical morphologic spectrum of TCC.

Small cell carcinoma of the urothelium is a remarkably aggressive malignancy and exhibits a similar propensity for spread to the brain as small cell carcinoma arising in other sites. Even in the setting of clinically localized disease, the prognosis with local therapy alone remains poor, reflecting the early development of micrometastases. Dysregulation of epithelial to mesenchymal transition networks and a urothelial to neural phenotypic switch appear are associated with this aggressive biology.[48] We strongly favor management of patients with cT2 or lower disease that is based on neoadjuvant chemotherapy followed by surgical consolidation.[49,50] In our hands, this provides about 70% cure.[50,51] Patients with locally advanced disease have a high incidence (8 of 16 in our series) of relapse in the brain,[51] and thus we believe these patients are candidates for prophylactic cranial irradiation. Patients with metastatic disease at presentation continue to have nearly a 100% response rate, with a 100% relapse rate and a median survival time of only 11 months.[51]

Plasmacytoid urothelial cancer is a very rare histology with very limited series reported to date.[52] These tumors typically appear mesenchymal with down regulation of E-cadherin[53,54] and consist of poorly cohesive tumor cells with perinuclear clearing reminiscent of plasma cells.[54,55] They also tend to be highly proliferative with abundant mitosis and staining for Ki-67. These tumors tend to have a unique spread pattern, often appearing as a linitis plastica with diffuse thickening of the bladder and rectum. Although plasmacytoid tumors appear to be sensitive to chemotherapy, even in the neoadjuvant setting with adequate downstaging to pathologic T0 disease, there are few long-term survivors.[52] These have also shown to have a high incidence of recurrence in the peritoneum in more than 50% of patients.[52]

Cancers arising in a urachal remnant, although not strictly "bladder cancers" in the sense of this chapter, merit a comment. These cancers typically involve the dome of the bladder and histologically are enteric-type adenocarcinomas. They are thought to reflect malignant transformation of an enteric epithelial rest within the urachal remnant, producing a cancer

readily recognized as a mucinous adenocarcinoma.[56] An early MDACC series suggested the risk of relapse was increased when an en-bloc resection was not performed and in the setting of positive margins, lymph node involvement, and tumor involving the peritoneal surface.[57] The Memorial Sloan Kettering Cancer Center (MSKCC) experience in 50 patients demonstrated long-term survival in 26 of 28 patients (93%) with pathologically localized disease, in nine of 13 (69%) patients with extension through the bladder or urachal cavity, and in none of nine patients with peritoneal involvement initially.[58] Similarly, the Mayo Clinic experience[59] in 49 patients demonstrated apparent cure in the majority of patients with confined disease and relapse in the majority with nonconfined disease, the latter group having a median survival period of only 16 months.[60] All investigators have emphasized the importance of an attempt at margin-negative, en-bloc resection that includes the umbilicus.

Urachal cancers have a tendency to recur locally, often with peritoneal carcinomatosis, and the typical metastatic sites are (about equally) lungs and liver. Although dramatic responses are infrequent, the use of modern combination regimens with activity in enteric adenocarcinoma is associated with about a 40% objective response rate. Thus, in essentially every clinical respect, urachal cancer behaves like colon cancer and based on the available data should be treated accordingly. The median survival time from the recognition of metastases was 24 months in our retrospective series of 26 patients with metastatic disease, although some patients with grossly metastatic disease have been long-term survivors.[57]

DIAGNOSIS, STAGING, AND PROGNOSIS

Presentation

About 80% of patients present with hematuria, usually painless. The "typical patient" is a smoker in his late 60s. Such patients frequently have pulmonary disease and cardiovascular disease, magnifying the morbidity of both chemotherapy and surgery. They are also at high risk for other smoking-related malignancies. A high percentage of patients have diminished renal function as a result of hypertension and obstructive nephropathy. Thus, the use of nephrotoxic chemotherapy is especially challenging in this population.

Irritative voiding symptoms, including frequency, dysuria, and dribbling, are important points in the medical history because the presence of irritative symptoms raises the possibility of extensive carcinoma in situ or large, infiltrative tumors that may be far more extensive than is revealed by the initial cystoscopy. Obstructive symptoms (nocturia, double voiding, overflow incontinence, low anterior abdominal pain) are frequent in patients with tumors of the bladder neck or prostatic urethra. Tumors in these locations are far less likely to be anatomically confined (ie, curable with surgery) than are similar MIBCs that are well away from these areas where the detrusor muscle is discontinuous.

In evaluating patients presenting with hematuria, it is mandatory to evaluate the upper urinary tracts. Even if a bladder tumor is confirmed on initial cystoscopy, excretory urography is still appropriate because synchronous or metachronous tumors of the upper tracts typically are not associated with specific symptoms.

Recently, several urine tests for cancer-associated antigens have been promulgated for diagnosis. None of these tests is yet sensitive and specific enough to replace cystoscopy and biopsy. The role of these tests for widespread screening is also not defined. Likewise, the role of urine cytology in initial diagnosis is unsettled. The yield is highly dependent on sample collection technique and the skill of the cytopathologist. As with many epithelial cancers, it is likely that DNA-based tests will eventually be widely used to find pathognomonic genetic alterations in urine and thus revolutionize the detection and clinical follow-up of patients with bladder cancer. The role of some form of surveillance in high-risk populations (eg, petrochemical workers) remains controversial. The relatively low positive and negative predictive values of cytology, even when applied to a high-risk group, make such screening difficult to justify.

Stage and Prognostic Classification

The dominant prognostic clinical variable is anatomic stage at diagnosis. Classically, this is defined by depth of invasion into the bladder wall. The currently used staging system is summarized in Figure 44–2.[61] This system is historically rooted in pathologic findings related to cystectomy specimens. As a result, it is not well suited for *clinical* staging. For example, the distinction between deep muscle invasion (T2b) and more superficial muscle invasion (T2a) cannot be reliably made by cystoscopic biopsy, and indeed the differentiation of muscle fibers in the lamina propria from muscularis propria (ie, the distinction between deep cT1 and cT2) is often problematic. Although previously categorized as stage 4 disease, a recent American Joint Committee on Cancer (AJCC) update now classifies N1-3 lymph nodes with stage 3B tumors.[61] Previous neoadjuvant trials excluded these patients from neoadjuvant trials because of the adverse impact of surgical debulking procedures on clinically involved nodes. As with most solid tumors, one must be extraordinarily

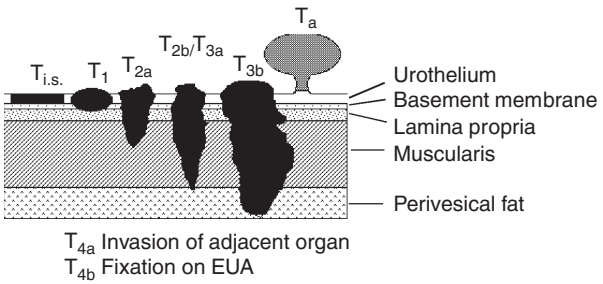


FIGURE 44–2 Current scheme for tumor (T) staging of urothelial cancer. EUA, examination under anesthesia.

careful regarding staging information, especially when comparing surgical and radiotherapy series, which necessarily rely on very different primary information.

Unfortunately, the AJCC staging system does not account for available information about tumor biology. Although "staging" has come to be understood as "prognostic assessment" for most cancers, urologic oncology lags behind in laying aside the historical notion of stage as essentially an anatomic concept. As noted earlier, the biology of papillary cancers is fundamentally different from that of nonpapillary cancers. Other biologic characteristics such as location of tumor within the bladder, the presence or absence of lymphovascular invasion (LVI), and the presence or absence of specific markers are known to influence prognosis, and thus there is a significant need to fully evaluate and standardize how such features are reported.

Although there is no official system for *clinical* staging, several important factors largely define prognosis that can be reasonably well assessed by clinical evaluation:

- The presence or absence of muscle invasion (ie, T1 vs ≥T2). This is frequently established by transurethral resection (TUR), especially if the surgeon provides deep enough samples that contain muscularis propria.
- The presence or absence of a definable mass (ie, assessable in three dimensions) by *examination under anesthesia* (EUA) after a "complete" TUR. This is the clinical definition of cT3b disease and is of critical prognostic importance. The role of cross-sectional imaging criteria for cT3b disease is controversial. We do not believe that routinely available studies can make this distinction reliably at the present time. The EUA is an essential component of the evaluation of a patient with MIBC[62] and is most informative when it is done after drainage of the bladder after the TUR has been completed. A proper EUA provides important staging information, complementing data obtained by imaging modalities such as computed tomography (CT) or magnetic resonance imaging (MRI). Whereas the presence of induration indicates deep muscle invasion, the palpation of a discreet, mobile, three-dimensional (3D) mass implies gross invasion into extravesical tissue and carries a significant risk (30%–40%) of occult lymph node metastasis. At EUA, it is possible to identify masses extending directly into the prostate in men or into the vagina in women. These findings are also associated with a high risk of occult lymph node metastasis. The finding of a mass by EUA, which extends and is fixed to the pelvic sidewall (ie, cT4b), indicates an unresectable cancer. These patients have a similar prognosis to those with overt distant metastases.
- The presence or absence of nodal disease is assessed clinically by CT or MRI imaging of the pelvis. Patients with radiographically detectable adenopathy should have a biopsy before surgery. If positive, primary chemotherapy is appropriate because distant recurrence dominates the clinical course in these patients. That being said, we advocate surgical consolidation with cystectomy and pelvic node dissection in patients with no clinical evidence of disease after chemotherapy.
- The presence or absence of LVI on the TUR biopsy specimen is also a powerful prognostic feature. The unequivocal finding of tumor cells in vascular spaces identifies a group of patients with a high risk of occult nodal involvement. In fact, LVI is associated with a risk of pN+ status of about 35%, comparable to the risk associated with a large cT3b tumor.

Other clinical factors that routinely "stay in the model" when investigators construct Cox proportional hazard models for the prognosis of urothelial cancer patients treated with cystectomy are age, gender (women consistently do worse), and time from diagnosis to definitive therapy.

From a medical oncology perspective, the most important issue is how to recognize which patients will benefit from the addition of systemic chemotherapy to definitive surgery. The current management guidelines for bladder cancer by the National Comprehensive Cancer Network (NCCN) suggest the use of neoadjuvant chemotherapy for patients with cT2 disease. In evaluating this recommendation, it should first be noted that cT2 cancers could easily be pT0 (ie, no residual disease in cystectomy specimen after initial TUR), pTis, pTa, pT1, pT2a, pT2b, or pT3a without constituting a clinical staging error. However, it is abundantly clear that the burden of residual disease (ie, the burden of disease found at cystectomy) after TUR is strongly related to the risk of disease relapse and death. In a series of 208 patients, Isbarn et al[63] demonstrated that those with residual invasive disease (ie, pT1 and pT2) were cured about 70% of the time, but all 55 of those with no residual invasive disease (pTa, pTis, or pT0) were cured.

To further highlight the enormous heterogeneity of patients with cT2 cancers, consider that we know of many features that have a dramatic influence on prognosis:

1. Cancers presenting with hydronephrosis from tumors in the region of the ureterovesical junctions (UVJs) have a very high rate of pT3b extension, occult nodal involvement, and inferior outcome. This was first reported in the 1980s and has been amply confirmed. In a study of 241 patients with cT2 disease treated by cystectomy,[64] the 5-year cause-specific survival rate (a very good surrogate for cure) was 63% for those without this feature versus 12% for those with hydronephrosis. This remained prognostically significant after accounting for pathologic stage. Similar results were obtained by Bartsch et al,[65] who observed a 68% versus a 30% survival rate, again remaining significant after accounting for pathologic stage.
2. As noted earlier, cancers exhibiting micropapillary, sarcomatoid, plasmacytoid, and small cell histology have a much more aggressive biology and inferior "stage-for-stage" outcome with cystectomy.
3. Large nonpapillary tumors (cut points range from 3–5 cm) that are muscle invasive over a broad front are much worse (ie, much more likely to be upstaged at cystectomy) than those with focal muscle invasion.
4. Cancers showing LVI, especially when appreciated in the TUR specimen, are associated with about a 30% rate of occult nodal involvement.[66]
5. In addition to these tumor characteristics, circulating levels of tumor markers are independent predictors of outcome. This has been demonstrated for human chorionic gonadotropin (hCG), cancer antigen 19-9 (CA19-9), and CA-125.[67–69]

On the basis of information that can be gathered preoperatively, it is possible to very substantially refine the clinical risk of a patient with cT2 bladder cancer. Vickers et al[70] have provided a compelling numerical analysis of just how powerful the application of a multivariate model to decision making can be and how this consistently outperforms the simple-minded notion that all patients with cT2 cancer should get chemotherapy.

In addition to these clinical features that can be ascertained preoperatively, there are surgical factors that impact outcome. For example, we know that outcome is dependent on the experience of both the surgeon and the center where surgery is performed[71,72] and that cure is consistently related to extent of pelvic node dissection,[73] and of course, patients with involved surgical margins have a higher risk of relapse.

CLINICAL MANAGEMENT

Management of Non–Muscle-Invasive Disease (cTa, cTis, N0M0)

The management of low-grade papillary disease is by TUR, and because these lesions recur but rarely progress, there is generally no thought of cystectomy except in the rare case that the bladder surface is a carpet of lesions. In such a case, just as with overwhelming colon polyposis, radical surgery to achieve appropriate tumor removal may be appropriate. After TUR, patients usually receive a single dose of immediate intravesical chemotherapy with gemcitabine or mitomycin within 24 hours of resection.[74]

High-grade noninvasive cancers present a difficult dilemma for urologists, who must balance the risk of recurrent, invasive disease (which occurs despite therapy and surveillance in at least 20% of patients) with the risk of overtreating patients not destined to have a threatening cancer. The presence of carcinoma in situ (CIS) increases the probability of both recurrence and progression. Typically, patients with either high-grade Ta disease or CIS (or both) are now treated with both TUR and intravesical immunotherapy with BCG. BCG is preferred over intravesical chemotherapy based on the results of several meta-analyses showing that BCG after TUR is superior to TUR and chemotherapy.[75,76]

Intravesical BCG was introduced in 1976, and since the first controlled trial establishing the efficacy of BCG was reported by Lamm et al in 1980,[77] it has had a remarkable impact on the clinical management of bladder cancer. It is important to note that complete responses to BCG are required for significant alteration of the natural history of the disease.[78] Partial responses should prompt referral for experimental therapy or consideration of early cystectomy. The decision to delay cystectomy in the face of less than an initial complete response to BCG is responsible for many deaths from disease that was not caught early enough, despite close surveillance.[79] In 2018, the FDA adopted the definition of BCG-Unresponsive Disease proposed by the International Bladder Cancer Group, which led to an explosion of clinical trials in this space.[80]

Until recently, treatment options were limited for cystectomy-ineligible patients with high-risk NMIBC unresponsive to BCG. In January 2020, the FDA approved pembrolizumab for the treatment of patients with BCG-unresponsive, high-risk, NMIBC with cTis who are ineligible for or have elected not to undergo cystectomy. Pembrolizumab approval was based on the results of a single-arm KEYNOTE-057 trial that enrolled 148 patients with high-risk NMIBC, two-thirds of whom had BCG-unresponsive cTis disease. The complete response rate in the cTis group was 41% with a median response duration of 16.2 months.[81]

Management of Minimally Invasive Disease (cT1, N0M0)

Patients with cancers that are invasive into the lamina propria (cT1) are at high risk of developing muscle-invasive disease. In general, patients with an invasive or high-grade component recognized on the initial TUR should have a reexcision approximately 4 to 6 weeks later.[82] A second TUR provides another opportunity to sample muscle and thus more definitively establish the status of muscle invasion, which is a key prognostic feature. In addition, the re-resection establishes which patients have persistent disease versus those who do not. Those with persistent disease have a prognosis similar to cT2 patients and should have a discussion regarding cystectomy. Conversely, a complete TUR, as demonstrated by a negative re-resection, may be adequate therapy for many patients with cT1 disease, especially if there is no CIS present and noninvolved muscle has been sampled. In the United States, most patients with cT1 disease receive BCG, and the caveats about BCG use as noted earlier apply even more strongly to this group. It is also important to recognize that tumors that overlie the ureteral orifices or involve the bladder neck are sometimes difficult to confirm as only T1 lesions and require a lower threshold for definitive surgery.

BCG Shortage

Because of increased global demand and limited supply, BCG shortage is anticipated for the foreseeable future. In the event of the shortage, treatment priority is for patients with cT1 high-grade and CIS disease. Patients who do not receive BCG may receive intravesical chemotherapy. Another alternative is to split a single dose of BCG into thirds and treat multiple patients with a single vial. Randomized trials demonstrated similar outcomes and minimally reduced recurrence rates when patients were treated with one-third dose BCG compared with full-dose BCG.[83–85] During these times of shortage, BCG induction therapy should be prioritized over BCG maintenance therapy.

Management of Clinically Localized, Muscle-Invasive Disease (cT2N0)

In the United States, radical cystectomy, which involves removal of the bladder and prostate in men and the bladder and adnexal structures in women, along with complete clearance of pelvic lymph nodes, is the standard therapy for MIBC. In older surgical series, cystectomy was curative in about half of these patients. More contemporary series typically report cure in the range of 80%, but this is on the basis of *pathologic stage*. Although it is true that in experienced centers, 80% to 85% of patients undergoing cystectomy for cancers that are found to be pathologically confined to the muscular wall of the bladder (ie, pT2b or less, N0) will be cured, it is not absolutely clear that the old figure of about 50% cure for *clinical stage* T2 patients is now obsolete. Modern series do seem to do better,[86] likely explained by better preoperative staging and patient selection, as well as better recognition of the need for an adequate lymph node dissection. Although randomized trials have not shown a benefit for extended lymph node dissection over standard lymph node dissection, we recommend that at the very least 10 lymph nodes be removed at the time of radical cystectomy.[87] Despite these advances, it must be recognized that a finding of muscle invasion signals a potentially life-threatening problem; in fact, this seems to constitute an oncologic urgency. In a study of 214 patients treated with cystectomy at the University of Michigan,[88] a cut point of 93 days from recognition of muscle invasion to surgery was associated with statistically inferior cause-specific and overall survival (OS). Specifically, about 60% of patients with timely surgery were long-term survivors versus about 40% of those with delay, even though there was no clinical or pathologic stage migration.

In view of available knowledge of prognostic features reviewed, it is clearly inappropriate in the current era to speak of "muscle-invasive" bladder cancer as though it were a single disease state with a well-defined prognosis and a single best management. We know that there are many patients with cT2 bladder cancer with such a favorable prognosis that no available systemic therapy would be expected to improve outcome over that achieved with radical cystectomy and template pelvic node dissection.[89] Likewise, we know that some patients at high risk benefit from currently available chemotherapy in addition to surgery. The challenge for clinicians, and especially for clinical investigators, is to better define those at each end of this spectrum and then continue to work on subdivision of the remaining patients in whom we currently do not know how to define the role of systemic chemotherapy. This issue of identifying the appropriate patients for systemic chemotherapy is the single most important question related to bladder cancer from a medical oncology perspective. There is no longer any question that perioperative chemotherapy can improve outcome for some patients; likewise, it is all too obvious that it can do much harm. Thus, as always, the central question for the medical oncologist is: How are we to balance risk and benefit for each patient?

Based on the impact of currently available therapy, it is our sense that patients with a 70% chance or more of cure should not be offered chemotherapy as it currently exists. Conversely, when the probability of surgical cure falls to about 40% or less, then it seems clear that chemotherapy should be offered. In between these extremes, the decision is a highly personal issue

of risk abatement versus burden of therapy. As a practical implementation that 40% cure probability is about the right threshold for chemotherapy plus surgery, we offer chemotherapy to patients with any of the following: direct invasion of the prostate or vagina (ie, cT4a disease), a 3D mass on EUA (ie, cT3b disease), LVI on TUR material, bladder neck involvement, and hydronephrosis or aggressive variant histology, including small cell, micropapillary, plasmacytoid, or sarcomatoid differentiation.

Primary Radiotherapy

In our view, radiotherapy is inferior to surgery as a local modality for bladder cancer. Available data clearly demonstrate that long-term control can be achieved in about 40% of patients with small primary tumors amenable to complete resection, not associated with CIS, not arising at the bladder neck or UVJ, and without hydronephrosis.[90] This is precisely the subset that have about an 80% cure with surgery, and claiming that the available results are "comparable" to surgical series is not justified.[91] Clearly, some patients could decide that the risks are acceptable and rationally choose radiotherapy, but this must not be presented as an option associated with a comparable outcome to surgery. When chosen as an option, we recommend the use of concomitant radiosensitizing chemotherapy.[92] Clinical trials are currently studying whether immunotherapy and radiation therapy combinations can improve the long-term control of localized urothelial cancer.

Management of Locally Advanced, Resectable Disease (High-Risk cT2N0, cT3bN0, cT4aN0)

Since the publication of the SWOG intergroup trial of neoadjuvant chemotherapy,[93] many, including the NCCN guidelines, advocate for neoadjuvant chemotherapy as the standard of care for patients with muscle-invasive urothelial carcinoma. Because in our hands, the cure fraction for patients with muscle-invasive disease only with surgery is around 85% and the use of systemic chemotherapy can be toxic in this often frail and older patient population, we have advocated for a more refined approach relying on the probability of recurrence as a guide for the use of neoadjuvant treatment. Tumors that are clinically beyond the bladder wall, (ie, those with a 3D mass at EUA) after thorough TUR of intravesical tumor carry a worse prognosis with a surgical cure rate of about 35%. Many patients with cT2 and high-risk features have a similar chance for surgical cure. The presence of LVI is associated with a high risk of nodal involvement, even in the setting of clinically negative lymph nodes on CT.

Patients with prostatic stromal involvement (from the bladder, *not* from TCC of prostatic ducts) or extension into the vaginal wall (ie, anatomic clinical stage cT4a) have a surgical cure rate in the range of 5% to 20%. A recent retrospective multicenter study of 583 patients with pT4 disease (all deemed resectable on clinical grounds) found a cause-specific survival rate of about 30%.[94] Univariate analysis confirmed female gender, LVI, nodal involvement, positive surgical margins, and pT4b substage to be associated with inferior outcome. None of these patients received neoadjuvant therapy. Collectively, these groups have what we term "locally advanced but resectable" disease, and at MDACC, they are treated primarily with chemotherapy followed by surgical consolidation as appropriate. Although this is a patient cohort with truly threatening disease, it is also true that this is the population for whom combined application of best systemic therapy and best surgical therapy has the greatest patient benefit. In the MDACC experience,[23,95,96] the benchmark outcome in this cohort is cure in about 60% of patients (by intent to treat), with about 40% having no residual invasive cancer in the resected specimen following chemotherapy (so-called "p-zero" status), which we and others[93] have noted to be a reliable indicator of long-term disease-free survival.

Recently several centers have reported on the use of dose-dense MVAC in the neoadjuvant setting for urothelial carcinoma.[23,97,98] The use of the dose-dense strategy has had multiple benefits, including a faster time to surgery with chemotherapy given on a 2-week schedule and an improved tolerance for chemotherapy. In one study, 93% of patients completed at least three cycles of neoadjuvant chemotherapy.[23] Pathologic T0 rates have been quite promising on the order of 39% with a long-term survival rate at least one center suggesting a cure fraction around 63% (Fig. 44–3).[23] Molecular characterization of urothelial tumors from the MDACC trial suggests that the basal subtype may be predictive for benefit from neoadjuvant chemotherapy,[23] a finding supported by additional retrospective evidence.[27] Further efforts in subtyping bladder cancer may yield a prognostic test available for community use that would allow us to discriminate which patients which patients are most likely to benefit from a neoadjuvant approach.

Management of Locally Advanced, Unresectable Disease (cT4b, cN1-3M0)

This group has a dismal prognosis. In our experience, patients presenting with large tumors that are clinically fixed to the rectum, pelvic sidewall, or pubic symphysis actually have a worse prognosis than patients with extrapelvic nodes or lung-only metastases. These patients are considered unresectable and are treated with chemotherapy initially and then reassessed for the possibility of surgical consolidation in light of the quality of response and their fitness for surgery postchemotherapy.[99]

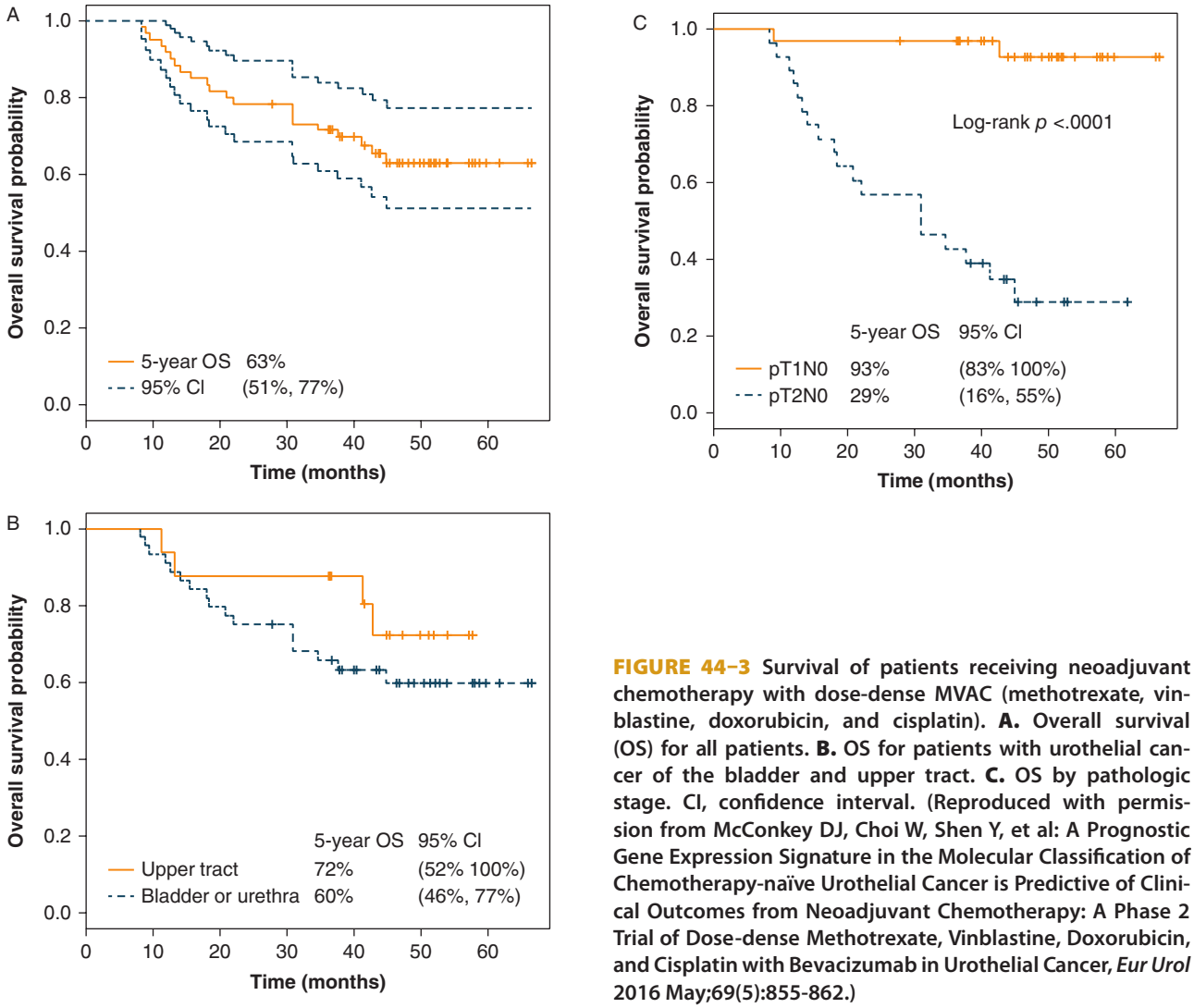


FIGURE 44–3 Survival of patients receiving neoadjuvant chemotherapy with dose-dense MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin). A. Overall survival (OS) for all patients. B. OS for patients with urothelial cancer of the bladder and upper tract. C. OS by pathologic stage. CI, confidence interval. (Reproduced with permission from McConkey DJ, Choi W, Shen Y, et al: A Prognostic Gene Expression Signature in the Molecular Classification of Chemotherapy-naïve Urothelial Cancer is Predictive of Clinical Outcomes from Neoadjuvant Chemotherapy: A Phase 2 Trial of Dose-dense Methotrexate, Vinblastine, Doxorubicin, and Cisplatin with Bevacizumab in Urothelial Cancer, *Eur Urol* 2016 May;69(5):855-862.)

Investigators from the MSKCC[100] and MDACC[101] have published their experience with this strategy. These data suggest that response to systemic therapy is the dominant prognostic feature and that surgical consolidation is both feasible and associated with long-term survival. This experience also confirmed that patients with significant residual disease after chemotherapy did not benefit from surgery, and that overall, the prognosis is still poor. Still, 22% to 40% survival rate among initially unresectable bladder cancer patients is much better than what could be expected of any single modality.

Radiotherapy has not been useful as a single modality with these large cancers. As with surgery, there probably is a role for radiotherapy in the "consolidation" of patients who show an excellent response to primary chemotherapy. It is worth emphasizing that sensitivity to chemotherapy and radiotherapy do tend to be parallel in the context of urothelial cancer. We have never seen a chemorefractory cancer respond to radiation, and we have seen some excellent long-term results from use of radiotherapy to consolidate an initially unresectable mass after an excellent response to combination chemotherapy.

Management of Distantly Metastatic Disease

Bladder cancer typically spreads first to regional nodes and then disseminates with about equal frequency to the lungs, liver, and bone. Late in the course, subcutaneous and brain metastases are common. Brain involvement is especially likely in patients who have elevated serum levels of β-hCG or variant histology, including small cell.

Even with strictly palliative goals in mind, most patients with metastatic bladder cancer should receive systemic therapy, pitched at their level of physiologic tolerance. Metastatic urothelial cancer is a very aggressive malignancy, with an untreated natural history

from the time it causes symptoms to death on the order of 3 to 4 months. Quality of life is essentially dependent on the efficacy of therapy. Even extraordinarily toxic regimens can be truly palliative in light of how rapidly (and morbidly) the disease progresses.

Since the mid-1980s, cisplatin-based combination chemotherapy has been the standard first-line therapy for advanced urothelial cancer. In the modern era with a bit of lead time bias compared with practice in the early 1980s, such treatment results in median survival of about 16 months, with few survivors beyond 3 years. This is the benchmark where therapy plateaued for more than a decade until the recent approval of five immune checkpoint inhibitors, antibody–drug conjugate EV, and erdafitinib (for patients with FGFR-mutated bladder cancer).

Surgical Consolidation

Of course, some patients with distantly metastatic disease still have disease restricted to one (or a few) anatomic areas, and one might imagine that local therapy would have a role in such a setting. However, in contrast to the situation with renal cell carcinoma, for example, surgery is almost never an appropriate initial intervention for metastatic urothelial cancer. Almost always, the disease is not really localized, and one finds rapid progression in the postoperative setting. Thus, even in cases of anatomically threatening lesions such as threatened cord compression, we generally advocate frontline chemotherapy to get the disease under some control that will then permit safe surgical intervention. Nonetheless, it is only natural to ask if there is a role for surgical consolidation after a good response to chemotherapy for (highly) selected patients with metastatic urothelial cancer. The MDACC experience with this strategy has been published in the setting of retroperitoneal lymph node metastases[99,102] and in a very small, select subset of patients with visceral metastases.[103] We have adopted the following guidelines. For patients with pelvic or retroperitoneal nodal involvement (below the renal vessels), we typically offer an extended node dissection to patients with a complete radiographic response to systemic chemotherapy. Because judging the "completeness" of response in a lymph node is problematic, we include in our working definition a negative biopsy for any node that is large enough for CT-guided biopsy. For patients with visceral involvement, we typically treat to maximum response and observe. Only when patients progress in the initially involved area (with no progression elsewhere) and then go on to have a significant response to a second course of chemotherapy do we consider surgical removal of residual metastatic disease. Just as with patients with germ cell cancers, failure of markers to normalize is nearly an absolute contraindication to surgical consolidation.

The exception to this is the rare patient with a long interval from initial management to the onset of resectable, oligometastatic visceral disease. In this setting, we typically give systemic therapy and then excise the lesions. Note that in our view, surgery without some form of systemic therapy is essentially never appropriate because these cancers have a high propensity of seeding surgical wounds. Even in the face of cord compression, chemotherapy followed by surgery is usually the preferred management.

FRONTLINE THERAPY FOR METASTATIC, SURGICALLY UNRESECTABLE UROTHELIAL CANCER

Cisplatin-Eligible Therapy

Currently, *combination therapy is standard* in the treatment of patients with metastatic TCC. The development of MVAC at MSKCC[104] was an important achievement. Subsequent landmark trials have confirmed that MVAC is superior to single-agent cisplatin[105]; the combination of cyclophosphamide, doxorubicin, and cisplatin[106]; the combination of 5-fluorouracil, IFN-α, and cisplatin[101]; and the combination of docetaxel and cisplatin.[107] In fact, there are at least nine randomized trials involving MVAC, and to date, the only challenger to even suggest improved clinical outcome was a trial of a dose-dense variant of MVAC given with granulocyte colony-stimulating factor support versus "classic" MVAC.[108] The dose-dense version was associated with markedly less mucositis, and the cycles are only 14 days (compared with 28 in the classic schedule), and thus this variant has supplanted the original. With overall response rates in the 50% to 60% range and up to 20% clinical complete response (CR) rate, there is no doubt that dose-dense MVAC provides meaningful palliation for most patients and can significantly change the natural history of the disease for a few.

In the setting of metastatic disease, for which the goals are clearly palliative, the doublet of gemcitabine and cisplatin (GC) has become a standard option. GC was compared with MVAC in a large international phase III trial.[109] This trial was negative trial that did not achieve its primary endpoint. However, the doublet was shown to be similar with respect to median survival and was associated with significantly less mucositis and neutropenic fever but more thrombocytopenia. As expected for two regimens with comparable efficacy, quality-of-life measures were not different between the two treatments despite the favorable treatment-related side effect profile of GC. In our view,

this is not a surprising finding but rather reinforces the notion that the burden of morbidity in patients with metastatic bladder cancer is far more likely to be due to the disease rather than secondary to the treatment.

Cisplatin-Ineligible Therapy

All patients considered for frontline chemotherapy should be evaluated for their ability to tolerate cisplatin-based chemotherapy. A consensus definition of patients with metastatic urothelial cancer who are unfit for cisplatin-based chemotherapy was established in 2011.[110] Based on the consensus definition, patients meeting at least one of the following are considered "unfit":

- WHO or Eastern Cooperative Oncology Group performance status of 2 or Karnofsky performance status of 60% to 70%
- Creatinine clearance less than 60 mL/min
- Common Terminology Criteria for Adverse Events (CTCAE) grade 2 or above audiometric hearing loss
- CTCAE grade 2 or above peripheral neuropathy
- New York Heart Association class III heart failure

For patients who are unfit for cisplatin-based chemotherapy but are otherwise candidates for combination chemotherapy, treatment options include a carboplatin-based therapy or a non–platinum-based combination. Carboplatin-based therapy was evaluated in the European Organization for Research and Treatment of Cancer trial 30986 that compared gemcitabine and carboplatin with methotrexate, carboplatin, and vinblastine in patients with impaired renal function of poor performance status. In this trial, carboplatin and gemcitabine therapy resulted in 41% objective response rate, 9-month median survival time, 6-month progression-free survival, and manageable toxicity with approximately 10% of patients developing grade 3 or greater adverse events.[111]

Non–platinum-based regimens present treatment options who are unfit to receive platinum-based chemotherapy. Gemcitabine and the taxanes[112,113] all have activity in urothelial cancer, and there have been many new doublets and triplets investigated over the past 10 years. From this experience, it is clear that all regimens substituting carboplatin for cisplatin show inferior results or even increased toxicity as was seen with the triplet combination of gemcitabine, paclitaxel, and carboplatin.[114]

Urothelial cancer is a disease of older adults. The lifetime accumulation of risk factors predisposing patients to bladder cancer often lead to other comorbid conditions such as coronary artery disease and chronic obstructive pulmonary disease. These diseases, in addition to other conditions, such as diabetes and hypertension, found in an aging population often contribute to poor renal function or a performance status unable to tolerate aggressive cisplatin- or ifosfamide-based therapy.

Ureteral obstruction is also a frequent factor contributing to diminished renal function, and nephrostomy tubes are an indispensable tool in the treatment of advanced bladder cancer. Nephrostomy tubes are much to be preferred over ureteral stents in patients undergoing chemotherapy for locally advanced bladder cancer. This is so because chemotherapy often engenders periods of neutropenia that can lead to chronic infection associated with foreign bodies. Nephrostomies are much more easily changed out than stents. Furthermore, stents are far more irritating and likely to bleed during periods of thrombocytopenia. It is common to have stents clog from bleeding, and this is much less problematic with nephrostomies. Finally, nephrostomies reliably decompress the kidneys, even if the cancer grows, but stents can be collapsed by tumor and even by desmoplastic reaction to therapy.

Relatively effective chemotherapy for patients with impaired renal function is now fairly easy to come by. Vinblastine, gemcitabine, taxanes, and doxorubicin can all be given safely in the context of renal insufficiency. At the present time, we favor a triplet of gemcitabine (900 mg/m^2 given over 90 minutes), paclitaxel (100 mg/m^2), and doxorubicin (30 mg/m^2) repeated every 14 days for patients with poor renal function. This regimen is reliably deliverable and has useful clinical activity.[115]

Frontline Immunotherapy

Both atezolizumab and pembrolizumab were originally approved for the frontline treatment of cisplatin-ineligible patients. The FDA then modified these recommendations, limiting their use to PD-L1–high tumors based on two frontline trials that showed patients treated with chemotherapy did better in the setting of PD-L1–low tumors. Currently, results from only one trial are available. The IMvigor130 trial compared frontline systemic platinum-based chemotherapy with chemotherapy plus atezolizumab versus atezolizumab alone. PD-L1 high was defined as immune cell expression in 5% or more of the specimen.[31] Survival favored atezolizumab monotherapy over platinum-based chemotherapy, with stratified hazard ratio (HR) for death of 0.68 (96% confidence ratio [CI], 0.43–1.08).

Frontline Maintenance Immunotherapy

Giving checkpoint inhibitors with frontline platinum-based chemotherapy has not shown evidence of definitive survival benefit. A recent "maintenance" strategy yielded positive results. Patients who received four to six cycles of platinum-based frontline chemotherapy and had stable disease or better were randomized to

either avelumab or best supportive care after a treatment-free interval of 4 to 10 weeks after the last dose of chemotherapy. The avelumab treated arm had a significantly improved median OS (median OS, 21.4 months vs 14.3 months, respectively; HR, 0.69; 95% CI, 0.56–0.86; $P = .001$). However, only 44% of the control group received second-line treatment with an immune checkpoint inhibitor, raising the question that some of this benefit reflects an "ever" immunotherapy versus "never" immunotherapy contribution.[116] A similar yet much smaller trial randomized patients to maintenance pembrolizumab versus placebo with pembrolizumab at progression. There was no significant difference in survival, with only half crossing over to pembrolizumab at progression by the time of the data lock.[117]

SECOND-LINE THERAPY FOR UROTHELIAL CANCER

Until a few years ago, there was no effective therapy for patients with platinum-resistant urothelial cancer. This second-line cohort includes patients who progress within 1 year of their last dose of neoadjuvant or adjuvant chemotherapy because of the similar prognosis. Single-agent taxanes were typically used or alternate combination chemotherapy. We have recently seen several new agents approved for this indication, including immune checkpoint inhibitors and now the first biomarker targeted therapy erdafitinib, which has efficacy in FGFR3-altered tumors. Only pembrolizumab has comparison data showing a survival benefit compared with single-agent taxanes.

Immune Checkpoint Inhibition

Currently, there are five immune checkpoint inhibitors approved for the second-line treatment of patients with metastatic urothelial cancer: pembrolizumab,[118] nivolumab,[29] atezolizumab,[119] durvalumab,[120] and avelumab.[121] Only pembrolizumab has level 1 evidence showing not only a survival benefit (10.3 months vs 7.4 months; HR, 0.73; $P = .0022$) but also an improved response rate and toxicity profile compared with single-agent taxanes.[118] Based on multiple phase 2 results, the other four checkpoint inhibitors appear to have similar activity, reporting response rates in the range of 15% to 20%, and a median OS ranging from 7.4 to 10.3 months, with potentially minor differences appearing most likely related to patient selection rather than a statement of differential activity for PD-1 or PD-L1 inhibition. Despite this "plethora" of checkpoint inhibitors, these appear to only reflect one "line" of therapy because there does not appear to be any appreciable benefit when switching from one checkpoint to another or sequencing from PD-L1 to PD-1 or vice versa. Biomarkers, including PD-L1 expression levels, tumor mutation burden, and a variety of other immune factors, have shown an increased likelihood of benefit from immunotherapy but do not provide any definitive direction as to who should or should not receive an immune checkpoint inhibitor. As a result, these measurements are not needed for treatment with second-line immune checkpoint inhibition.

FGFR3-Targeted Therapy

FGFR point mutations and fusions are present in up to 20% of locally advanced or metastatic urothelial cancers of the bladder and up to 35% of upper tract urothelial cancers.[122] Erdafitinb has pan-FGFR3 inhibition across FGFR1-4, with IC50 in the single-digit nanomolar range. A recent phase 2 trial of erdafitinib in patients with FGFR3-altered, previously treated urothelial cancer showed evidence of clinical activity with an objective response rate of 40% and median OS of 13.8 months (Fig. 44–4), resulting in accelerated approval of erdafitinib in April 2019.[32] A retrospective look at investigator reported response to previous checkpoint inhibition found a low response rate of 1 of 22 patients, suggesting that these FGFR3 altered tumors may benefit more from an FGFR3-targeted strategy as a result of their enrichment for an "immunologically cold" tumor profile. A more recent study from the second-line nivolumab and atezolizumab trial datasets suggest that FGFR3-altered urothelial cancers do respond to immunotherapy, although long-term outcomes of benefit were not included. The THOR clinical trial[34] randomizes FGFR3 altered urothelial cancer patients to either erdafitinib or pembrolizumab and will definitively determine whether FGFR3-altered tumors benefit more from second-line immunotherapy or FGFR3-targeted therapy.

THIRD-LINE THERAPY FOR UROTHELIAL CANCER

Antibody–drug conjugates are showing promise in the treatment of urothelial cancer. EV is an antibody conjugate targeting nectin-4 expression, which is present on 94% of metastatic urothelial cancers. After selectively targeting urothelial cancer cells, the cleavable linker releases auristatin, a microtubule agent, directly into the tumor cell. This third-line trial had reported a response rate of 44% with a median survival period of around 11 months, resulting in FDA-accelerated approval in December 2019.[35] Current studies combining EV with pembrolizumab in the frontline treatment of patients with metastatic urothelial cancer are

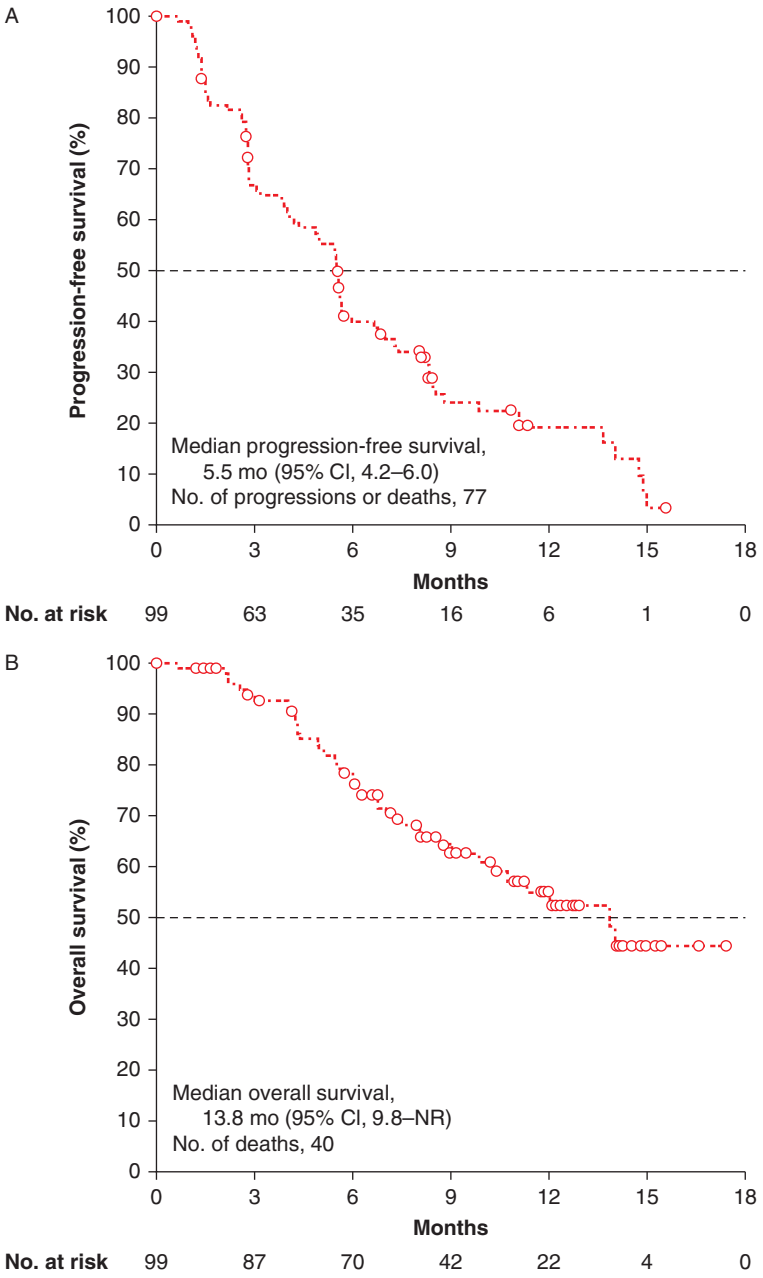


FIGURE 44–4 **Progression-free survival and overall survival of patients after continuous daily treatment with erdafitinib. (Reproduced with permission from Loriot Y, Necchi A, Park SH, et al: Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma, *N Engl J Med* 2019 Jul 25;381(4):338-348.)**

showing impressive early evidence of clinical activity with objective responses greater than 60%, so it seems likely that we will see EV moving to the frontline setting as well.

FUTURE PROSPECTS

The future is looking bright for patients with urothelial cancer. Multiple current clinical trials are investigating the impact of combining immunotherapy with systemic chemotherapy for the treatment of patients with advanced urothelial cancer and in the neoadjuvant setting. Combinations with other checkpoint targets including anti–CTLA-4 (cytotoxic T-cell lymphocyte antigen-4) antibodies appear promising as well, with response rates around 38% with a combination of nivolumab 1 mg/kg with ipilimumab 3 mg/kg.[123] A phase 3 trial is evaluating the benefit of this combination in the frontline setting. However, it appears that many of these IO combinations have greater benefit in the PD-L1–high tumor groups.

Improving antitumor activity of checkpoint inhibitors in the "immunologically cold" PD-L1–low tumors remains an unmet need, with trials currently accruing to overcome this limitation. Bempegaldesleukin is an IL-2 analogue stimulating selective proliferation of lymphocytes associated with the immune response. Early results from an expansion cohort of a phase 1 trial reported response rates of nearly 50%, regardless of PD-L1 expression levels or CD8+ T-cell presence.[124] Another trial, NORSE, builds on the developments in FGFR3 inhibition by combining erdafitinib with the PD-1 inhibitor cetrelimab. Early results from the phase 1 portion suggest object response rates greater than 50% in previously treated urothelial cancer patients.[125] Another tyrosine kinase inhibitor, sitravatinib, targets the TAM family of receptors and when combined with nivolumab had an objective response rate (ORR) of greater than 30% in patients who progressed after treatment with a checkpoint inhibitor.[126]

Additional antibody–drug conjugates are also being developed in urothelial cancer patients. SG targets trop-2 on tumor cells, bringing a payload of a topoisomerase inhibitor to the tumor, is also showing a promising response rate in the third-line setting. Sirtratumab targeting SLTRK and others targeting Her-2 are also being explored for evidence of clinical activity. With the promising activity of EV with pembrolizumab reported earlier, it seems likely that checkpoint inhibitors will be become the backbone of multiple combinations treating patients with urothelial cancer.

Urothelial cancer is no longer just one disease. Novel agents and selection strategies have now come to this disease, with an energy and optimism that we are moving from cytotoxic strategies to immunologic and targeted interventions that will be embraced by physicians and will enhance the lives of our patients. The era of personalized medicine is indeed upon us.

MD ANDERSON PRACTICE TIPS

- It is important for pathologists to recognize the presence of variant histology because it could alter therapy. One example is the strong recommendation for neoadjuvant chemotherapy for small cell urothelial cancer.
- Although neoadjuvant chemotherapy is currently recommended for patients with muscle-invasive urothelial cancer, there is a group of "low-risk" patients who do well with surgery alone. We currently advocate for neoadjuvant cisplatin-based chemotherapy when the following high-risk features are present: cT3b disease (typically by EUA at MDACC), LVI, hydronephrosis, or variant histology, including micropapillary, sarcomatoid, or small cell. When absent, we would offer initial surgery, and adjuvant chemotherapy if upstaging occurs to pT3b or greater or N+ disease.
- Although the "consensus" definition for cisplatin eligibility includes a creatinine clearance of 60 mL/min or greater, several trials suggest one can treat to a lower clearance. At MDACC, we give full-dose cisplatin for a clearance of 50 mL/min or greater and split-dose cisplatin (35 mg/m^2 on days 1 day 2) for a clearance of 40 mL/min or greater. This strategy incorporates aggressive fluid hydration and use of nephrostomy tubes in the setting of obstruction.
- There is currently much debate as to whether maintenance immunotherapy with avelumab is better than immunotherapy at progression. Our current view is that both are good standards and reasonable to consider. This debate may disappear if immunotherapy becomes a frontline standard when considering the early evidence suggesting an excellent response rate with frontline EV with pembrolizumab.
- Erdafitinib dosing with uptitration on day 15 based on target phosphorous levels may induce a better response to erdafitinib. However, most patients cannot continue on a 9-mg/day dose indefinitely and may have their responses maintained at lower doses. We view this treatment as an "induction-maintenance" approach in which the higher dose induces a deeper response that may be maintained at lower doses of erdafitinib.
- It is important to follow fasting glucose levels before each dose of EV and hold therapy for a glucose level greater than 250 mg/dL. Increasing glucose and difficult to control diabetic ketoacidosis despite insulin drip with death occurred in earlier EV trials, which led to this recommendation. Although the mechanism is not definitively known, this author (ASR) hypothesizes it could reflect liver toxicity from auristatin impacting the ability to store glycogen. We advise caution on use of this therapy in patients with cirrhosis.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70:7-30.
2. Wu X, Ros MM, Gu J, et al. Epidemiology and genetic susceptibility to bladder cancer. *BJU Int*. 2008;102:1207-1215.
3. Michaud DS, Spiegelman D, Clinton SK, et al. Fluid intake and the risk of bladder cancer in men [see comment]. *N Engl J Med*. 1999;340:1390-1397.
4. Levine LA, Richie JP. Urological complications of cyclophosphamide. *J Urol*. 1989;141:1063-1069.
5. Ross RK, Paganini-Hill A, Landolph J, et al. Analgesics, cigarette smoking, and other risk factors for cancer of the renal pelvis and ureter. *Cancer Res*. 1989;49:1045-1048.
6. Jelakovic B, Karanovic S, Vukovic-Lela I, et al. Aristolactam-DNA adducts are a biomarker of environmental exposure to aristolochic acid. *Kidney Int*. 2012;81:559-567.
7. Groah SL, Weitzenkamp DA, Lammertse DP, et al. Excess risk of bladder cancer in spinal cord injury: evidence for an association between indwelling catheter use and bladder cancer. *Arch Phys Med Rehabil*. 2002;83:346-351.
8. Moore LE, Baris DR, Figueroa JD, et al. GSTM1 null and NAT2 slow acetylation genotypes, smoking intensity and bladder cancer risk: results from the New England bladder cancer study and NAT2 meta-analysis. *Carcinogenesis*. 2011;32:182-189.
9. Rothman N, Garcia-Closas M, Chatterjee N, et al. A multistage genome-wide association study of bladder cancer identifies multiple susceptibility loci. *Nat Genet*. 2010;42:978-984.
10. Dinney CPN, McConkey DJ, Millikan RE, et al. Focus on bladder cancer. *Cancer Cell*. 2004;6:111-116.
11. Hernandez S, Lopez-Knowles E, Lloreta J, et al. Prospective study of FGFR3 mutations as a prognostic factor in nonmuscle invasive urothelial bladder carcinomas. *J Clin Oncol*. 2006;24:3664-3671.
12. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of urothelial bladder carcinoma. *Nature*. 2014;507:315-322.
13. Hurst CD, Platt FM, Taylor CF, et al. Novel tumor subgroups of urothelial carcinoma of the bladder defined by integrated genomic analysis. *Clin Cancer Res*. 2012;18:5865.
14. Lindgren D, Liedberg F, Andersson A, et al. Molecular characterization of early-stage bladder carcinomas by expression profiles, FGFR3 mutation status, and loss of 9q. *Oncogene*. 2006;25:2685-2696.
15. Gao J, Shi LZ, Zhao H, et al. Loss of IFN-gamma pathway genes in tumor cells as a mechanism of resistance to anti-CTLA-4 therapy. *Cell*. 2016;167:397-404 e9.
16. Billerey C, Chopin D, Aubriot-Lorton MH, et al. Frequent FGFR3 mutations in papillary non-invasive bladder (pTa) tumors. *Am J Pathol*. 2001;158:1955-1959.
17. di Martino E, L'Hôte CG, Kennedy W, et al. Mutant fibroblast growth factor receptor 3 induces intracellular signaling and cellular transformation in a cell type- and mutation-specific manner. *Oncogene*. 2009;28:4306-4316.
18. Platt FM, Hurst CD, Taylor CF, et al. Spectrum of phosphatidylinositol 3-kinase pathway gene alterations in bladder cancer. *Clin Cancer Res*. 2009;15:6008-6017.
19. Jebar AH, Hurst CD, Tomlinson DC, et al. FGFR3 and Ras gene mutations are mutually exclusive genetic events in urothelial cell carcinoma. *Oncogene*. 2005;24:5218-5225.
20. Pietzak EJ, Bagrodia A, Cha EK, et al. Next-generation sequencing of nonmuscle invasive bladder cancer reveals potential biomarkers and rational therapeutic targets. *Eur Urol*. 2017;72:952-959.
21. Solomon DA, Kim J-S, Bondaruk J, et al. Frequent truncating mutations of STAG2 in bladder cancer. *Nat Genet*. 2013;45:1428-1430.
22. Choi W, Porten S, Kim S, et al. Identification of distinct basal and luminal subtypes of muscle-invasive bladder cancer with different sensitivities to frontline chemotherapy. *Cancer Cell*. 2014;25:152-165.
23. McConkey DJ, Choi W, Shen Y, et al. A prognostic gene expression signature in the molecular classification of chemotherapy-naive urothelial cancer is predictive of clinical outcomes from neoadjuvant chemotherapy: a phase 2 trial of dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin with bevacizumab in urothelial cancer. *Eur Urol*. 2016;69:855-862.
24. Robertson AG, Kim J, Al-Ahmadie H, et al. Comprehensive molecular characterization of muscle-invasive bladder cancer. *Cell*. 2017;171:540-556 e25.
25. Sjodahl G, Lauss M, Lovgren K, et al. A molecular taxonomy for urothelial carcinoma. *Clin Cancer Res*. 2012;18:3377-3386.
26. Damrauer JS, Hoadley KA, Chism DD, et al. Intrinsic subtypes of high-grade bladder cancer reflect the hallmarks of breast cancer biology. *Proc Natl Acad Sci U S A*. 2014;111:3110-3115.
27. Seiler R, Ashab HAD, Erho N, et al. Impact of molecular subtypes in muscle-invasive bladder cancer on predicting response and survival after neoadjuvant chemotherapy. *Eur Urol*. 2017;72:544-554.
28. Kamoun A, de Reyniès A, Allory Y, et al. A consensus molecular classification of muscle-invasive bladder cancer. *Eur Urol*. 2020;77:420-433.
29. Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. *Lancet Oncol*.. 2017;18(3):312-322.
30. Bellmunt K, de Wit R, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med*. 2017;376:1015-1026.
31. Galsky MD, Arija JÁA, Bamias A, et al. Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet*. 2020;395:1547-1557.
32. Loriot Y, Necchi A, Park SH, et al. Erdafitinib in locally advanced of metastatic urothelial carcinoma. *N Engl J Med*. 2019;381:338-348.
33. Wang L, Gong Y, Saci A, et al. Fibroblast growth factor receptor 3 alterations and response to pd-1/pd-l1 blockade in patients with metastatic urothelial cancer. *Eur Urol*. 2019;76:599-603.
34. Clinical Trials.Gov, 2020.
35. Rosenberg JE, O'Donnell PH, Balar AV, et al. Pivotal trial of enfortumab vedotin in urothelial carcinoma after platinum and anti-programmed death 1/programmed death ligand 1 therapy. *J Clin Oncol*. 2019;37:2592-2600.
36. Tagawa ST, Faltas BM, Lam ET, et al. Sacituzumab govitecan (IMMU-132) in patients with previously treated metastatic urothelial cancer (mUC): results from a phase I/II study. *J Clin Oncol*. 2019;37:354-354.
37. Msaouel P, Thall PF, Yuan Y, et al. A phase I/II trial of sitravatinib (sitra) combined with nivolumab (nivo) in patients (pts) with advanced clear cell renal cell cancer (aCCRCC) that progressed on prior VEGF-targeted therapy. *J Clin Oncol*. 2020;38:612-612.
38. Huddart RA, Siefker-Radtke AO, Balar AV, et al. PIVOT-10: a phase II study of bempegaldesleukin (NKTR-214) in combination with nivolumab (NIVO) in cisplatin (cis) ineligible patients with previously untreated locally advanced or metastatic urothelial cancer (mUC). *J Clin Oncol*. 2020;38:TPS589-TPS589.
39. Epstein JI, Amin MB, Reuter VR, et al. The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Bladder Consensus Conference Committee. *Am J Surg Pathol*. 1998;22:1435-1448.
40. Humphrey PA, Moch H, Cubilla AL, et al. The 2016 WHO classification of tumours of the urinary system and male

genital organs—part B: prostate and bladder tumours. *Eur Urol*. 2016;70:106-119.
41. Mitra AP, Datar RH, Cote RJ. Molecular pathways in invasive bladder cancer: new insights into mechanisms, progression, and target identification. *J Clin Oncol*. 2006;24:5552-5564.
42. Spiess PE, Czerniak B. Dual-track pathway of bladder carcinogenesis: practical implications. *Arch Pathol Lab Med*. 2006;130:844-852.
43. Amin MB, Ro JY, el-Sharkawy T, et al. Micropapillary variant of transitional cell carcinoma of the urinary bladder. Histologic pattern resembling ovarian papillary serous carcinoma. *Am J Surg Pathol*. 1994;18:1224-1232.
44. Kamat AM, Dinney CPN, Gee JR, et al. Micropapillary bladder cancer: a review of the University of Texas M.D. Anderson Cancer Center experience with 100 consecutive patients. *Cancer*. 2007;110:62-67.
45. Ohtsuki Y, Kuroda N, Umeoka T, et al. KL-6 is another useful marker in assessing a micropapillary pattern in carcinomas of the breast and urinary bladder, but not the colon. *Med Mol Morphol*. 2009;42:123-127.
46. Sangoi AR, Higgins JP, Rouse RV, et al. Immunohistochemical comparison of MUC1, CA125, and Her2Neu in invasive micropapillary carcinoma of the urinary tract and typical invasive urothelial carcinoma with retraction artifact. *Mod Pathol*. 2009;22:660-667.
47. Guo CC, Dadhania V, Zhang L, et al. Gene expression profile of the clinically aggressive micropapillary variant of bladder cancer. *Eur Urol*. 2016;70:611-620.
48. Yang G, Bondaruk J, Cogdell D, et al. Urothelial-to-neural plasticity drives progression to small cell bladder cancer. *iScience*. 2020;23:101201.
49. Siefker-Radtke AO, Dinney C, Abrahams N, et al. Is there a role for pre-operative chemotherapy in small cell carcinoma? The M.D. Anderson experience. *J Urol*. 2003;169:335.
50. Lynch S, Shen Y, Kamat A, et al. Neoadjuvant chemotherapy in small cell urothelial cancer improves pathologic downstaging and long-term outcomes: results from a retrospective study at the M.D. Anderson Cancer Center. *Eur Urol*. 2013;64(2):307-313.
51. Siefker-Radtke AO, Kamat AM, Grossman HB, et al. Phase II clinical trial of neoadjuvant alternating doublet chemotherapy with ifosfamide/doxorubicin and etoposide/cisplatin in small-cell urothelial cancer. *J Clin Oncol*. 2009;27:2592-2597.
52. Dayyani F, Czerniak BA, Sircar K, et al. Plasmacytoid urothelial carcinoma, a chemosensitive cancer with poor prognosis, and peritoneal carcinomatosis. *J Urol*. 2013;189:1656-1661.
53. Keck B, Wach S, Stoehr R, et al. Plasmacytoid variant of bladder cancer defines patients with poor prognosis if treated with cystectomy and adjuvant cisplatin-based chemotherapy. *BMC Cancer*. 2013;13:71.
54. Lopez-Beltran A, Requena MJ, Montironi R, et al. Plasmacytoid urothelial carcinoma of the bladder. *Hum Pathol*. 2009;40:1023-1028.
55. Ro JY, Shen SS, Lee HI, et al. Plasmacytoid transitional cell carcinoma of urinary bladder: a clinicopathologic study of 9 cases. *Am J Surg Pathol*. 2008;32:752-757.
56. Siefker-Radtke A. Urachal adenocarcinoma: a clinician's guide for treatment. *Semin Oncol*. 2012;39:619-624.
57. Siefker-Radtke AO, Gee J, Shen Y, et al. Multimodality management of urachal carcinoma: the M.D. Anderson Cancer Center experience. *J Urol*. 2003;169:1295-1298.
58. Herr HW, Bochner BH, Sharp D, et al. Urachal carcinoma: contemporary surgical outcomes. *J Urol*. 2007;178:74-78; discussion 78.
59. Molina JR, Quevedo JF, Furth AF, et al. Predictors of survival from urachal cancer: a Mayo Clinic study of 49 cases. *Cancer*. 200110:2434-2440.
60. Ashley RA, Inman BA, Sebo TJ, et al. Urachal carcinoma: clinicopathologic features and long-term outcomes of an aggressive malignancy. *Cancer*. 2006;107:712-720.
61. Bochner B, Hansel D, Efstathiou J. et al. Urinary bladder. In: Edge SB, Byrd DR, Compton CC, et al, eds. *AJCC Cancer Staging Manual*. 8th edition. Springer; 2017:765-775.
62. Wijkstrom H, Norming U, Lagerkvist M, et al. Evaluation of clinical staging before cystectomy in transitional cell bladder carcinoma: a long-term follow-up of 276 consecutive patients. *Br J Urol*. 1998;81:686-691.
63. Isbarn H, Karakiewicz PI, Shariat SF, et al. Residual pathological stage at radical cystectomy significantly impacts outcomes for initial T2N0 bladder cancer. *J Urol*. 2009;182:459-465; discussion 465.
64. Resorlu B, Baltaci S, Resorlu M, et al. Prognostic significance of hydronephrosis in bladder cancer treated by radical cystectomy. *Urol Int*. 2009;83:285-288.
65. Bartsch GC, Kuefer R, Gschwend JE, et al. Hydronephrosis as a prognostic marker in bladder cancer in a cystectomy-only series. *Eur Urol*. 2007;51:690-697; discussion 697-698.
66. Quek ML, Stein JP, Nichols PW, et al. Prognostic significance of lymphovascular invasion of bladder cancer treated with radical cystectomy. *J Urol*. 2005;174:103-106.
67. Margel D, Tal R, Baniel J. Serum tumor markers may predict overall and disease specific survival in patients with clinically organ confined invasive bladder cancer. *J Urol*. 2007;178:2297-2300; discussion 2300-2301.
68. Margel D, Tal R, Neuman A, et al. Prediction of extravesical disease by preoperative serum markers in patients with clinically organ confined invasive bladder cancer. *J Urol*. 2006;175:1253-1257; discussion 1257.
69. Pectasides D, Bafaloucos D, Antoniou F, et al. TPA, TATI, CEA, AFP, beta-HCG, PSA, SCC, and CA 19-9 for monitoring transitional cell carcinoma of the bladder. *Am J Clin Oncol*. 1996;19:271-277.
70. Vickers AJ, Cronin AM, Kattan MW, et al. Clinical benefits of a multivariate prediction model for bladder cancer: a decision analytic approach. *Cancer*. 2009;115:5460-5469.
71. Herr HW. Extent of surgery and pathology evaluation has an impact on bladder cancer outcomes after radical cystectomy. *Urology*. 2003;61:105-108.
72. Elting LS, Pettaway C, Bekele BN, et al. Correlation between annual volume of cystectomy, professional staffing, and outcomes: a statewide, population-based study. *Cancer*. 2005;104:975-984.
73. Herr HW, Faulkner JR, Grossman HB, et al. Pathologic evaluation of radical cystectomy specimens: a cooperative group report. *Cancer*. 2004;100:2470-2475.
74. Bosschieter J, Nieuwenhuijzen JA, van Ginkel T, et al. Value of an immediate intravesical instillation of mitomycin c in patients with non-muscle-invasive bladder cancer: a prospective multicentre randomised study in 2243 patients. *Eur Urol*. 2018;73:226-232.
75. Sylvester RJ, van der Meijden AP, Witjes JA, et al. Bacillus Calmette-Guerin versus chemotherapy for the intravesical treatment of patients with carcinoma in situ of the bladder: a meta-analysis of the published results of randomized clinical trials. *J Urol*. 2005;174:86-91; discussion 91-92.
76. Han RF, Pan JG. Can intravesical bacillus Calmette-Guérin reduce recurrence in patients with superficial bladder cancer? A meta-analysis of randomized trials. *Urology*. 2006;67:1216-1223.
77. Lamm DL, Thor DE, Harris SC, et al. Bacillus Calmette-Guerin immunotherapy of superficial bladder cancer. *J Urol*. 1980;124:38-40.
78. Lerner SP, Tangen CM, Sucharew H, et al. Failure to achieve a complete response to induction BCG therapy is associated with increased risk of disease worsening and death in patients

with high risk non-muscle invasive bladder cancer. *Urol Oncol*. 2009;27:155-159.
79. Herr HW, Sogani PC. Does early cystectomy improve the survival of patients with high risk superficial bladder tumors? *J Urol*. 2001;166:1296-1299.
80. Kamat AM, Sylvester RJ, Bohle A, et al. Definitions, end points, and clinical trial designs for non-muscle-invasive bladder cancer: recommendations from the International Bladder Cancer Group. *J Clin Oncol*. 2016;34:1935-1944.
81. Keytruda (pembrolizumab). Package insert, Merck: 2021.
82. Herr HW. The value of a second transurethral resection in evaluating patients with bladder tumors. *J Urol*. 1999;162:74-76.
83. Martínez-Piñeiro JA, Martínez-Piñeiro L, Solsona E, et al. Has a 3-fold decreased dose of bacillus Calmette-Guerin the same efficacy against recurrences and progression of T1G3 and Tis bladder tumors than the standard dose? Results of a prospective randomized trial. *J Urol*. 2005;174:1242-1247.
84. Pfister C, Kerkeni W, Rigaud J, et al. Efficacy and tolerance of one-third full dose bacillus Calmette-Guérin maintenance therapy every 3 months or 6 months: two-year results of URO-BCG-4 multicenter study. *Int J Urol*. 2015;22:53-60.
85. Yokomizo A, Kanimoto Y, Okamura T, et al. Randomized controlled study of the efficacy, safety and quality of life with low dose bacillus Calmette-Guérin instillation therapy for nonmuscle invasive Bladder Cancer. *J Urol*. 2016;195:41-46.
86. Madersbacher S, Hochreiter W, Burkhard F, et al. Radical cystectomy for bladder cancer today—a homogeneous series without neoadjuvant therapy. *J Clin Oncol*. 2003;21:690-696.
87. Kassouf W, Agarwal PK, Herr HW, et al. Lymph node density is superior to TNM nodal status in predicting disease-specific survival after radical cystectomy for bladder cancer: analysis of pooled data from MDACC and MSKCC. *J Clin Oncol*. 2008;26:121-126.
88. Lee CT, Madii R, Daignault S, et al. Cystectomy delay more than 3 months from initial bladder cancer diagnosis results in decreased disease specific and overall survival. *J Urol*. 2006;175:1262-1267; discussion 1267.
89. Herr HW. Extent of pelvic lymph node dissection during radical cystectomy: where and why! *Eur Urol*. 2010;57:212-213.
90. Shipley WU, Zietman AL, Kaufman DS, et al. Selective bladder preservation by trimodality therapy for patients with muscularis propria-invasive bladder cancer and who are cystectomy candidates—the Massachusetts General Hospital and Radiation Therapy Oncology Group experiences. *Semin Radiat Oncol*. 2005;15:36-41.
91. Logothetis CJ. Organ preservation in bladder carcinoma: a matter of selection. *J Clin Oncol*. 1991;9:1525-1526.
92. James ND, Hussain SA, Hall E, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. *N Engl J Med*. 2012;366:1477-1488.
93. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer [see comment][erratum appears in N Engl J Med. 2003 Nov 6;349(19):1880]. *N Engl J Med*. 2003;349:859-866.
94. Tilki D, Svatek RS, Karakiewicz PI, et al. Characteristics and outcomes of patients with pT4 urothelial carcinoma at radical cystectomy: a retrospective international study of 583 patients. *J Urol*. 2010;183:87-93.
95. Millikan R, Dinney C, Swanson D, et al. Integrated therapy for locally advanced bladder cancer: final report of a randomized trial of cystectomy plus adjuvant M-VAC versus cystectomy with both preoperative and postoperative M-VAC. *J Clin Oncol*. 2001;19:4005-4013.
96. Siefker-Radtke AO, Dinney CP, Shen Y, et al. A phase 2 clinical trial of sequential neoadjuvant chemotherapy with ifosfamide, doxorubicin, and gemcitabine followed by cisplatin, gemcitabine, and ifosfamide in locally advanced urothelial cancer: final results. *Cancer*. 2013;119:540-547.
97. Plimack ER, Hoffman-Censits JH, Viterbo R, et al. Accelerated methotrexate, vinblastine, doxorubicin, and cisplatin is safe, effective, and efficient neoadjuvant treatment for muscle-invasive bladder cancer: results of a multicenter phase II study with molecular correlates of response and toxicity. *J Clin Oncol*. 2014;32:1895-1901.
98. Choueiri TK, Jacobus S, Bellmunt J, et al. Neoadjuvant dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin with pegfilgrastim support in muscle-invasive urothelial cancer: pathologic, radiologic, and biomarker correlates. *J Clin Oncol*. 2014;32:1889-1894.
99. Sweeney P, Millikan R, Donat M, et al. Is there a therapeutic role for post-chemotherapy retroperitoneal lymph node dissection in metastatic transitional cell carcinoma of the bladder? *J Urol*. 2003;169:2113-2117.
100. Donat SM HH, Bajorin DF, Fair WR, et al. Methotrexate, vinblastine, doxorubicin and cisplatin chemotherapy and cystectomy for unresectable bladder cancer. *J Urol*. 1996;156:368-371.
101. Siefker-Radtke AO, Millikan RE, Tu SM, et al. Phase III trial of fluorouracil, interferon alpha-2b, and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in metastatic or unresectable urothelial cancer. *J Clin Oncol*. 2002;20:1361-1367.
102. Ho PL, Willis DL, Patil J, et al. Outcome of patients with clinically node-positive bladder cancer undergoing consolidative surgery after preoperative chemotherapy: the M.D. Anderson Cancer Center experience. *Urol Oncol*. 2016;34:59 e1-8.
103. Siefker-Radtke AO, Walsh GL, Pisters LL, et al. Is there a role for surgery in the management of metastatic urothelial cancer? The MD Anderson experience. *J Urol*. 2004;171:145-148.
104. Sternberg CN, Yagoda A, Scher HI, et al. Preliminary results of M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for transitional cell carcinoma of the urothelium. *J Urol*. 1985;133:403-407.
105. Loehrer PJ Sr, Einhorn LH, Elson PJ, et al. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. *J Clin Oncol*. 1992;10:1066-1073.
106. Logothetis CJ, Dexeus FH, Finn L, et al. A prospective randomized trial comparing MVAC and CISCA chemotherapy for patients with metastatic urothelial tumors. *J Clin Oncol*. 1990;8:1050-1055.
107. Bamias A, Aravantinos G, Deliveliotis C, et al. Docetaxel and cisplatin with granulocyte colony-stimulating factor (G-CSF) versus MVAC with G-CSF in advanced urothelial carcinoma: a multicenter, randomized, phase III study from the Hellenic Cooperative Oncology Group. *J Clin Oncol*. 2004;22:220-228.
108. Sternberg CN, de Mulder PH, Schornagel JH, et al. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol no. 30924. *J Clin Oncol*. 2001;19:2638-2646.
109. von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol*. 2000;18:3068-3077.
110. Galsky MD, Hahn NM, Rosenberg J, et al. A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. *Lancet Oncol*. 2011;12:211-214.
111. De Santis M, Bellmunt J, Mead G, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/

carboplatin/vinblastine in patients with advanced urothelial cancer "unfit" for cisplatin-based chemotherapy: phase II—results of EORTC study 30986. *J Clin Oncol*. 2009;27:5634-5639.
112. Tu SM, Hossan E, Amato R, et al. Paclitaxel, cisplatin and methotrexate combination chemotherapy is active in the treatment of refractory urothelial malignancies. *J Urol*. 1995;154:1719-1722.
113. Bellmunt J, Guillem V, Paz-Ares L, et al. Phase I-II study of paclitaxel, cisplatin, and gemcitabine in advanced transitional-cell carcinoma of the urothelium. Spanish Oncology Genitourinary Group. *J Clin Oncol*. 2000;18:3247-3255.
114. Smith DC, Mackler NJ, Dunn RL, et al. Phase II trial of paclitaxel, carboplatin and gemcitabine in patients with locally advanced carcinoma of the bladder. *J Urol*. 2008;180:2384-2388; discussion 2388.
115. Pagliaro L, Munsell M, Harris D, et al. Gemcitabine, paclitaxel, and doxorubicin for patients with urothelial carcinoma and renal insufficiency: preliminary results of a multicenter phase II study. *J Clin Oncol*. 2011;29(7 suppl):246.
116. Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. *N Engl J Med*. 2020;383(13):1218-1230.
117. Galsky MD, Mortazavi A, Milowsky MI, et al. Randomized double-blind phase II study of maintenance pembrolizumab versus placebo after first-line chemotherapy in patients with metastatic urothelial cancer. *J Clin Oncol*. 2020;38:1797-1806.
118. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med*. 2017;376(11):1015-1026.
119. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet*. 2016;387:1909-1920.
120. Massard C, Gordon MS, et al. Safety and efficacy of durvalumab (MEDI4736), an anti–programmed cell death ligand-1 immune checkpoint inhibitor, in patients with advanced urothelial bladder cancer. *J Clin Oncol*. 2016;34:3119-3127.
121. Apolo AB, Infante JR, Balmanoukian A, et al. Avelumab, an anti-programmed death-ligand 1 antibody, in patients with refractory metastatic urothelial carcinoma: results from a multicenter, phase Ib study. *J Clin Oncol*. 2017;35:2117-2124.
122. Weinstein JN, Akbani R, Broom BM, et al. Comprehensive molecular characterization of urothelial bladder carcinoma. *Nature*. 2014;507:315-322.
123. Sharma P, Siefker-Radtke A, de Braud F, et al. Nivolumab alone and with ipilimumab in previously treated metastatic urothelial carcinoma: CheckMate 032 nivolumab 1 mg/kg plus ipilimumab 3 mg/kg expansion cohort results. *J Clin Oncol*. 2019;37:1608-1616.
124. Siefker-Radtke AO, Fishman MN, Balar AK, Bilen MA. NKTR-214 + nivolumab in first-line advanced/metastatic urothelial carcinoma (mUC): updated results from PIBOT-02. *J Clin Oncol*. 2019;37(suppl 7S):388.
125. Siefker-Radtke A, Loriot Y, Siena S, et al. 752P Updated data from the NORSE trial of erdafitinib (ERDA) plus cetrelimab (CET) in patients (pts) with metastatic or locally advanced urothelial carcinoma (mUC) and specific fibroblast growth factor receptor (FGFR) alterations. *Ann Oncol*. 2020;31(4 suppl):S584-S585.
126. Msaouel P, Siefker-Radtke R, Sweis R, et al. Sitravatinib in combination with nivolumab demonstrates clinical activity in platinum-experienced patients with urothelial carcinoma (UC) who progressed on prior immune checkpoint inhibitor (CPI). *J Immunother Cancer*. 2019;7(1):283.

This page intentionally left blank

45 Prostate Cancer

Patrick Pilié
Paul Viscuse
Christopher J. Logothetis
Paul G. Corn

KEY CONCEPTS

- Risk categories (low, intermediate, and high) for localized prostate cancer based on T-stage, grade grouping, and prostate-specific antigen at diagnosis help guide treatment approaches. Whereas men with low-risk prostate cancer should be considered for active surveillance, men with high-risk disease should be considered for definitive therapy after confirming no evidence of distant metastatic disease. Although favorable intermediate-risk disease can also be considered for active surveillance, definitive treatment of patients with unfavorable intermediate-risk disease is recommended if life expectancy is 10 years or longer and can be considered on a patient-by-patient basis depending on comorbid conditions.
- For men with high-risk localized prostate cancer, multiple studies have confirmed the additive benefit of androgen-deprivation therapy (ADT) plus radiation over either modality alone. Furthermore, the addition of second-generation antiandrogens (eg, abiraterone acetate and prednisone) has been shown to improve disease-free survival over ADT alone when given with radiation therapy. The optimal duration of androgen ablative therapy in this setting is still under investigation.
- ADT remains the backbone of treatment for men with recurrent prostate cancer. However, prolonged ADT has high potential morbidity, and recurrent prostate cancer is a heterogeneous disease. For nonmetastatic castrate-sensitive recurrence after definitive local therapy, intermittent ADT can be considered. For metastatic castrate-sensitive disease, intermittent ADT failed to show noninferiority to continuous ADT; however, with second-generation antiandrogens being moved into the metastatic castrate-sensitive space, the treatment decision should be made on a patient-by-patient basis.
- Androgen biosynthesis inhibition as well as androgen receptor inhibitors have been moved earlier in the treatment of patients with prostate cancer with multiple approvals in the nonmetastatic castrate-resistant setting (darolutamide, apalutamide, enzalutamide) and the M1 castrate-sensitive setting (abiraterone acetate with prednisone, enzalutamide, and apalutamide). Choice of inhibitor should be based on side effect profile and the patient's comorbid conditions.
- All men with metastatic prostate cancer, as well as those with high-risk localized prostate cancer, should be considered for germline genetic testing regardless of family history. This test should include analysis for variants in *BRCA1/2*, and other DNA damage response (DDR) genes should be considered for testing. Men with localized disease that is not high risk should be considered for genetic testing if there is a strong family history of hereditary prostate cancer or concern for hereditary breast and ovarian cancer syndrome. Men with deleterious variants in *BRCA1/2* (somatic or germline) with prostate cancer who have progressed on standard-of-care second-generation antiandrogen(s) should be considered for treatment with poly (ADP-ribose) polymerase (PARP) inhibition (eg, olaparib [PROfound] or rucaparib [TRITON]). In addition, men with DDR gene alterations or hypermutated cancers (eg, high microsatellite instability or loss of mismatch repair protein expression) should be considered for immune checkpoint blockade because trials have shown these alterations can predict for response to immune checkpoint blockade (CheckMate 650).
- AVPC (androgen-indifferent) and neuroendocrine prostate cancer are molecularly characterized by aberrations in *TP53, RB1*, and/or *PTEN*. These cancers have been shown to benefit from carboplatin-based chemotherapy (eg, carboplatin with cabazitaxel). Active research is ongoing to better define and treat these aggressive prostate cancer subtypes.

Over the past decade, insight into the biological basis of prostate cancer development and progression has influenced our approach to treating patients with the disease. Although research efforts have historically focused on the prostate cancer epithelial cell, there is growing evidence that interactions between the host tissue microenvironment and the cancer epithelial cell are critical for tumorigenesis. Understanding the bidirectional cancer cell–host interaction now dominates prostate cancer research.

Prostate cancers have recognizable clinical features that allow anticipation of their clinical behavior. Fortunately, the progression from localized, androgen-dependent disease to castration-resistant disease with bone-forming metastases occurs in only a minority of patients. To conceptualize the clinical heterogeneity displayed along this continuum, patients have historically been assigned to different "clinical states" (eg, metastatic castrate vs noncastrate) to help structure treatment recommendations and therapy development.[1,2] However, this approach has been limited by the fact that patients within each state display wide biological heterogeneity and response to therapy. To address this, improved classification of the disease based on the underlying molecular mechanisms of progression is necessary. This effort will create a "marker-driven" strategy to more reliably predict prostate cancer progression, permit optimal selection of specific therapies for individual patients, and apply therapy to only those patients who need it. This tailored approach can favorably improve the outcome of selected patients threatened by their disease while avoiding unnecessary morbidity associated with treatment to the majority who are not.

EPIDEMIOLOGY AND CLINICAL FEATURES

Prostate cancer is a major health care challenge in the United States.[3] It is the second most common cancer in men (behind skin cancer) and the second leading cause of cancer-related death after lung cancer. There are several unique clinical features of prostate cancer that distinguish it from other solid tumor types:

1. Despite the high prevalence of prostate cancer, the majority of men diagnosed with the disease ultimately die from other causes.
2. Cancer of the prostate often has a prolonged natural history. This is evidenced by a high incidence of occult malignancy in autopsy series of men who die from nonprostate cancer causes and in clinically normal prostates of men undergoing cystoprostatectomy for bladder cancer. Therefore, over the course of a normal lifetime, most men will develop "clinically occult" prostate cancer that will never produce symptoms, require treatment, or cause death.
3. The incidence of detected carcinoma increases with age.
4. Androgens are a major driving force in normal prostate development and are implicated in tumorigenesis.
5. Prostate cancer is typically multifocal, commonly presenting as synchronous carcinomas arising in multiple locations, and the malignant potential is determined by the sum of the primary and secondary grades (Gleason score). Thus, biologic heterogeneity is an inherent property of each tumor.
6. Clinical prostate cancer is more prevalent in men from Western compared with Eastern societies, although incidence rates increase for men from China and Japan who immigrate to the United States. This observation implicates environmental factors (eg, diet, lifestyle, etc) in prostate cancer development.
7. Prostate cancers have a predictable rate and pattern of progression, with bone-forming metastases dominating the clinical progression in the majority of patients with advanced disease. This observation supports the hypothesis that the bone-epithelial interaction is central to the progression of prostate cancer.

Aging

It has long been recognized that prostate cancer is a disease of older adults. Epidemiologic data demonstrate that rates of prostate cancer incidence and mortality increase with age.[4] Although prostate-specific antigen (PSA) screening has led to an earlier average age at diagnosis, deaths are still largely seen in patients 70 years of age or older. As the longevity of populations increases worldwide, the burden of prostate cancer creates a significant health care challenge. This has generated a sense of urgency among physicians to refine our ability to predict cancer virulence and escalate therapy for patients who truly need it.

Endocrine

Androgens are central to the normal growth, differentiation, and function of the prostate gland, although the role of androgen-receptor (AR) signaling in prostate carcinogenesis and progression has not been fully elucidated. Even in the clinically castrate state (serum testosterone <50 ng/mL), there is growing evidence that prostate cancer cells continue to rely on AR signaling for proliferation.[5] One of the principal mechanisms

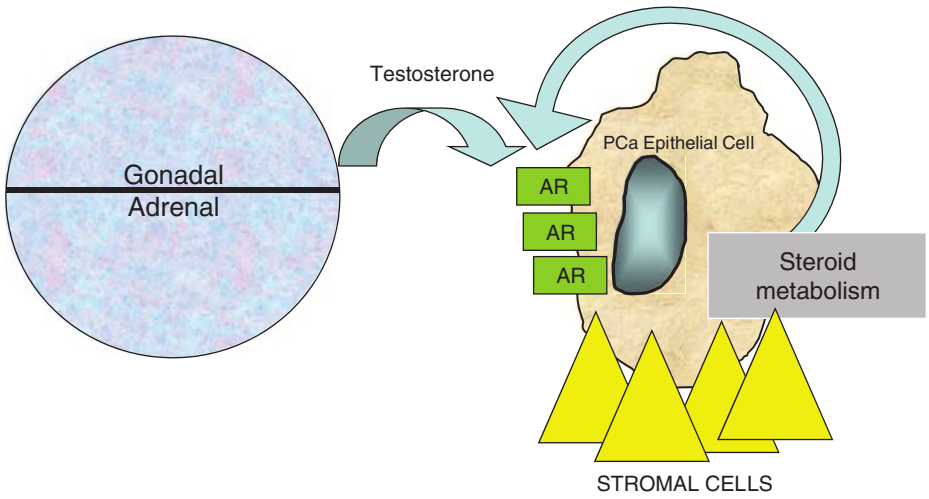


FIGURE 45–1 **Androgen sources switch from endocrine to paracrine and autocrine during disease progression. PCa, prostate cancer.**

for this involves a gradual shift from endocrine sources of androgens (ie, from the testes and adrenal glands) to paracrine, autocrine, and intracrine (ie, intratumoral) sources during prostate cancer progression (Fig. 45–1). This occurs through the peripheral conversion of adrenal steroid precursors (eg, dehydroepiandrosterone and androstenedione) in prostate and bone tissues expressing CYP17 enzymes.[6] Other mechanisms accounting for castrate resistance include intratumoral amplification of AR, mutations of AR, changes in levels of AR cofactors, and ligand-independent activation of AR (see Fig. 45–1).

Diet and Obesity

Several lines of clinical and experimental evidence support a central role of a high-fat diet, caloric intake, and obesity in the development of prostate cancer with lethal potential. Obesity, defined as body mass index (BMI) above 30, is manifested by overgrowth of white adipose tissue (WAT). Obesity has been associated with incidence, progression, and mortality of prostate cancer.[7,8] The mechanism for the association between obesity and prostate cancer progression is poorly understood. Further complicating the understanding of how obesity influences prostate cancer outcomes is studies showing that obesity and increasing adiposity in men with metastatic castration-resistant prostate cancer (mCRPC) may actually have improved clinical outcomes, a potential "obesity paradox."

A large genetic epidemiologic study of predetermined genetic variants associated with increased height, BMI, or both did not predict for prostate cancer risk; lifestyle factors such as diet and physical activity may contribute to prostate cancer development and progression. For example, a preclinical model of prostate cancer revealed that high-fat diet led to activation of MYC transcriptional program with subsequent cancer cell growth and increased tumor burden. In addition, studies have shown that WAT itself may have direct effects on cancer cell growth across a variety of cancer cell histologies.

Mechanisms linking obesity and aggressive prostate cancer include signaling through insulinlike growth factor 1 (IGF-1) and adipokines.[9] The insulin–IGF-1 axis has been widely implicated in obesity-induced tumorigenesis, including prostate cancer.[10] Primary human prostate cancer commonly expresses the insulin receptor, suggesting insulin may stimulate tumor growth.[11] Both excess body weight and a high plasma concentration of C-peptide are associated with increased prostate cancer–specific mortality.[12] In addition, the antidiabetic agent metformin has been shown to reduce all-cause and prostate cancer–specific mortality rates among men with diabetes.[13]

Beyond changes in insulin, obesity alters levels of adipokines (eg, leptin, adiponectin) because of chronic subclinical inflammation. Leptin is associated with in vitro protumor effect in human prostate cancer cell lines,[14] but epidemiologic studies have failed to consistently establish an association with prostate cancer risk and mortality.[15] In contrast to leptin, adiponectin serum levels are reduced in obesity and have largely antitumor effects.[16]

Race and Ethnicity

African American men are at higher risk of developing and dying from prostate cancer. The reasons behind why prostate cancer tends to display a more aggressive phenotype in African American men are thought to be multifactorial. A recent study of more

than 300,000 men with prostate cancer showed that Black men who were followed and treated in Veterans Affairs health system and National Cancer Institute–sponsored randomized clinical trials did not display inferior prostate-cancer–specific mortality, thus suggesting that equitable access to care and standardized treatment plays a significant role in increased mortality from prostate cancer in Black men. Genomic studies of prostate cancer tumors from Black men have revealed *ERF* deletions in 3% of primary prostate cancers and mutations or deletions in *ERF* in 3% to 5% of lethal castration-resistant prostate cancers (CRPCs), as well as frequent mutations in DNA damage response (DDR) gene pathways, including nucleotide excision repair. As discussed further later, now that clinical genetic testing includes sequencing of the entire exome of certain cancer-related genes (instead of just hot spot mutation testing), it has been shown that African American men are also equally likely to carry deleterious hereditary variants in DDR genes, such as *BRCA2*, which significantly increase the risk of developing aggressive prostate cancer.

It is imperative that clinical trials be more inclusive and representative of our diverse population, and it is also exceedingly important for further research to be done on disparities and health care access issues for minority men in terms of prostate cancer screening and treatment and to enact policy changes to resolve these systemic barriers to quality care for all.

Genetic Predisposition

Prostate cancer has been shown to cluster within families and exhibit Mendelian inheritance patterns. Family history of prostate cancer has been shown to increase prostate cancer risk whereby the risk is influenced by (1) the number of affected family members, (2) first-degree affected relatives compared with those who are more distantly related, and (3) the presence of early-onset cancers in a pedigree (typically men diagnosed at or before age 55 years). Early genome-wide linkage studies focusing on families with a history of hereditary prostate cancer resulted in the identification of a number of potential candidate loci. A recurrent mutation was identified in the *HOXB13* gene, a member of the homeobox gene family, which resulted in a nonconservative substitution of glutamic acid for glycine (G84E). Multiple studies of men with prostate cancer of European ancestry have shown that *HOXB13* G84E increases the risk of prostate cancer, with cancer onset at earlier age and more likely to be found in men with a family history of prostate cancer. However, the molecular mechanism by which *HOXB13* G84E promotes prostate cancer development remains unknown.

Deleterious variants in DDR genes, most notably in *BRCA2*, have been shown across multiple studies to significantly increase the risk of prostate cancer. Men with metastatic and high-risk localized prostate cancer are enriched (≥15%) for deleterious germline variants in cancer-related genes, particularly DDR genes, regardless of family history. Men with prostate cancer with distinct phenotypes, such as early-age onset of prostate cancer (younger than 55 years old) or multiple primary malignancy phenotype, have also been shown to be enriched for hereditary variants in cancer-related genes. These findings have led to the recommendation for universal germline genetic testing in men with metastatic or localized high-risk prostate cancer, regardless of family cancer history. In terms of which genes to test, there is consensus for *BRCA1* and *BRCA2*, with recommended testing of other DDR genes as well, with most patients receiving a panel-based test. Variants in other DDR genes including but not limited to *ATM*, *CHEK2*, and mismatch repair (MMR) genes have low to moderate penetrance in prostate cancer, with testing results often yielding variants of unknown significance; however, they should be considered in panel germline testing for patients with prostate cancer. It is imperative to perform germline testing because positive results can inform the patient's risk for other cancer types and risk of cancer for family members and can also now guide targeted treatment as discussed later in this chapter.

Cohort studies of men with hereditary *BRCA2* mutations show an increased risk for prostate cancer and for higher grade disease and shorter time to cancer progression, with these men showing a significantly reduced cause-specific survival from time of diagnosis of mCRPC. Furthermore, men with deleterious germline variants in DDR genes, including *BRCA2*, display similar outcomes to frontline chemotherapy or androgen-signaling inhibition as do their DDR-germline wildtype matched counterparts, but preliminary data suggest that mutation carriers may do better with frontline AR-signaling inhibition than with docetaxel chemotherapy. As discussed further in this chapter, men with deleterious *BRCA2* variants are most likely to derive benefit from poly (ADP-ribose) polymerase (PARP) inhibitors and possibly platinum chemotherapy.

RELEVANT HISTOMORPHOLOGY OF PROSTATE CANCER

Most epithelial cancers arise from the prostatic acinus, with fewer than 10% having a pure ductal origin. (This is the opposite of the pattern seen in cancers of the pancreas and breast, in which ductal cancers are far more common than those arising in the acinar portion of the secretory unit.) The majority show glandular differentiation (ie, adenocarcinoma) (Fig. 45–2A).

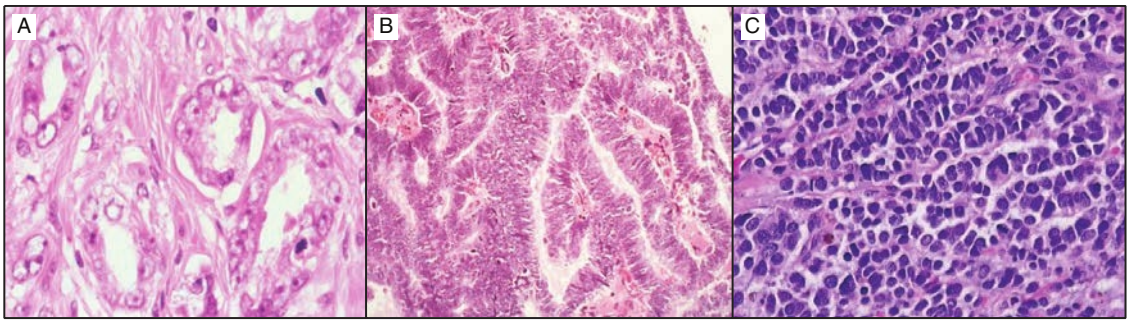


FIGURE 45–2 **A. Architecture of prostate adenocarcinoma. B. Architecture of prostate ductal carcinoma. C. Architecture of prostate small cell carcinoma.**

Importantly, mucin is essentially never seen in prostate cancer. Historically, numerous grading systems have been devised using all of the typical morphologic criteria by which pathologists can sometimes infer biologic potential. Although more than 20 systems have been put forward, prostate cancers are now almost universally graded according to the Gleason system.

Gleason Grading System

The Gleason system is unique among pathologic grading systems because it is a composite classification based on a combination of architectural and cellular features often considered in the grading of other epithelial cancers. As originally described, the Gleason system includes two components:

1. There are five patterns, or grades, ranging from normal architecture to arrays of cells without any glandular organization at all. At our institution, because unequivocal criteria for malignancy already correspond to Gleason grade 2 and the Gleason grade 1 category is rarely reported, prostate cancers are assigned Gleason grades ranging from 3 through 5.
2. Gleason score is obtained by assigning one Gleason grade to the most dominant (ie, "primary") pattern and another to the next most common (ie, "secondary") pattern. By convention, such data are expressed as a sum, with the primary pattern listed first. Thus, the Gleason score can range from 2 (ie, 1 + 1) to 10 (5 + 5). At MD Anderson Cancer Center (MDACC), these scores range from 6 to 10, reflecting our decision not to assign a Gleason grade of 1.

A major advantage of the Gleason grading system is its reproducibility and ability to distinguish different cancer phenotypes that influence clinical management. The system is most useful for tumors falling at one the extremes (eg, Gleason score ≤6 vs Gleason score 8–10). However, a major disadvantage of the system is that it does not provide a refined view of Gleason 7 tumors, the most commonly reported type. Gleason 7 cancers (ie, 3 + 4 or 4 + 3) represent a clinically heterogeneous group with variable biologic potential and clinical outcome.[17] Despite efforts to improve stratification of Gleason 7 tumors, it is clear the Gleason system is inherently limited by light microscopic methodology to evaluate morphology. Thus, most investigators are now looking to incorporate molecular characterization of tumors into the current grading system.

Assessment of Prostate Biopsies and Prostatectomy Specimens

Gleason grading is a validated system to prognosticate untreated prostate cancers sampled at initial diagnosis. However, the common practice of applying Gleason grading to treated cancers may be misleading. At MDACC, for example, pathology reports of specimens obtained after hormone ablation typically indicate "hormonal treatment effect" rather than a Gleason grade per se. Thus, Gleason scores from serial biopsies obtained pre- and posttherapy from the same patient should be interpreted with careful regard to treatment effects. To address this problem, our group has proposed a novel "posttherapy" histologic classification to introduce uniformity in analysis of treated tissue specimens.[18] If prospectively validated, this system should prove useful in prognosticating preoperatively treated prostate cancers.

An additional confounding variable is tissue sampling. We recognize that there is intratumoral heterogeneity of grade within individual prostate cancers. Thus, it logically follows that the extent and areas of sampling affect the accuracy of grading and staging. The development of techniques to obtain prostate tissue samples with ultrasound guidance and limited patient morbidity has had a major effect on stage and grade assignment. We increasingly find that the completeness of tissue sampling as measured by the number and distribution of transrectal biopsies greatly influences the adequacy of tumor staging and grading. Biopsy algorithms have been developed

to ensure adequate number and distribution of the biopsies.[19]

Many of the challenges attributed to the sampling errors that occur with needle biopsies can be overcome with proper handling of the prostate after surgery. Assigning a primary and secondary Gleason score is straightforward in a properly processed specimen. This requires great attention to detail in assessing whether the cancer has invaded beyond the prostate capsule (extracapsular) or beyond the margin of resection (margin positive). Effective communication between the surgeon and pathologist is essential to properly identify the extent and site of surgical margin involvement. As the therapeutic benefit of postoperative radiation therapy is better appreciated, the importance of these aspects has proportionally increased.

Molecular Genetics of Prostate Cancer

In prostate cancer, gene fusions between *TMPRSS2* (21q22.3), an androgen-regulated gene, and *ERG*, from the ETS family of transcription factors (21q22.2), are common.[20] However, the functional and prognostic significance of *TMRPSS2-ERG* remain poorly understood. Currently, detection and measurement of *TMPRSS2-ERG* are not performed in standard clinical practice.

Additional studies have sought to refine the diagnostic classification of prostate cancer through molecular methods. Unfortunately, no consensus yet exists about the usefulness of molecular phenotypic (or genotypic) characterization in prostate cancer. Using immunohistochemistry, we do know that expression of specific proteins in human specimens has been linked to the clinical course of the disease. For example, loss of functional PTEN (phosphatase and tensin homolog), mutations in p53, and increased expression of Bcl-2 are some of the widely reported gain- and loss-of-function changes that have been correlated with prostate cancer progression and mechanistically linked to castration-resistant growth.[21,22] Despite this link to biology and correlation with clinical outcome, the methods provide insufficient additional clinical information to justify their routine use.

Prostate Cancer Variants

Ductal Cancers

The ductal variant of prostate cancer in its pure form is unusual. More often, ductal and acinar components are mixed, and the relative contribution of the ductal variant to the clinical phenotype of the cancer is unclear. Our impression of the behavior of ductal cancers of the prostate is based on tumors that are either dominant or pure ductal in origin (Fig. 45–2B). The clinical features that lead us to suspect its presence include the lack of proportional rises in serum PSA concentrations with invasion of the base of the bladder (occasionally mistaken for urothelial cancer), soft tissue distribution of metastases, or lytic bone metastases. For localized disease, patients with pure ductal adenocarcinoma have a better clinical outcome after radical prostatectomy than patients with mixed ductal adenocarcinoma.[23] Men with de novo metastatic ductal cancers display poor outcomes with prostate cancer that is typically resistant to multiple therapies, and men with ductal features display more aggressive disease and a higher probability of developing visceral metastases than pure acinar adenocarcinomas.

Small Cell and Aggressive Variant Prostate Cancers

Small cell prostate cancer (SCPC) is a histologically defined variant demonstrating "salt-and-pepper" chromatin, neuroendocrine marker expression (ie, chromogranin, synaptophysin), and a high nuclear-to-cytoplasm ratio (Fig. 45–2C). It is androgen-indifferent and clinically virulent with higher frequency of visceral metastases (eg, liver or lung), bulky lymph node involvement, lytic rather than blastic bone metastases, and little to no PSA production. The classic clinical presentation is a patient with a precipitously enlarging prostate associated with obstructive symptoms and very little (to no) PSA production. It can arise de novo or, more commonly, as a delayed manifestation of progression in patients with a history of high-grade adenocarcinomas after therapy (hormone ablation, radiation therapy, or chemotherapy). As a result, a biopsy should be obtained from a metastatic site if atypical clinical features develop after treatment for conventional adenocarcinoma, particularly if the PSA is lower than would be expected for the volume of disease. Interestingly, the evolution to a neuroendocrine phenotype is often associated with expression of carcinoembryonic antigen, which may be a more useful monitoring tool than PSA. Tumor testing for neuroendocrine markers (chromogranin, synaptophysin, CD56, neuron-specific enolase, or bombesin) may be performed though expression is not particularly sensitive or specific for a virulent clinical course in our experience.

Increasingly, biopsies of metastatic lesions demonstrating characteristic atypical features of SCPC are found to be adenocarcinomas with variable neuroendocrine marker expression. We have termed these tumors *aggressive variant prostate cancer* (AVPC), replacing the previous term "anaplastic," which is reserved as a histologic description. AVPC clinical criteria include exclusive visceral metastases, radiographically evident

lytic bone metastases, bulky lymphadenopathy (≥5 cm) or a bulky high-grade mass (≥5 cm, Gleason ≤8) in the prostate or pelvis, low PSA (≤10 ng/mL) at initial presentation (before androgen-deprivation therapy [ADT] or symptomatic progression of castrate-resistant disease) plus high-volume (≤20) bone metastases, or short interval (≤6 months) to androgen-independent progression after initiation of hormonal therapy. Preclinical studies have found that AVPC are characterized by a molecular signature containing one or more deleterious alterations in the tumor suppressor genes *TP53, RB1,* and *PTEN.*

Candidate Premalignant Lesions

Prostatic Intraepithelial Neoplasia

The search for premalignant lesions of the prostate has resulted in the identification of two candidate morphologic lesions.[24] The first and most promising premalignant lesion is prostatic intraepithelial neoplasia (PIN). Grades I and II PIN are observed but have not been reliably associated with cancer or linked with confidence to prostate cancer development or progression. Thus, the reporting of grades I and II PIN has fallen into disfavor at MDACC and at most other leading institutions. Grade III PIN has been linked to the presence of cancer in many studies, but it does not justify a therapeutic intervention (eg, prostatectomy). Rather, its presence leads to the recommendation of a more thorough biopsy to search for coexistent cancer or a repeat biopsy within 6 to 12 months. Grade III PIN is frequently linked to the presence of established cancer in other regions of the prostate, and as a consequence, it rarely serves as a useful early predictive marker. Therein lies the difficulty of performing prevention studies targeting PIN. Most MDACC clinicians share the view that a report of multifocal PIN III is nearly identical to a report of low-grade prostate cancer but with the important caveat that there is insufficient evidence to justify routine intervention (surgery or radiation).

The second potential premalignant lesion is proliferative inflammatory atrophy (PIA).[25] Histologically, these lesions are characterized by inflammatory infiltrates associated with atrophic epithelium. Compared with normal epithelium, there is an increased fraction of proliferating epithelial cells within PIAs. These lesions are thought to provide a mechanistic link between chronic infection or inflammation and the predisposition to develop prostate cancer. However, in contrast to PINs, adenocarcinomas rarely arise from PIAs, and PIAs are often observed in prostate biopsies that have no evidence of cancer. Thus, it remains unclear if PIAs are truly precursor lesions for prostate cancer. Ongoing studies seek to address this.

Staging

It is difficult to precisely assess the extent of prostate cancer on clinical criteria alone. The major benchmark of local extent that influences treatment—organ confined versus non–organ confined—is essentially impossible to distinguish by rectal examination and is not easily appreciated by any imaging modality. Furthermore, PSA levels do not accurately inform about extraprostatic extension of disease. Thus, it is common to use an array of modalities, including transrectal ultrasonography, computed tomography, conventional magnetic resonance imaging (MRI), MRI with an endorectal receiver coil, complex biopsy strategies designed to sample the seminal vesicles and extraprostatic space, and even pelvic lymph node sampling, to determine disease extent. Clearly, each of these modalities offers a different level of sensitivity for detecting lesions and can vary markedly in efficacy. In the final analysis, the concept of clinical stage is meaningless without proper context. One must ask, What is the clinical stage by a particular set of diagnostic tests?

The Case for Prostate Cancer Screening

With the advent of PSA screening, there has been a dramatic increase in the number of younger men detected with localized disease. Along with improved outcomes for local therapy (surgery or radiation), it logically follows that PSA screening has contributed to the improved survival rates for men diagnosed with localized prostate cancer. However, the benefits of PSA screening remain controversial for clinicians and a source of confusion for patients. For clinicians, there has been a lack of level 1 evidence supporting the use of PSA screening. The two large, randomized screening trials (with >250,000 patients) has not helped clarify the issue because one trial did not show a survival benefit (the prostate, lung, colorectal, and ovarian cancer screening trial (PLCO) Cancer Screening Trial in the United States), but the other one did (the European Randomized study of Screening for Prostate Cancer (ERSPC) trial in Europe).[26,27] Although confounding factors to each study limit a definitive conclusion about PSA screening, the enormous expense and time required may discourage future PSA screening trials. Available evidence favors clinician discussion of the pros and cons of PSA screening with average-risk men aged 55 to 69 years. Other strategies to mitigate the potential harms of screening include considering biennial screening, a higher PSA threshold for biopsy, and conservative therapy for men receiving a new diagnosis of prostate cancer.

Although the US Preventive Services Task Force no longer recommends routine screening,[28] in our practice, we recommend annual PSA and digital rectal examination (DRE) for all healthy men starting at

TABLE 45–1 Rationale for Prostate Cancer Screening

• Reduction in prostate cancer mortality rates coincide with the introduction of routine PSA screening.
• Patients whose cancers are detected with PSA screening have early-stage disease.
• Long-term disease-free survival is linked to treatment of early-stage disease.
• Randomized trials demonstrate a survival advantage for early surgical intervention for early-stage disease.

PSA, prostate-specific antigen.

age 50 years or age 40 years for those at high risk (eg, men with a family history or African Americans). Early inclusion of the patient in the decision-making process is essential to optimize patient care given the ambiguities regarding the cost effectiveness and clinical value of widespread screening for prostate cancer. The rationale for routine screening that justifies routine application is outlined in Table 45–1.

PATIENT MANAGEMENT BY DISEASE STATE

Clinically Localized Disease at Presentation

As a result of widespread screening of men by PSA and DRE, the majority of patients are seen with clinically localized disease at diagnosis. Unfortunately, it is not always obvious how to match the individual patient with the most appropriate management. In an abstract sense, patients with clinically localized prostate cancer fall into one of four theoretical categories:

1. Those not destined to have any clinical manifestations of their disease. These patients are actually harmed by any intervention, including further surveillance.
2. Those destined to have a clinical manifestation of cancer but will not die of it. These patients might benefit from definitive therapy (eg, prostatectomy or radiation) but would likely benefit equally from less-morbid intervention (eg, minimally invasive surgery).
3. Those destined to have life-threatening disease for whom definitive therapy will be curative. Patients who can be cured, or for whom there will be a substantial alteration of the natural history of their disease, constitute the group that will unequivocally benefit from definitive local therapy.
4. Those destined to have life-threatening disease for whom the opportunity to cure by means of local therapy either never existed or passed. For these patients, however, control of the primary tumor could still be an important component of an overall treatment strategy that considers the probability of local versus distant progression, comorbidity, and other factors.

The common practice of urologists and radiation therapists is to assume that nearly every patient falls into the third category, and thus they recommend definitive therapy for the vast majority of newly diagnosed cases of localized prostate cancer. Unfortunately, available evidence suggests that fewer than half of patients are in category 3, so it is not surprising that understanding the role of definitive therapy in eliminating prostate cancer morbidity and mortality has been both difficult and controversial. In fact, these issues underscore the fact that overtreatment of patients with "clinically insignificant" prostate cancers certainly occurs. The significant cost and morbidity associated with local treatment also adds to the difficulty of managing these patients (whether the patient ultimately benefits from the therapy or not).

In patients with newly diagnosed localized disease, current prognostic and predictive models rely on data derived from large prostatectomy series conducted at major academic centers. For example, investigators at Johns Hopkins initially published a predictive model relating the rate of finding disease that is not confined to the prostate (by assessing the surgical specimen) as a function of three readily available preoperative clinical parameters: PSA, Gleason score from the core biopsy, and the clinical stage based on DRE.[29,30] The correlation of these features with pathologically organ-confined disease, summarized in the famous "Partin tables," provided sobering evidence that commonly encountered subsets of patients had a surprisingly high risk of disease that was not confined to the prostate. Of course, not all patients with pathologically organ-confined disease relapse, and not all patients with pathologically organ-confined cancers are cured. Thus, the importance of this particular surrogate outcome was and remains uncertain. Nevertheless, the effect of the Partin tables on clinical practice has been profound. They have driven the application of prostatectomy to patients with smaller and smaller volumes of cancer. It is clear that although more patients are remaining free of disease after prostatectomy, this comes paradoxically at the cost of operating on many patients who may not have needed surgery or not operating on many patients who would have benefited from good local control even if the surgery were not curative.

Additional models have been developed to predict outcomes after radical prostatectomy or radiation therapy. Based on the work of D'Amico et al,[31] a combination of pretherapy PSA, Gleason score, and clinical stage can be used to stratify patients into low (T1–T2a

TABLE 45–2 Rationale for Use of Predictive Nomograms

- Gleason grade, clinical stage, and initial PSA are predictive of surgical stage, risk of subsequent relapse, and risk of cancer-specific mortality.
- Improving the ability to predict outcome will inform both physicians and patients about the risks and benefits of local therapy.
- Fewer patients will undergo unnecessary or futile surgery.

PSA, prostate-specific antigen.

and Gleason score 2–6 and PSA <10 ng/mL), intermediate (T2b-T2c or Gleason score 7 or PSA 10–20 ng/mL), high (T3a or Gleason score 8-10 or PSA >20 ng/mL), and locally advanced (T3b–T4) groups that predict risk for both biochemical recurrence and survival following definitive local therapy (radical prostatectomy or radiation). Similarly, Kattan et al[32] developed postoperative nomograms for predicting prostate cancer recurrence after radical prostatectomy. These tools not only help guide recommendations for individual patients but also help stratify patients for clinical trials. For example, low-risk patients can be directed toward "active surveillance" trials, and high-risk patients can be direct toward adjuvant or neoadjuvant trials. The rationale for the use of predictive nomograms is outlined in Table 45–2.

Despite the efforts detailed previously, tumors with identical morphology and clinicopathologic characteristics often display biologic heterogeneity (ie, some "low-risk" tumors rapidly progress, but some "high-risk" tumors are relatively indolent). Thus, more refined models are needed. Recent efforts have sought to incorporate genetic tests to enhance current clinicopathologic risk stratification for patients newly diagnosed with localized prostate cancer. For example, PROLARIS (Myriad Genetics, Inc.) directly measures expression of 46 different genes in formalin-fixed paraffin-embedded tissue obtained by biopsy or prostatectomy,[33–35] including 31 cell cycle progression genes and 15 housekeeper genes that correlate with proliferation of prostate cancer. Whereas low expression is associated with a low risk of disease progression, high expression is more indicative of higher risk of disease progression, suggesting either close monitoring or additional therapy for the latter group of patients.

Other investigational approaches to improve risk stratification include assessing suspicious nodes or small-volume extracapsular extension by MRI or positron emission tomography, staging biopsies of seminal vesicles and extraprostatic tissue, and incorporation of molecular signatures. Within our group, a significant effort is under way to relate the expression of genes that may affect apoptotic threshold, invasion, angiogenesis, and AR signaling to biologic potential and ultimately clinical outcome of localized tumors. These data suggest that both loss of tumor suppressor pathways (eg, p53) and gain of oncogene–anti-apoptotic pathways (eg, Bcl-2) contributes to prostate cancer progression. In addition to these and other "epithelial" events, the importance of the host–epithelial interaction in prostate cancer progression has been supported by evidence that pathways involved in paracrine regulation of normal stromal–epithelial interactions have also been implicated in prostate cancer progression.[36–38]

Therapy

Localized Low-Stage Prostate Cancer

In patients with localized low-stage disease (generally including low- and intermediate-risk groups based on the D'Amico risk stratification groups), the options offered include active surveillance, surgery, radiation, and presurgical clinical trials. Educating the patient about his treatment options is critical to make the best decision for each individual. Patients who are undecided or request more information about treatments and side effects are seen in our multidisciplinary clinic.

Critical evaluation of the relative merits of different therapies for localized low-stage prostate cancer is difficult. This is because patients in this category have a greater than 80% chance of 10-year progression-free survival (PFS) after local therapy.[39–41] Prostate cancer has a long natural history, and 10-year data for patients with low-risk prostate cancer remain immature with respect to cause-specific and disease-free survival. The contribution of delayed hormonal therapy and the appreciation that not all patients with a delayed PSA recurrence after local therapy are threatened by their disease have made comparisons between different treatment modalities difficult. As a consequence, the modification of older therapies or the application of new ones (eg, brachytherapy, cryoablation, or proton beam therapy) is often judged by their complication profile and the rate of PSA-free survival with a relatively short follow-up. Although seemingly logical, interpreting potential benefit from "new and improved" therapies is challenged by the impact of "stage migration" on outcomes. Stage migration refers to the fact that as a consequence of awareness and PSA screening, younger patients with lower-stage cancer are diagnosed with increasing frequency. This trend of earlier therapy in younger patients with earlier-stage disease likely has an effect on the analysis of therapy efficacy and morbidity for low-stage cancer. Therefore, the practice of deriving conclusions from the comparison of nonrandomized study groups in low-stage prostate cancer is a dubious exercise.

In fact, in localized, low-stage prostate cancer, the principal therapeutic dilemma is whether to intervene at all. Increasingly, many investigators are recognizing that not all patients diagnosed with prostate cancer by histologic criteria have a disease that has lethal potential.[42] Hence, many clinicians have explored a strategy of observation followed by delayed therapy if required. This strategy has historically been called "watchful waiting," but in recent years, we have adopted the term *active surveillance*. This is because the definition of watchful waiting is ambiguous and includes the practice of not following or evaluating patients after diagnosis until they present with a prostate cancer–associated symptom(s). In contrast, active surveillance implies regular follow-ups with PSA evaluation, DRE, and repeat biopsies as indicated to inform the need for local therapy. Active surveillance acknowledges the reality that many patients with prostate cancer survive despite diagnosis and therapy, as opposed to benefiting directly from the intervention. At MDACC, the rationale for offering active surveillance is the idea that carefully monitored patients require therapy with curative intent only if accompanied by objective evidence that their cancer has become life threatening. In this way, patients with truly indolent disease can be spared the morbidities of local therapy, and patients who show progression over time to potentially lethal disease will preserve the opportunity for curative therapy.

Active Surveillance with Deferred Treatment

Two categories of patients with low-stage disease are generally considered for active surveillance: (1) men who have a higher probability of dying from a comorbid illness (eg, coronary artery disease) than from prostate cancer and (2) men whose cancer poses some risk for lethality but choose active surveillance because of concerns about consequences of therapy (eg, impotence or incontinence). The rationale for active surveillance is outlined in Table 45–3.

There are two central challenges of the active surveillance strategy. The first is that we do not yet have a validated method to anticipate progression of the disease to avoid "closing the window" on curative therapy. The second is that we lack methods to ensure reliable selection of all patients in whom the disease will be unlikely to spread while excluding all patients who will have lethal progression of the disease despite its initial morphologic appearance as low stage. Thus, this strategy, although supported by compelling logic, must be regarded as unproven. This is particularly true for patients with a life expectancy of 15 years or more. As a patient's life span shortens because of comorbid conditions, the unproven nature of this strategy has less predicted impact on outcome. Thus, outside a clinical trial, active surveillance in our practice is routinely reserved for patients with low-stage disease and an expected survival of less than 10 years because of comorbidities.

TABLE 45–3 Rationale for Active Surveillance

• A significant portion of newly diagnosed patients will not develop clinical progression.
• Complications of local therapy exceed benefits in some patients.
• Close monitoring of selected patients with serial PSA measurements may avoid or delay initiation of potentially morbid or unnecessary therapy.

PSA, prostate-specific antigen.

Active surveillance for category 1 patients is not codified, and follow-up strategies (eg, annual PSA checks) are designed by mutual agreement between the physician and patient. Select older adult patients whose cancer diagnosis was precipitated by an ill-advised PSA screening test may choose no further follow-up. In contrast, active surveillance for category 2 patients involves close observation with quarterly PSA checks and annual prostate biopsies. Often, these patients elect to undergo local therapy as the physical and emotional burden of close observation becomes more obvious. Despite the intensity of follow-up, the ability to anticipate progression of disease based on true biologic evidence as opposed to apparent progression caused by the randomness of the biopsies remains a major problem. These problems will be clarified with prospective studies accruing at several institutions.

Treatment of Low-Stage Disease with Available Therapy

Although there is much debate about the relative merits of radiation therapy and surgery for patients with localized low-stage prostate cancer, the inescapable conclusion is that both treatment groups have excellent survival, and the principal issues influencing choice are related to therapy-associated morbidity. Interestingly, competition between radiation therapy and surgery has resulted in the reduction of morbidity to both therapies. The morbidity of radiation therapy—while retaining its effectiveness—has been greatly reduced, as has morbidity related to improvements in surgical techniques. Thus, for low-stage prostate cancer, the principal therapeutic recommendation is to treat patients who have a greater than 15-year expected life expectancy. The primary recommendation is surgery or radiation therapy, with a bias toward surgery for patients with an expected longevity of more than 20 years and a bias toward radiation therapy for patients with an expected longevity of 15 years or less (Table 45–4).

TABLE 45–4 Rationale for Selection of Local Treatment Modality

• There are no clinical trials showing a therapeutic advantage of surgery over radiation therapy for localized disease.
• Either approach is associated with some risk of significant morbidity (initial impotence rates are higher with surgery).
• There is a reduction in impotence rates over time with radiation.
• Surgery provides better assessment of risk for future relapse by allowing molecular-pathologic analysis of the radical prostatectomy specimen.
• Radiation is ideally suited for patients who are physically unfit for surgery and those who have disease extending beyond the bounds of traditional surgical fields.
• Surgery improves symptom-free and overall survival in patients with localized disease.

Presurgical Trials for Low-Stage Disease

Presurgical trials facilitate the development of novel therapies and treatment strategies in prostate cancer by providing proof of "target engagement" by the drug(s) and modulation of the tumor phenotype in a therapeutically favorable manner.[43] The principal goal of a *preoperative* clinical trial is to identify short-term molecular and pathologic tissue surrogates that establish target engagement and modulation of key signaling pathways by the drug(s). Because surgery is performed before cytoreduction or significant changes in the tumor phenotype are expected (as opposed to *neoadjuvant* trials), preoperative trials provide only limited inferences about the therapeutic potential of the drug(s) being tested. However, data from preoperative trials help identify the most promising therapeutic candidates worthy of further study. Preoperative studies of low-stage prostate cancer seek to identify molecular markers that characterize response to therapy and predict tumor biology.

High-Risk and Locally Advanced Prostate Cancer

As a general principle of oncology, high-risk and locally advanced tumors are best treated with a combination of systemic therapy and aggressive local therapy. This strategy addresses occult disseminated disease while preventing local complications of the primary tumor. Despite the widely recognized poor outcomes for patients with seminal vesicle or regional node involvement, the application of optimum local control with systemic therapy has only recently become accepted.[44]

Current multimodal therapies include radiation plus hormones and neoadjuvant therapy plus surgery. It is now well established that the addition of hormones to radiation therapy is superior to radiation therapy or hormones alone for patients with high-risk and locally advanced tumors.[45] The duration and sequence of the combination are important in maximizing therapy benefit from the combination. Several lines of evidence suggest that initiating the androgen ablation 2 months before the radiation therapy is more effective than combined therapy from the outset or sequential therapy with radiation followed by androgen ablation. The available data demonstrate an increase in survival with a 3-year period of androgen ablation. However, the optimal duration of androgen ablation in the context of locally advanced prostate cancer treated with radiation remains an area of investigation. Recent data have shown that shorter durations (eg, 18 months vs 24 months) of androgen ablative therapy in the adjuvant setting after radiation may be noninferior, with biomarker-directed strategies in development. In addition, there is a general trend that earlier use of second-generation antiandrogens is warranted for men with high-risk localized prostate cancer treated with definitive radiotherapy and ADT. The Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) study assessed the use of abiraterone acetate with ADT in men with hormone-naïve prostate cancer, including a cohort of men with high-risk localized disease treated with radiotherapy. This study showed significant benefit for the abiraterone acetate arm over the ADT only arm, thus leading to NCCN guidelines including abiraterone acetate with radiotherapy and ADT as standard of care for men with high-risk localized disease.

It also appears that improved local control represents another strategy to improve overall survival (OS) in patients with T3N0M0 (tumor, node, metastasis [TNM]) tumors. Randomized controlled trials have demonstrated that adjuvant radiation therapy after radical prostatectomy for T3N0M0 tumors significantly reduces the risk of metastases and improves OS.[46] These data support the hypothesis that untreated residual disease at the primary site can act as a source for metastatic progression.

Neoadjuvant Trials in High-Risk and Locally Advanced Prostate Cancer

At MDACC, we recognize two different categories of patients with high-risk or locally advanced disease: (1) those we believe can be effectively treated with hormones and radiation therapy and (2) those we believe will not be effectively treated with this approach because of the extent of their disease, adverse histologic features of the tumor, or the relative youth and expected long survival of the patient. Patients in the second category are candidates for a novel preoperative therapy given before prostatectomy. The rationale for

neoadjuvant therapy in this setting is based on progress made in other cancer types and is described as follows: (1) in high-risk and locally advanced disease, the post-therapy pathology specimen will inform both prognosis and future treatment decisions, and (2) controlling the primary tumor is an essential part of an integrated strategy for patients with high-risk and locally advanced disease (although this strategy is not always curative).[47] We are using neoadjuvant trial designs with increasing frequency to develop novel agents (eg, angiogenesis inhibitors) in prostate cancer. Analysis of the prostatectomy specimen permits detailed analysis of molecular (eg, apoptosis) and pathologic surrogates for therapy benefit (eg, achievement of pathologic 0 stage [P0]). We believe the preoperative model will significantly enhance our ability to identify the most promising agents worthy of development in a time-efficient manner.

A promising combined modality approach has recently been reported using maximal androgen blockade of both endocrine (using luteinizing hormone–releasing hormone agonists) and paracrine, autocrine, and intracrine (using abiraterone, a CYP17 inhibitor) testosterone sources. Two recent phase 2 studies demonstrated that combination leuprolide–abiraterone was clinically superior to leuprolide alone with respect to PSA responses and cytoreduction.[48,49] A subset of patients in both trials achieved P0 (or near P0) in the surgical specimen, a relatively common phenomenon in neoadjuvant trials of other epithelial cancers (eg, breast and bladder) but essentially unprecedented in prostate cancer.

Castration-Resistant Locally Advanced Prostate Cancer

CRPC is an umbrella term that encompasses a spectrum of disease states ranging from rising PSA alone to rising PSA associated with osseous or soft tissue metastases.[1] Furthermore, patients receiving combined androgen blockade are typically screened for an antiandrogen withdrawal response before being considered castration resistant. Patients with CRPC and PSA-only recurrence are discussed in the next section.

For patients with castration-resistant locally advanced prostate cancer, clinical progression presents significant clinical symptoms (pain, hematuria, bladder outlet and bowel obstruction), but optimal management remains a difficult therapeutic problem. The critical decision is whether to offer consolidative therapy. For patients without metastatic disease, we offer neoadjuvant chemotherapy followed by surgery for consolidation. If not used as primary therapy, salvage radiation therapy is another rational strategy, particularly for patients who are not candidates for salvage surgery.

For patients with both castration-resistant locally advanced and metastatic disease, these approaches are more controversial. Nonetheless, we recognize that

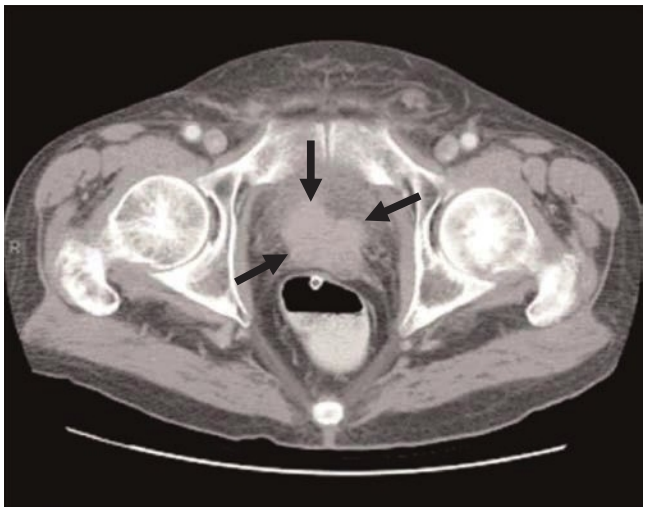


FIGURE 45–3 **Recurrent prostate cancer invading the base of the bladder.**

these patients experience significant morbidity from local tumor progression that is comparable to patients without metastases. Thus, for select candidates, we still offer consolidative therapy. As an example, consider the case of a patient who presented with metastatic prostate cancer at diagnosis and was successfully treated with androgen ablation for 10 years. He then developed castration-resistant progression and presented with invasion of his primary tumor into the bladder (Fig. 45–3). To relieve painful voiding symptoms attributed to the bladder invasion, induction chemotherapy followed by salvage cystoprostatectomy was performed. At 3-year follow-up, the patient continued to have evidence of active metastases but was free of cancer-associated local symptoms. Although this patient benefited longer than most, striking relief of intractable symptoms is common using this approach. The clinical rationale to apply chemotherapy followed by salvage surgery is summarized in Table 45–5.

Rising Prostate-Specific Antigen After Definitive Local Therapy

The utility of PSA measurements is greatest in monitoring cancer progression and effects of therapy in patients with radiographic evidence of disease. In contrast, the significance of PSA in patients without

TABLE 45–5 Rationale for Salvage Surgery

• Patients can avoid significant morbidity associated with local progression.
• Improved local control may contribute to longer overall survival.
• Patients who develop a delayed local relapse after treatment with primary radiation therapy may still have surgically curable disease.

detectable disease is less clear. Although available evidence suggests that patients with a measurable PSA after prostatectomy will eventually develop a recurrence given sufficient time, these recurrences are not uniformly fatal. Furthermore, in patients treated with radiation therapy, interpretation of PSA posttherapy is very different compared with patients treated with surgery.

Significance of Prostate-Specific Antigen After Prostatectomy

The serum PSA concentration should be undetectable using standard commercial assays within 6 weeks of prostatectomy. Persistent PSA after surgery usually indicates persistent cancer secondary to inadequate surgery, persistent cancer despite adequate surgery, or the presence of occult metastases. The experience from Johns Hopkins suggests that given sufficient time, patients with early PSA recurrence (≤2 years) or short PSA doubling time (<10 months) will develop metastatic disease within 15 years of surgery.[50–52] In contrast, patients with late PSA recurrence or a longer PSA doubling time are more likely to have a recurrence confined to the prostatic fossa. Patients who have a striking discordance between the predicted behavior of the cancer (eg, low stage) and early elevations of postoperative serum PSA may have had inadequate surgery and are considered for adjuvant radiation therapy. In patients who undergo nerve-sparing prostatectomy, consideration must also be given to the possibility that normal prostate gland left behind at surgery is producing PSA.

Significance of Prostate-Specific Antigen After Radiation Therapy

In contrast to surgery, serum PSA concentrations are not expected to become undetectable after curative therapy. In addition, the phenomenon of a PSA "bounce" is well described after radiation of the primary tumor.[53] The PSA bounce is a modest, self-limited rise in PSA concentration without evidence of cancer progression. It typically occurs within the first 18 months after completion of radiation and can last for as long as 3 months before reaching a plateau and then declining. The central clinical dilemma with PSA bounces is that their presence can only be determined with confidence in retrospect. Thus, clinicians need to be aware of this phenomenon and show restraint in introducing therapy to patients displaying delayed PSA elevation after radiation without evidence for metastases.

Management of Patients with Prostate-Specific Antigen–Only Recurrence

The scenario of the patient with PSA-only recurrence poses a therapeutic dilemma for physicians and considerable anxiety for patients, with a desire to avoid treating based just on a number but also initiate systemic therapy at the most appropriate juncture to avoid disease progression. It is clear that PSA-only recurrences do not uniformly portend morbidity or mortality from the disease. Our general approach is to offer hormone ablative therapy (commonly using an intermittent strategy) during the androgen-dependent phase of the disease.[54] Recently, darolutamide, a novel AR-signaling inhibitor, was approved by the Food and Drug Administration (FDA) for the treatment of patients with nonmetastatic CRPC based on large phase III trial data Androgen Receptor Antagonizing Agent for Metastasis-free Survival (ARAMIS) showing significant improvement in metastasis-free survival for darolutamide compared with continued ADT alone (hazard ratio [HR], 0.41; 95% confidence interval [CI], 0.34–0.50; P <.001), without a significant increase in adverse events. Subsequently, apalutamide Selective Prostate Androgen Receptor Targeting with ARN-509 (SPARTAN) and enzalutamide Safety and Efficacy Study of Enzalutamide in Patients With Nonmetastatic Castration-Resistant Prostate Cancer (PROSPER) were also approved in this setting. Subsequent data from these three trials have shown significant improved in OS in the patients treated with AR-signaling inhibition, and thus all three now can be used as standard of care in this setting. Notably, we never use chemotherapy for PSA-only recurrences that occur in the setting of CRPC.

Metastatic Cancer

Metastatic Androgen-Dependent Disease

For patients with M1 castrate-sensitive prostate cancer, there are multiple approved AR-signaling targeted therapies in recent years that provide OS benefit above ADT alone as described later. For patients with de novo metastatic disease and primary tumors in place, there are also ongoing clinical trials (eg, NCT01751438) to test best systemic therapy versus best systemic therapy plus definitive treatment (radiation or surgery) of the prostate to learn if control of the primary tumor improves the clinical outcome in patients with metastatic disease.

The role of cytotoxic chemotherapy in patients with androgen-dependent disease remains nuanced. The Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) trial compared "up-front" chemotherapy plus ADT to ADT alone in men with metastatic prostate cancer. The results showed that the median OS was 57.6 months with docetaxel plus ADT compared with 44.0 months with ADT, a difference of 13.6 months (HR, 0.61; P <.001). The benefit was primarily observed in men with high-volume

disease (49.2 months vs 32.2 months), which was defined as the presence of visceral metastases or four or more bone metastases. However, men with low-volume disease did not experience a survival benefit (HR, 1.04). Arm C of the multiarm STAMPEDE trial compared ADT plus docetaxel with or without zoledronic acid with ADT alone in men with high-risk locally advanced, metastatic, or recurrent prostate cancer starting first-line, long-term hormone therapy. Compared with a median OS of 71 months with ADT alone, ADT plus docetaxel was 81 months (HR, 0.78; P = .006). The addition of zoledronic acid did not demonstrate a survival benefit.

However, in contrast to those data, other large phase 3 studies of similar design have been negative.[55,56] The GETUG-AFU 15 trial recently reported no differences in OS between patients with noncastrate metastatic disease receiving ADT plus docetaxel versus ADT alone (median, OS was 58.9 months in the group given ADT plus docetaxel and 54.2 months in the group given ADT).[56] It is likely that differences in patient populations (eg, volume of disease at baseline) and treatments after progression explain the disparate results between these trials. At our institution, although our clinical experience strongly supports the notion that some patients with metastatic disease will benefit from early application of cytotoxic chemotherapy (eg, patients with small cell or aggressive variant features or patients with high-burden of metastatic disease and associated symptoms), we make that decision collectively with the patient based on each individual's case.

Newer generation antiandrogen agents have also been studied in the castrate-sensitive setting. Both the LATITUDE study and STAMPEDE study showed that the addition of abiraterone acetate plus prednisone to ADT led to a significant improvement in OS and radiographic PFS compared with placebos plus ADT in men with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (mCSPC). Apalutamide (Erleada, Janssen Biotech) is an oral nonsteroidal antiandrogen that directly binds the AR to prevent receptor translocation and activity. The TITAN trial demonstrated a significant benefit in 2-year radiographic PFS with apalutamide plus ADT compared with ADT plus placebo in mCSPC regardless of disease volume and may have received prior local therapy with or without docetaxel. Notable adverse events experienced with apalutamide include rash, hypothyroidism, fracture, and ischemic heart disease.

Enzalutamide (Xtandi, Medivation/Astellas) is an oral small molecule that directly binds the AR to competitively inhibit endogenous androgen binding and antagonize AR function. It has a higher affinity for the AR than first-generation nonsteroidal antiandrogens (eg, bicalutamide). The ENZAMET trial compared enzalutamide plus ADT versus ADT plus a first-generation nonsteroidal antiandrogen with concurrent docetaxel administration allowed in each group per physician discretion. A benefit was seen in PFS and OS at a median follow-up period of 34 months. The ARCHES trial also studied enzalutamide in castrate-sensitive prostate cancer by comparing enzalutamide plus ADT with ADT alone with stratification by disease volume and prior docetaxel use. At a median follow-up period of 14.4 months, median radiographic PFS was not yet reached in the enzalutamide group compared with 19.0 months with placebo. Notable adverse events with enzalutamide include fatigue, lowering of seizure threshold, and hypertension.

Castration-Resistant Progression

Second-Line Hormonal Therapies

During castrate-resistant progression, there is a gradual "switch" in sources of androgens that sustain tumor growth from endocrine to intratumoral (paracrine, autocrine, and intracrine). Second-line hormonal therapies that block these alternative sources have long been of interest as cancer therapeutics. For example, considerable advances have been made in developing small molecule inhibitors that block CYP17, a key enzyme involved in androgen biosynthesis expressed in testes, adrenal glands, and tumor tissues.[57] Ketoconazole is an antifungal agent with weak and nonspecific CYP17 inhibitory properties that has been available for decades. Although ketoconazole is active in prostate cancer, its application has been limited because of extremely poor tolerance. In contrast, several new agents, including abiraterone, have proven more successful. Abiraterone is a potent irreversible inhibitor of CYP17, and two large, randomized phase 3 studies have demonstrated clinical benefit in both chemotherapy-naïve and docetaxel-treated patients with mCRPC.[58,59]

The PREVAIL and AFFIRM studies have demonstrated a survival benefit with enzalutamide in chemotherapy-naïve and docetaxel-treated mCRPC, respectively. Because enzalutamide can potentially address molecular resistance mechanisms to abiraterone monotherapy, and vice versa, studies of combination abiraterone and enzalutamide are also under way. More specifically, resistance to abiraterone is associated with increased nuclear AR copy number (theoretically blocked with enzalutamide), and resistance to enzalutamide is associated with increased microenvironment testosterone levels (theoretically blocked with abiraterone).[60,61] Preliminary analysis suggested that a higher percentage of patients experience favorable PSA response profiles than seen with either agent alone, and the combination appears to be well

tolerated.[62] Despite breakthroughs in the treatment of mCRPC, approximately 20% to 40% of patients have no response to these agents (primary refractory). Furthermore, among patients who initially have a response to enzalutamide or abiraterone, virtually all eventually acquire secondary resistance. For example, the emergence of mutations (eg, a single F876L amino acid substitution) in the AR can confer resistance to enzalutamide. Antonarakis et al[63] reported detection of AR-V7 in circulating tumor cells from patients with CRPC may be associated with resistance to enzalutamide and abiraterone.

Chemotherapy

Chemotherapy is routinely applied to patients with castration-resistant locally advanced or metastatic disease. For more than a decade, patients have been treated with docetaxel-based regimens. However, although these therapies improve quality of life, prolongation in survival is modest. Faced with these challenges, the approach at MDACC has been to delay cytotoxic therapy until second-line hormonal (or experimental options) have been explored. Of course, patients with rapidly progressive disease causing (or expecting to cause) symptoms are offered chemotherapy sooner rather than later, particularly when additional hormonal manipulations are predicted to fail (eg, in patients with small cell or anaplastic tumors). The rationale for the use of chemotherapy is outlined in Table 45–6.

Given the limitations of docetaxel-based chemotherapy, there has been a global research initiative to improve on it, principally by combining docetaxel with other agents. However, these efforts have met with little success. For example, antiangiogenic drugs such as sunitinib and Avastin did not improve OS compared with placebo in docetaxel-refractory mCRPC.[64,65] Similarly, bone microenvironment targeting agents such as zibotentan, atrasentan, and dasatinib were each tested in phase III trials, and all failed to improve on standard docetaxel.[66–68] Interestingly, each of these agents showed promise in phase II studies, and some (eg, Avastin and sunitinib) did result in improvements in median PFS. These results suggest that a subset of patients did benefit and that moving forward, clinical trial designs that incorporate predictive biomarkers to enrich for patients most likely to respond will be necessary to develop novel treatment strategies.

TABLE 45–6 Rationale for the Use of Chemotherapy

- Chemotherapy palliates or prevents symptoms associated with progression of disease.
- Docetaxel-based regimens result in modest improvements in survival in patients with metastatic castration-resistant cancer.
- Other active agents in prostate cancer (eg, mitoxantrone and prednisone) can be used as second-line therapy.

Optimizing Therapy Sequence in Metastatic Castration-Resistant Prostate Cancer

The concept that patients can respond to another taxane after progressing on docetaxel is important. The recent approval of cabazitaxel by the FDA, based on the results of the phase III TROPIC study, provided further validation of this concept.[69] Cabazitaxel is a novel semisynthetic taxane developed specifically to overcome docetaxel resistance, and it is typically offered as second-line therapy for patients with mCRPC previously treated with docetaxel. There are now multiple approved therapies for men with metastatic prostate cancer that improve PFS and OS; thus, it is important to understand treatment sequencing. The recent CARD study evaluating cabazitaxel versus an androgen signaling–targeted agent in patients with mCRPC who had been previously treated with docetaxel, and the alternative androgen signaling–targeted agent (abiraterone or enzalutamide) showed significantly better outcomes for the men treated with cabazitaxel.

Beyond docetaxel and cabazitaxel, multiple chemotherapy regimens with modest activity are routinely applied in a sequential manner to patients in the salvage setting. Examples include CVD (cyclophosphamide, vincristine, and dexamethasone), KAVE (ketoconazole plus doxorubicin alternating with vinblastine plus estramustine), TEC (paclitaxel, estramustine, and carboplatin), and TEE (paclitaxel, estramustine, and etoposide). However, there is no standard chemotherapy in the salvage setting, and we do not have randomized comparisons testing whether the sequential application of therapy prolongs survival.

More recent studies have demonstrated clinical responses to platinum-based therapy in combination with taxanes.[70–72] Ross et al[73] tested the activity of docetaxel–carboplatin in patients who had progressed during or within 45 days after the completion of docetaxel. PSA declines of 50% or greater were noted in 18% of patients, and measurable responses occurred in 14% of patients. Because patients in this study would not be anticipated to respond to "rechallenge" with docetaxel alone, these results support the hypothesis that carboplatin has the potential to overcome docetaxel resistance mechanisms.

We have performed a randomized phase I/II study of cabazitaxel with or without carboplatin in patients with mCRPC (NCT01505868), showing that the addition of carboplatin improved the median PFS from 4·to 5 months (95% CI, 3.5–5.7) to 7·3 months (95% CI, 5.5–8.2; HR, 0.69; 95% CI, 0.50–0.95; P =·.018). The

combination arm did show increased side effects, most notably fatigue and cytopenias.

Precision Medicine and Targeted Therapies

Men with advanced prostate cancer have a 10% to 15% risk of carrying a hereditary, or germline, variant in a DDR gene, as previously discussed. Pathogenic or deleterious variants in these same DDR genes can also be found at the somatic, or tumor-associated level, in up to 25% of mCRPC. Precision medicine currently centers mostly on discovering these somatic aberrations through DNA sequencing to then guide targeted treatment selection for patients with advanced cancer. Compared with other solid tumors such as melanoma and urothelial cancers, advanced prostate cancer overall displays relatively low tumor mutational burden (TMB), with rare exceptions, including tumors with MMR deficiency or subsequent high microsatellite instability (MSI-H). Defective MMR genes or MSI-H is seen in about 3% to 8% of prostate cancers, with the majority being of sporadic origin and with Lynch syndrome not displaying high penetrance in prostate cancer.

BRCA2 is by far the most frequently altered homologous recombination repair (HRR) gene in the in prostate cancer, and variants in other HRR-related genes such as *BRCA1, ATM*, and *CDK12* can also be seen.

Multiple approved tumor and liquid somatic sequencing platforms are available to clinicians. Each platform may slightly differ in terms of the genes included on the panel, as well as their coverage. Currently, there are three FDA-approved therapies (pembrolizumab, rucaparib, and olaparib) for patients with advanced prostate cancer with associated DNA-based biomarkers for patient selection. Briefly, pembrolizumab, a well-known immune checkpoint blockade therapy, was approved by the FDA for treating patients with advanced MMR-deficient and MSI-high cancers, agnostic of tissue origin. Testing methods for identifying these cancers include MMR protein staining, MMR gene sequencing, MSI polymerase chain reaction testing, and TMB via next-generation sequencing. Rucaparib and olaparib, two drugs in the class of PARP inhibitors were both recently approved by the FDA for biomarker-selected, previously treated advanced prostate cancer. Rucaparib was granted accelerated approval for men with mCRPC with deleterious variants in *BRCA1* or *BRCA2* only (somatic or germline origin) based on data from the ongoing TRITON2 study (NCT02952534) showing a promising objective response rate (ORR) and duration of response for rucaparib 600 mg twice a day, with a phase III confirmatory trial pending. Olaparib was approved for men with advanced prostate cancer who previously progressed on abiraterone or enzalutamide and have a deleterious HRR gene variant (somatic or germline) based on statistically significant improvement in radiographic PFS compared with the alternative androgen-signaling directed agent, with statistically significant benefit in OS and ORR also seen in cohort A of the study that included men with *BRCA1*, *BRCA2*, and/or *ATM* variants. Although olaparib received FDA approval for a broader list of deleterious HRR genes outside of just *BRCA2*, it is evident from multiple studies that the majority of benefit from single-agent PARP inhibitor is seen in patients with deleterious *BRCA2* variants or other very closely related genes such as *PALB2*. Targeting ATM-aberrant prostate cancer warrants further research, with some preliminary promising data for the use of ATR inhibitors for these patients.

CDK12 has previously been implicated in regulating the expression of HRR genes, and loss of function in CDK12 has been shown to result in a distinct immunophenotype in prostate cancer. Thus, CDK12 alterations held promise as a potential predictive biomarker for PARP inhibition as well as immune checkpoint blockade. However, clinical data thus far have been mixed, in which CDK12 alterations more clearly portend for worse outcomes to both AR-directed therapy and chemotherapy but have yet to show clear benefit to PARP inhibitor or immune therapy.

Missense mutations in the SPOP gene are frequently seen in localized primary prostate cancer and to a lesser degree in metastatic disease. Multiple studies have shown that patients with *SPOP* variants display a better prognosis and good response to androgen-targeted therapies. The underlying biological reasoning and mechanisms for this improved response are an active area of investigation.

Androgen-Indifferent Prostate Cancer Treatment

Because of characteristic androgen indifference, pure SCPC does not respond to available androgen-directed therapies. Therapeutic recommendations are extrapolated from small cell carcinoma of the lung using etoposide plus cisplatin or carboplatin as first-line therapy. Despite platinum sensitivity, the responses are typically short-lived, and prognosis remains poor. SCPC is more commonly identified as a mixed histology with adenocarcinoma that can be treated with therapies for either histology. Approved androgen-directed therapies should not be withheld based on neuroendocrine marker expression alone in the absence of small cell histology.

The AVPC clinical and molecular criteria seem to enrich for the platinum sensitivity seen in SCPC, though responses remain short-lived. This is supported

by a phase 2 study showing a survival benefit with docetaxel plus carboplatin in tumors with atypical clinical features regardless of histology or neuroendocrine marker expression. A phase 1/2 study of cabazitaxel plus carboplatin versus cabazitaxel alone demonstrated a significant benefit with the addition of carboplatin when stratifying by presence of AVPC molecular criteria. An ongoing study is assessing the efficacy of maintenance PARP inhibition after use of carboplatin–cabazitaxel in AVPC tumors (NCT03263650), and another study is being planned to explore the addition of immune checkpoint blockade to this regimen. However, available AVPC criteria are prognostic but not predictive, and responses to platinum-based therapy remain heterogeneous. Further study is warranted to discover biomarkers that (1) define androgen-indifferent tumors regardless of morphology, (2) predict for response to current platinum-based therapies, and (3) enable development of targets for more effective therapies.

Stromal-Targeting Therapies

Bone-targeting radiopharmaceuticals are examples of stromal-targeting agents in prostate cancer. The merits of targeting the bone microenvironment have been established by the use of strontium 89 (pure β-emitter radiopharmaceutical) as a single agent or in combination with cytotoxic therapy[74] (Table 45–7). Emerging data support the view that targeting bone will prolong overall patient survival, even in those with advanced-stage disease. Samarium-153 conjugated to ethylene-diamine-tetra-methylenephosphonic acid is a β- and γ-emitter radiopharmaceutical. It was approved by the FDA in 1997 after the landmark study that showed palliation of pain associated with metastatic bone cancer using samarium-153 lexidronam.[75] However, marrow toxicity remains the principal side effect. The radioactive calcium mimetic radium-223 dichloride (Xofigo, Bayer), which specifically targets bone metastases (present in 80%–90% of patients with metastatic CRPC), is the newest treatment for patients with mCRPC. A phase III, randomized, double-blind, placebo-controlled study (ALSYMPCA) investigated the use of radium-223 in men with CRPC and bone metastases; radium-223 showed improved OS in this patient population.[76] This study led to its FDA approval for CRPC with bone metastases in 2013.

Bisphosphonates were the first class of agents investigated for prevention of skeletal-related events (SREs) in patients with mCRPC. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma showed zoledronic acid reduced SREs in patients with prostate cancer with bone metastases.[77] Currently, zoledronic acid is the only bisphosphonate approved to prevent SREs in patients with mCRPC.

Denosumab is a fully humanized monoclonal antibody that binds to the RANKL (receptor activator of nuclear factor κ-B ligand), which results in inhibition of RANK-L–mediated bone resorption. A phase III study of men with CRPC with bone metastases and no previous exposure to intravenous bisphosphonate compared denosumab with zoledronic acid for prevention of SREs.[78] Denosumab was superior to zoledronic acid in delaying or preventing SREs, but there was no significant difference between treatments in survival or disease progression.[78] It was approved by the FDA in 2010 for prevention of SREs in patients with bone metastases.

TABLE 45–7 Rationale for Bone-Targeted Therapy

• Osseous metastases are the preferred site of castration-resistant progression.
• Osseous metastases significantly contribute to the morbidity and mortality of prostate cancer.
• Bone-targeting radiopharmaceuticals prolong symptom-free survival in patients with castration-resistant progression and skeletal metastases.

Immune-Based Therapies

Historically, there has been long-standing interest in stimulating a patient's immune system as a therapy strategy for prostate cancer. Despite enthusiasm for this paradigm, studies have consistently demonstrated no clinical benefit. Recently, several new strategies have emerged that reveal the potential of immunotherapy in treating prostate cancer. Randomized, placebo-controlled phase III trials demonstrated an OS benefit for men with CRPC treated with sipuleucel-T.[79] GVAX, a cellular vaccine product that uses exogenous tumor cells that secrete granulocyte-macrophage colony-stimulating factor, has shown promising activity in phase II studies,[80] although it failed to meet its primary end point of OS compared with docetaxel in a phase III study.[81,82] Ipilimumab is a humanized anti–CTLA-4 (cytotoxic T-cell lymphocyte antigen-4) antibody; data from a phase III trial of a single dose of radiation treatment followed by ipilimumab or placebo in previously treated patients showed the primary endpoint (ie, OS) was not met (ipilimumab vs placebo, 11.2 vs 10.0 months, respectively; however, there was an improvement in PFS and PSA responses).[83] Further development of these agents (and others) could dramatically change the way we treat prostate cancer in the coming decade.

FUTURE DIRECTIONS

The majority of patients with advanced prostate cancer demonstrate a predictable clinical pattern of progression. As elucidation of the biologic events responsible for prostate cancer progression evolves, better classification of the disease based on the underlying molecular mechanisms of progression will facilitate the implementation of current and emerging therapies. To reflect this, we have recently proposed a "spiral" model for prostate cancer progression that describes underlying biology to predict response to therapy[84] (Fig. 45–4). The model proposes three main phases in prostate cancer progression: (1) the dihydrotesterone (DHT)-dependent phase, (2) the microenvironment-dependent phase, and (3) the cell-autonomous phase.

The first phase is the *DHT-dependent phase*, during which the tumor is responsive to 5-α-reductase inhibitor treatments. In the PSA era, this phase typically occurs when patients are initially diagnosed with

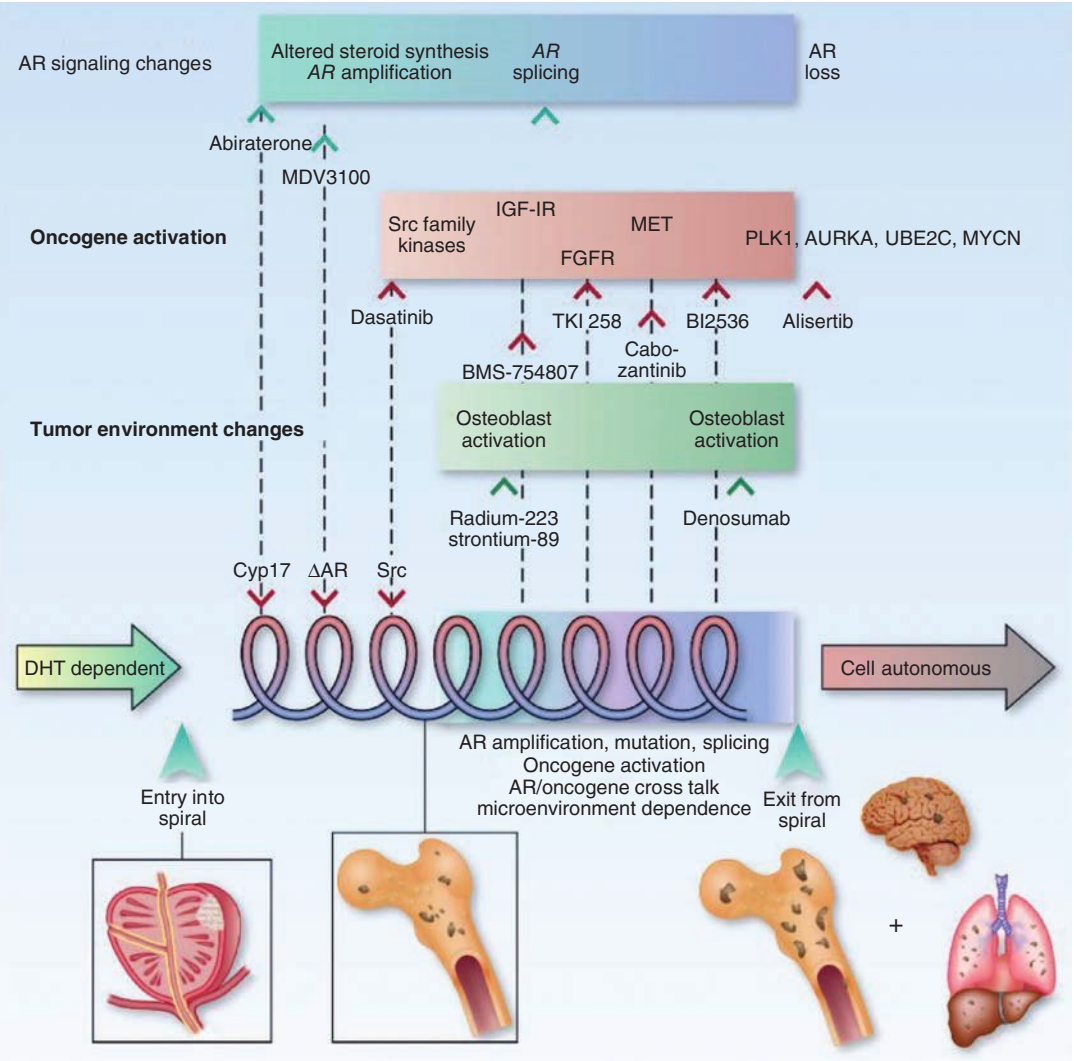


FIGURE 45–4 **Spiral model for prostate cancer progression. The first phase is the *dihydrotesterone (DHT)-dependent phase*. The second phase is the *microenvironment-dependent phase*. The third phase is the *cell-autonomous phase*. Each "turn" is defined by a predictive marker(s) that can be targeted. The pitch in each spiral reflects the duration that the tumors remain responsive to a specific therapy. The adaptive changes in tumors in response to therapy account for resistance, leading the tumor to progress to the next turn of the progression spiral, which signals additional alterations in the tumor and its microenvironment. Tumors in this new "turn" require different therapeutics that specifically target the altered properties that define the turn. Markers that reflect the biology that drives each turn can be used to guide timely therapy application in anticipation of progression. AR, androgen receptor; FGF, fibroblast growth factor; IGF, insulinlike growth factor. (Reproduced with permission from Logothetis CJ, Gallick GE, Maity SN, et al. Molecular classification of prostate cancer progression: foundation for marker-driven treatment of prostate cancer. *Cancer Discov*. 2013;3(8):849-861.)**

early-stage, localized prostate cancer. Tumors in this phase would be predicted to respond optimally to chemoprevention strategies.

The second phase is the *microenvironment-dependent phase*, when the tumor enters a progression spiral in which multiple factors, including AR-signaling changes, oncogene activation, tumor suppressor gene loss, and microenvironment changes, affect tumor progression. Tumors in this phase would be predicted to respond optimally to inhibitors of intratumoral androgen signaling (eg, with abiraterone and enzalutamide). Over time, however, adaptive changes in response to therapy promote resistance, leading the tumor to progress to the next turn of the progression spiral, which signals additional molecular alterations in the tumor and its microenvironment. Tumors in a new turn of the spiral will require different therapeutics that specifically target the altered molecular events that drive each turn (eg, inhibitors of Src, fibroblast growth factor, c-MET). Predictive biomarkers corresponding to each turn can be used to guide timely therapy application.

The third phase is the *cell-autonomous phase*, whereby cancers exit the spiral when a series of mutations arise, including the loss of AR, RB, or p53; upregulation of polo-like kinase 1 (PLK1) and Aurora kinase A (AURKA); and amplification of *MYCN*. At this stage, the prostate cancer cells are no longer regulated by the microenvironment and become tumor cell autonomous. Cancers in this phase would be predicted to respond optimally to chemotherapy.

Along with the integration of improved predictive and prognostic markers, we believe it is realistic to expect individualized treatment algorithms for prostate cancer patients as details of the spiral evolve. The application of biologically based, rational therapy is the foundation of our mission at MDACC to cure prostate cancer. Recent progress has created a strong sense of hope that we are well on our way to achieving this goal.

MD ANDERSON PRACTICE TIPS

- Men with low-risk and favorable intermediate-risk prostate cancer should be considered for active surveillance.
- Despite additive benefit of androgen deprivation and radiation for men with high-risk localized prostate cancer, there has been no benefit shown to date for adjuvant ADT after prostatectomy.
- The decision on when to initiate ADT in asymptomatic men with castrate-sensitive PSA recurrence after definitive therapy is a patient-to-patient decision that should be tailored based on the patient's age, functional status, and comorbid conditions. Rapid PSA doubling time or change in the velocity of PSA rise should prompt further investigation and consideration of initiating ADT.
- Multiple phase III studies of AR-signaling blockade in conjunction with ADT have shown clinical benefit for men with metastatic castrate-sensitive disease over ADT alone, leading to multiple FDA-approved options in this space. It is not recommended to switch to an alternative second-generation antiandrogen signaling agent after progression on one because there is cross-resistance and been shown to be inferior to switching to chemotherapy (CARD trial).
- Carboplatin with cabazitaxel should be considered for treating men with AVPC (androgen-indifferent prostate cancer), with continued ADT.
- Precision medicine in prostate cancer is actively evolving. Alterations in DDR genes (eg, *BRCA2*) at the somatic or germline level are relatively frequent in prostate cancer (≤25% of metastatic prostate cancer). A deleterious alteration in a DDR gene aids in treatment selection (eg, PARP inhibition in *BRCA2*-aberrant tumors). Tumors with MSI-H, MMR protein loss, or high TMB can be considered for treatment with pembrolizumab. Alterations in *SPOP* are associated with an overall good prognosis and display better response to antiandrogen therapy. The impact of variants in other genes on prostate cancer phenotype and treatment (eg, *CDK12*, *ATM*, *CHEK1/2*) are under active investigation.

REFERENCES

1. Scher HI, Heller G. Clinical states in prostate cancer: toward a dynamic model of disease progression. *Urology*. 2000;55(3):323-327.
2. Chang AJ, Autio KA, Roach M 3rd, Scher HI. High-risk prostate cancer-classification and therapy. *Nat Rev Clin Oncol*. 2014;11(6):308-323.
3. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin*. 2014;64(1):9-29.
4. Patel AR, Klein EA. Risk factors for prostate cancer. *Nat Clin Pract Urol*. 2009;6(2):87-95.
5. Scher HI, Sawyers CL. Biology of progressive, castration-resistant prostate cancer: directed therapies targeting the androgen-receptor signaling axis. *J Clin Oncol*. 2005;23(32):8253-8261.
6. Ebos JM, Lee CR, Bogdanovic E, et al. Vascular endothelial growth factor-mediated decrease in plasma soluble vascular endothelial growth factor receptor-2 levels as a surrogate biomarker for tumor growth. *Cancer Res*. 2008;68(2):521-529.
7. Renehan AG, Tyson M, Egger M, et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*. 2008;371(9612):569-578.
8. Golabek T, Bukowczan J, Chlosta P, et al. Obesity and prostate cancer incidence and mortality: a systematic review of prospective cohort studies. *Urol Int*. 2014;92(1):7-14.
9. Roberts DL, Dive C, Renehan AG. Biological mechanisms linking obesity and cancer risk: new perspectives. *Annu Rev Med*. 2010;61:301-316.
10. Rowlands MA, Gunnell D, Harris R, et al. Circulating insulin-like growth factor peptides and prostate cancer risk: a systematic review and meta-analysis. *Int J Cancer*. 2009;124(10):2416-2429.
11. Cox ME, Gleave ME, Zakikhani M, et al. Insulin receptor expression by human prostate cancers. *Prostate*. 2009;69(1):33-40.
12. Ma J, Li H, Giovannucci E, et al. Prediagnostic body-mass index, plasma C-peptide concentration, and prostate cancer-specific mortality in men with prostate cancer: a long-term survival analysis. *Lancet Oncol*. 2008;9(11):1039-1047.
13. Margel D, Urbach DR, Lipscombe LL, et al. Metformin use and all-cause and prostate cancer-specific mortality among men with diabetes. *J Clin Oncol*. 2013;31(25):3069-3075.
14. Huang CY, Yu HS, Lai TY, et al. Leptin increases motility and integrin up-regulation in human prostate cancer cells. *J Cell Physiol*. 2011;226(5):1274-1282.
15. Baillargeon J, Platz EA, Rose DP, et al. Obesity, adipokines, and prostate cancer in a prospective population-based study. *Cancer Epidemiol Biomarkers Prev*. 2006;15(7):1331-1335.
16. Goktas S, Yilmaz MI, Caglar K, et al. Prostate cancer and adiponectin. *Urology*. 2005;65(6):1168-1172.
17. Stark JR, Perner S, Stampfer MJ, et al. Gleason score and lethal prostate cancer: does 3 + 4 = 4 + 3? *J Clin Oncol*. 2009;27(21):3459-3464.
18. Efstathiou E, Abrahams NA, Tibbs RF, et al. Morphologic characterization of preoperatively treated prostate cancer: toward a post-therapy histologic classification. *Eur Urol*. 2010;57(6):1030-1038.
19. Srigley JR, Humphrey PA, Amin MB, et al. Protocol for the examination of specimens from patients with carcinoma of the prostate gland. *Arch Pathol Lab Med*. 2009;133(10):1568-1576.
20. Petrovics G, Liu A, Shaheduzzaman S, et al. Frequent overexpression of ETS-related gene-1 (ERG1) in prostate cancer transcriptome. *Oncogene*. 2005;24(23):3847-3852.
21. McDonnell TJ, Navone NM, Troncoso P, et al. Expression of bcl-2 oncoprotein and p53 protein accumulation in bone marrow metastases of androgen independent prostate cancer. *J Urol*. 1997;157(2):569-574.
22. Assikis VJ, Do KA, Wen S, et al. Clinical and biomarker correlates of androgen-independent, locally aggressive prostate cancer with limited metastatic potential. *Clin Cancer Res*. 2004;10(20):6770-6778.
23. Tu SM, Lopez A, Leibovici D, et al. Ductal adenocarcinoma of the prostate: clinical features and implications after local therapy. *Cancer*. 2009;115(13):2872-2880.
24. Epstein JI. Precursor lesions to prostatic adenocarcinoma. *Virchows Arch*. 2009;454(1):1-16.
25. De Marzo AM, Platz EA, Sutcliffe S, et al. Inflammation in prostate carcinogenesis. *Nat Rev Cancer*. 2007;7(4):256-2569.
26. Andriole GL, Crawford ED, Grubb RL 3rd, et al. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med*. 2009;360(13):1310-1319.
27. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med*. 2009;360(13):1320-1328.
28. US Preventive Services Task Force. Prostate cancer: screening. http://www.uspreventiveservicestaskforce.org/Page/Topic/recommendation-summary/prostate-cancer-screening
29. Partin AW, Kattan MW, Subong EN, et al. Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer. A multi-institutional update. *JAMA*. 1997;277(18):1445-1451.
30. Makarov DV, Trock BJ, Humphreys EB, et al. Updated nomogram to predict pathologic stage of prostate cancer given prostate-specific antigen level, clinical stage, and biopsy Gleason score (Partin tables) based on cases from 2000 to 2005. *Urology*. 2007;69(6):1095-1101.
31. Hernandez DJ, Nielsen ME, Han M, Partin AW. Contemporary evaluation of the D'Amico risk classification of prostate cancer. *Urology*. 2007;70(5):931-935.
32. Kattan MW, Wheeler TM, Scardino PT. Postoperative nomogram for disease recurrence after radical prostatectomy for prostate cancer. *J Clin Oncol*. 1999;17(5):1499-1507.
33. Cuzick J, Berney DM, Fisher G, et al. Prognostic value of a cell cycle progression signature for prostate cancer death in a conservatively managed needle biopsy cohort. *Br J Cancer*. 2012;106(6):1095-1099.
34. Cooperberg MR, Simko JP, Cowan JE, et al. Validation of a cell-cycle progression gene panel to improve risk stratification in a contemporary prostatectomy cohort. *J Clin Oncol*. 2013;31(11):1428-1434.
35. Cuzick J, Swanson GP, Fisher G, et al. Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study. *Lancet Oncol*. 2011;12(3):245-255.
36. Sanchez P, Hernandez AM, Stecca B, et al. Inhibition of prostate cancer proliferation by interference with SONIC HEDGEHOG-GLI1 signaling. *Proc Natl Acad Sci U S A*. 2004;101(34):12561-12566.
37. Zunich SM, Douglas T, Valdovinos M, et al. Paracrine sonic hedgehog signalling by prostate cancer cells induces osteoblast differentiation. *Mol Cancer*. 2009;8:12.
38. Park SI, Zhang J, Phillips KA, et al. Targeting SRC family kinases inhibits growth and lymph node metastases of prostate cancer in an orthotopic nude mouse model. *Cancer Res*. 2008;68(9):3323-3333.
39. Holmberg L, Bill-Axelson A, Helgesen F, et al. A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. *N Engl J Med*. 2002;347(11):781-789.
40. Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med*. 2005;352(19):1977-1984.
41. D'Amico AV, Moul J, Carroll PR, et al. Cancer-specific mortality after surgery or radiation for patients with clinically localized

prostate cancer managed during the prostate-specific antigen era. *J Clin Oncol*. 2003;21(11):2163-2172.
42. Johansson JE, Holmberg L, Johansson S, et al. Fifteen-year survival in prostate cancer. A prospective, population-based study in Sweden. *JAMA*. 1997;277(6):467-471.
43. Efstathiou E, Kim J, Logothetis CJ. Informative clinical investigation: a demanding taskmaster. *J Clin Oncol*. 2009;27(30):4937-498.
44. Messing EM, Manola J, Sarosdy M, et al. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. *N Engl J Med*. 1999;341(24):1781-1788.
45. Bolla M, Collette L. pT3N0M0 prostate cancer: a plea for adjuvant radiation. *Nat Rev Urol*. 2009;6(8):410-412.
46. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol*. 2009;181(3):956-962.
47. Pettaway CA, Pisters LL, Troncoso P, et al. Neoadjuvant chemotherapy and hormonal therapy followed by radical prostatectomy: feasibility and preliminary results. *J Clin Oncol*. 2000;18(5):1050-1057.
48. Taplin ME, Montgomery B, Logothetis CJ, et al. Intense androgen-deprivation therapy with abiraterone acetate plus leuprolide acetate in patients with localized high-risk prostate cancer: results of a randomized phase II neoadjuvant study. *J Clin Oncol*. 2014;32(33):3705-3715.
49. Efstathiou E, Davis J, Troncoso P, et al. Cytoreduction and androgen signaling modulation by abiraterone acetate (AA) plus leuprolide acetate (LHRHa) versus LHRHa in localized high-risk prostate cancer (PCa): preliminary results of a randomized preoperative study. *J Clin Oncol*. 2012;30(suppl):4557.
50. Pound CR, Partin AW, Eisenberger MA, et al. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA*. 1999;281(17):1591-1597.
51. Han M, Partin AW, Pound CR, et al. Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy. The 15-year Johns Hopkins experience. *Urol Clin North Am*. 2001;28(3):555-565.
52. Cannon GM Jr, Walsh PC, Partin AW, Pound CR. Prostate-specific antigen doubling time in the identification of patients at risk for progression after treatment and biochemical recurrence for prostate cancer. *Urology*. 2003;62(suppl 1):2-8.
53. Rosser CJ, Kuban DA, Levy LB, et al. Prostate specific antigen bounce phenomenon after external beam radiation for clinically localized prostate cancer. *J Urol*. 2002;168(5):2001-2005.
54. Bhandari MS, Crook J, Hussain M. Should intermittent androgen deprivation be used in routine clinical practice? *J Clin Oncol*. 2005;23(32):8212-8218.
55. Millikan RE, Wen S, Pagliaro LC, et al. Phase III trial of androgen ablation with or without three cycles of systemic chemotherapy for advanced prostate cancer. *J Clin Oncol*. 2008;26(36):5936-5942.
56. Gravis G, Fizazi K, Joly F, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2013;14(2):149-158.
57. Reid AH, Attard G, Barrie E, de Bono JS. CYP17 inhibition as a hormonal strategy for prostate cancer. *Nat Clin Pract Urol*. 2008;5(11):610-620.
58. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011;364(21):1995-2005.
59. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. 2013;368(2):138-148.
60. Efstathiou E, Titus M, Tsavachidou D, et al. Effects of abiraterone acetate on androgen signaling in castrate-resistant prostate cancer in bone. *J Clin Oncol*. 2012;30(6):637-643.
61. Efstathiou E, Titus M, Wen S, et al. Molecular characterization of enzalutamide-treated bone metastatic castration-resistant prostate cancer. *Eur Urology*. 2015;67(1):53-60.
62. Efstathiou E, Titus MA, Wen S, et al. Enzalutamide (ENZA) in combination with abiraterone acetate (AA) in bone metastatic castration resistant prostate cancer (mCRPC) [abstract 5000]. *J Clin Oncol*. 2014;32(suppl):5S.
63. Antonarakis ES, Lu C, Wang H, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. *N Engl J Med*. 2014;371(11):1028-1038.
64. Michaelson MD, Oudard S, Ou YC, et al. Randomized, placebo-controlled, phase III trial of sunitinib plus prednisone versus prednisone alone in progressive, metastatic, castration-resistant prostate cancer. *J Clin Oncol*. 2014;32(2):76-82.
65. Kelly WK, Halabi S, Carducci M, et al. Randomized, double-blind, placebo-controlled phase III trial comparing docetaxel and prednisone with or without bevacizumab in men with metastatic castration-resistant prostate cancer: CALGB 90401. *J Clin Oncol*. 2012;30(13):1534-1540.
66. Fizazi K, Higano CS, Nelson JB, et al. Phase III, randomized, placebo-controlled study of docetaxel in combination with zibotentan in patients with metastatic castration-resistant prostate cancer. *J Clin Oncol*. 2013;31(14):1740-1747.
67. Quinn DI, Tangen CM, Hussain M, et al. Docetaxel and atrasentan versus docetaxel and placebo for men with advanced castration-resistant prostate cancer (SWOG S0421): a randomised phase 3 trial. *Lancet Oncol*. 2013;14(9):893-900.
68. Araujo JC, Trudel GC, Saad F, et al. Docetaxel and dasatinib or placebo in men with metastatic castration-resistant prostate cancer (READY): a randomised, double-blind phase 3 trial. *Lancet Oncol*. 2013;14(13):1307-1316.
69. de Bono JS, Oudard S, Ozguroglu M et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet*. 2010;376(9747):1147-1154.
70. Kelly WK, Curley T, Slovin S, et al. Paclitaxel, estramustine phosphate, and carboplatin in patients with advanced prostate cancer. *J Clin Oncol*. 2001;19(1):44-53.
71. Oh WK, Halabi S, Kelly WK, et al. A phase II study of estramustine, docetaxel, and carboplatin with granulocyte-colony-stimulating factor support in patients with hormone-refractory prostate carcinoma: Cancer and Leukemia Group B 99813. *Cancer*. 2003;98(12):2592-2598.
72. Regan MM, O'Donnell EK, Kelly WK, et al. Efficacy of carboplatin-taxane combinations in the management of castration-resistant prostate cancer: a pooled analysis of seven prospective clinical trials. *Ann Oncol*. 2010;21(2):312-318.
73. Ross RW, Beer TM, Jacobus S, et al. A phase 2 study of carboplatin plus docetaxel in men with metastatic hormone-refractory prostate cancer who are refractory to docetaxel. *Cancer*. 2008;112(3):521-526.
74. Tu SM, Lin SH. Current trials using bone-targeting agents in prostate cancer. *Cancer J*. 2008;14(1):35-39.
75. Serafini AN, Houston SJ, Resche I, et al. Palliation of pain associated with metastatic bone cancer using samarium-153 lexidronam: a double-blind placebo-controlled clinical trial. *J Clin Oncol*. 1998;16(4):1574-1581.
76. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369(3):213-223.
77. Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst*. 2002;94(19):1458-1468.

78. Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet*. 2011;377(9768):813-822.
79. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. 2010;363(5):411-422.
80. Higano CS, Corman JM, Smith DC, et al. Phase 1/2 dose-escalation study of a GM-CSF-secreting, allogeneic, cellular immunotherapy for metastatic hormone-refractory prostate cancer. *Cancer*. 2008;113(5):975-984.
81. Higano C, Saad, F, Somer SB, et al. A phase III trial of GVAX immunotherapy for prostate cancer vs docetaxel plus prednisone in asymptomatic, castration-resistant prostate cancer (CRPC). Genitourinary Cancer Symposium [abstract LBA150]. *Proc Am Soc Clin Oncol*. 2009;27(suppl 15S).
82. Small E, Demkow T, Gerritsen W, et al. A phase III trial of GVAX immunotherapy for prostate cancer in combination with docetaxel vs docetaxel plus prednisone in symptomatic, castration-resistant prostate cancer (CRPC). Genitourinary Cancer Symposium [abstract 7]. *Proc Am Soc Clin Oncol*. 2009.
83. Kwon ED, Drake CG, Scher HI, et al. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2014;15(7):700-712.
84. Logothetis CJ, Gallick GE, Maity SN, et al. Molecular classification of prostate cancer progression: foundation for marker-driven treatment of prostate cancer. *Cancer Discov*. 2013;3(8):849-861.

46 Penile Cancer

Jad Chahoud
Curtis A. Pettaway

KEY CONCEPTS

- Human papillomavirus infection appears to be the possible cause of 30% to 50% of penile cancer cases and appears to have a prognostic impact on clinical outcomes among patients with advanced disease.
- Penile-preserving strategies should be strongly considered among patients with low-stage tumors, especially those limited to the skin and the distal glans penis.
- The presence and the extent of metastasis to the inguinal region are the most important prognostic factors for survival in patients with squamous cell carcinoma of the penis.
- Penile tumor T stage ≥ T1b, grade, lymphovascular invasion, and perineural invasion appear to be the most important pathologic prognostic factors for nodal spread. Their presence is used to determine the need for inguinal staging procedures among patients with no clinically apparent inguinal metastases.
- Patients with bulky lymphadenopathy should undergo a multimodal therapeutic approach to include neoadjuvant platinum-based chemotherapy with paclitaxel, ifosfamide, and cisplatin (TIP) for four cycles followed by consolidation surgical lymph node dissection among responding patients.
- Patients with relapsed or refractory penile cancer to platinum-based chemotherapy have poor outcomes with current therapy modalities, and every effort should be made to enroll these patients on novel therapeutic clinical trials.

INCIDENCE

Penile cancer most commonly affects men between 50 and 70 years of age. The tumor is not unusual in younger men; in one large series, 22% of patients were younger than 40 years, and 7% were younger than 30 years.[1] In 2018, there were an estimated 1820 new cases in the United States.[2] The annual incidence of penile cancer cases in total per year worldwide has been estimated at approximately 35,000.[3] Penile cancer accounts for less than 1% of all malignant neoplasms among men in the United States and Europe,[2,4,5] but it may represent up to 10% of cancers in men in some Asian, African, and South American countries.[1] These differences are thought to be related to the prevalence of neonatal circumcision, human papillomavirus (HPV) infection, and cultural practices. Among uncircumcised tribes of Africa and within uncircumcised Asian cultures, penile cancer may amount to 10% to 20% of all malignant neoplasms in men.1 Squamous cell carcinoma (SCC) is the most common histologic subtype, accounting for more than 95% of cases (Table 46–1).[6]

TABLE 46–1 Histopathology Subtypes of Penile Cancer

Squamous cell carcinoma
Verrucous carcinoma
Papillary carcinoma, not otherwise specified
Adenosquamous carcinoma
Sarcomatoid squamous carcinoma
Basaloid carcinoma
Papillary-basaloid carcinoma
Warty carcinoma
Warty-basaloid carcinoma
Clear cell carcinoma
Adenocarcinoma
Lymphoma
Melanoma
Kaposi sarcoma
Leiomyosarcoma

RISK FACTORS

Lack of Circumcision

The risk of penile cancer varies according to circumcision practice, phimosis, HPV infection, and smoking.[7–13] Neonatal circumcision has been considered a prophylactic measure that removes many of the risks of penile carcinoma because it eliminates the closed preputial environment where penile cancer most commonly develops. This increased risk appears to be related to a history of phimosis, which is a diagnosis of circumferential fibrosis of preputial tissue leading to an inability to retract the penile foreskin over the glans penis.[11] These findings were confirmed by a systematic review and meta-analysis that found a strong protective effect of childhood circumcision on invasive penile cancer (overall survival [OR], 0.33; 95% confidence interval [CI], 0.13–0.83; three studies).[14] Phimosis is found in 25% to 75% of patients with penile carcinoma described in most large series. Epithelial atypia was found in around 30% of patients who underwent circumcision with phimosis.[15] Also, a large case series showed the protective benefit from neonatal circumcision, but circumcision delayed until after puberty was not beneficial.[16]

Human Papillomavirus

Although the etiology for penile cancer development is not unique nor clarified, it is thought that HPV infection probably plays an important factor in the development of some penile cancer, with evidence that 31% to 63% of tumors are HPV related.[17–19] The presence of HPV in tumor tissue is established using numerous methods, such as polymerase chain reaction (PCR) amplification for the detection of HPV DNA. PCR is a highly sensitive method that can detect both transient and persistent HPV infections.[20] Also, p16INK4a expression has been used as a cost- and time-efficient surrogate marker of transforming HPV infections based on the strong correlation between transcriptionally active HPV and p16INK4a overexpression in cancer cells.[21] HPV is most associated with the basaloid and warty tumor subtypes, which were found to contain HPV DNA in 80% to 100% of cases. The largest meta-analysis of the prevalence of HPV infection in 4000 penile cancer cases showed a pooled HPV DNA prevalence of 50.8% in penile cancer. Basaloid SCCs (84%) and warty-basaloid carcinoma (75.7%) had a particularly high HPV DNA prevalence.[17] They found that HPV16 is by far the most common HPV type in both penile cancer and penile intraepithelial neoplasia. This meta-analysis also assessed pooled data from 2000 penile cancer cases and 167 penile intraepithelial neoplasia (PIeN) to show p16INK4a positivity amount to 41.6% for penile cancer and 49.5% for PIeN.[17]

Patients with HPV-related penile cancer appear to have a better prognosis than those with HPV-unrelated tumors. A population-based study found that the detection of HPV DNA in penectomy specimens was associated with a significant advantage in disease-specific survival (96% vs 82%).19 Immunohistochemical detection of p16, which is a marker for HPV infection, was also associated with improved outcome.[22] Whether HPV is predictive of response to treatment (eg, chemotherapy or radiation therapy) remains unknown.

MOLECULAR FEATURES

Overview of Molecular Features

The etiology of penile squamous cell carcinoma (PSCC) is multifactorial with limited information available of any familial inheritance pattern for PSCC, and a family history of PSCC is not considered a risk factor. As of today, no cancer susceptibility syndrome is definitively linked with an increased risk of PSCC.

There has only been one large long-term follow-up study among Nordic twins, which evaluated the familial and environmental influence for 23 types of cancers that included PSCC cases. In this analysis within the Nordic Twin Study of Cancer (NorTwinCan), all of the reported PSCC cases were discordant in monozygotic twins ($n = 15$ PSCC cases) and dizygotic twins ($n = 34$ cases).[23,24]

The viral oncogenesis of HPV-related PSCC is initiated by the viral E6 and E7 oncoproteins' expression in host cells, and they are known to interact with the *RB1* and *TP53* tumor suppressor pathways.[18] These molecular events are known to play a critical role in the development of cervical cancer,[25] and a similar mechanism probably exists in HPV-related cases of penile cancer.[18,26] This leads to the degradation of the tumor suppressor p53 and the binding to the tumor suppressor gene Rb causing autonomous cell proliferation followed by a malignant transformation from the precursor lesion to invasive PSCC.[27,28] HPV-associated cancers express high levels of p16(INK4A) as a response to E7 oncoprotein expression, causing enhanced expression and cellular accumulation of p16INK4a in the basal and parabasal epithelial cells of HPV-related PSCC. On the other hand, HPV-negative PSCC carcinogenesis is poorly understood but has been linked to the tumor suppressor gene p53 mutations and other tumor suppressor genes that are discussed later in more detail.

Over the past 5 years, research efforts continue to improve our understanding of three important cornerstones of the molecular landscape of PSCC:

(1) bettering our understanding of the differences in molecular pathways implicated in the development and progression of HPV-related PSCC compared with HPV-negative PSCC,[29,30] (2) assessing the genomic similarity between PSCC and other HPV-related SCCs,[31,32] and (3) the identification of potentially targetable recurrent somatic alterations that could impact clinical trial development in PSCC.[31,32]

PATTERN OF METASTASIS

Anatomy of Lymphatic Drainage

Penile cancers have a predictable pattern of local, regional, and systemic spread. The earliest route of dissemination from the penis is metastasis to the regional inguinal and iliac nodes. The lymphatics of the prepuce form a connecting network that joins with the lymphatics from the skin of the shaft. These tributaries drain into the superficial inguinal nodes. The lymphatics of the glans join the lymphatics draining the corporal bodies, and they form a collar of connecting channels at the base of the penis that also drain by way of the inguinal lymph nodes. From there, drainage is to the pelvic nodes (external iliac, internal iliac, and obturator). Multiple cross connections exist at all levels of drainage, so that penile lymphatic drainage is bilateral to both inguinal areas.[33]

Frequency of Metastases: Prognostic Factors

Tumor grade, lymphovascular invasion (LVI), and perineural invasion appear to be the most important pathologic prognostic factors for nodal spread and mortality.[34] Other frequently cited risk factors are pathological T stage it is a known staging nomenclature (pT) classification, tumor thickness, anatomical site (proximal vs distal), pathologic subtype, urethral invasion, and positive margins of resection.

LVI in the primary tumor has significant prognostic importance. Studies have assessed its presence or absence and found that it was an important predictor of nodal metastasis.[35] Perineural invasion was present in 36% of cases analyzed in a multi-institutional dataset of 134 patients and was also a strong predictor of lymph node metastasis.[36] The pathologist should specifically comment on the presence or absence of vascular invasion, tumor grade, and perineural invasion in the surgical specimen.

Distant Metastasis and Mortality

Metastatic penile cancer is characterized by a relentlessly progressive course, causing death for most of the untreated patients within less than 2 years.[37–40] Metastatic enlargement of the regional nodes eventually leads to skin necrosis, chronic infection, sepsis, hemorrhage secondary to erosion into the femoral vessels, and failure to thrive.

Clinically detectable distant metastatic lesions to the lung, liver, bone, or brain are uncommon at initial presentation.[41] Such metastases usually occur late in the course of the disease after the local lesion has been treated. Distant metastases in the absence of regional node metastases are unusual.

EVALUATION OF THE PATIENT

Staging System

The American Joint Committee on Cancer's eighth edition[42] tumor, node, metastasis (TNM) staging system for penile cancer (Table 46–2) is used for staging in the United States since 2018 and differs from the seventh edition.[43] A major difference in the current TNM staging system compared with the previous version is the presence of perineural invasion, which was added as another factor to separate pT1a disease from pT1b disease. Another difference is the nodal category of pN1, which is now defined as two or fewer unilateral inguinal metastases with no extranodal extension. Additionally, pN2 is now defined as three or more unilateral inguinal metastases or bilateral metastases.[42]

Evaluation of Palpable Lymph Nodes

Palpable inguinal lymph nodes are found at presentation in 28% to 64% of patients with penile cancer, but not all of these represent metastatic tumor. Lymphadenopathy is caused by metastasis in 47% to 85% of these cases; the rest are secondary to inflammation.[41,44,45] Approximately 25% of patients with palpable lymph nodes have bilateral metastases. Careful note should be made of the uni- or bilateral location of palpable adenopathy, diameter, number in each inguinal area, whether they are mobile or fixed, their relationship to other structures (eg, skin) with respect to infiltration or perforation, and the presence of leg or scrotal edema.[39,46] The National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) guidelines for penile cancer recommend fine-needle aspiration (FNA) of palpable inguinal lymph nodes.[39,46]

Staging Groin Dissection

Although treatment of the primary tumor and a period of antibiotics may be useful to help sterilize the inguinal region, this practice is no longer advocated as a

TABLE 46–2 Definitions of Tumor (T), Node (N), Metastasis (M)

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Ta	Noninvasive verrucous carcinoma
T1a	Tumor is without lymphovascular invasion or perineural invasion and is not high Grade (ie, grade 3 or sarcomatoid)
T1b	Tumor exhibits lymphovascular invasion and/or perineural invasion or is high grade (ie, grade 3 or sarcomatoid)
T2	Tumor invades into corpus spongiosum (either glans or ventral shaft) with or without urethral invasion
T3	Tumor invades into corpora cavernosum (including tunica albuginea) with or without urethral invasion
T4	Tumor invades into adjacent structures (ie, scrotum, prostate, pubic bone)
Regional Lymph Nodes (N)	
Clinical Stage Definition	
CNX	Regional lymph nodes cannot be assessed
cN0	No palpable or visibly enlarged inguinal lymph nodes
cN1	Palpable mobile unilateral inguinal lymph node
cN2	Palpable mobile ≥2 unilateral inguinal nodes or bilateral inguinal lymph nodes
cN3	Palpable fixed inguinal nodal mass or pelvic lymphadenopathy unilateral or bilateral
Pathologic Stage Definition	
PNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	≤2 unilateral inguinal metastases, no ENE
pN2	≥3 unilateral inguinal metastases or bilateral metastases
pN3	ENE of lymph node metastases or pelvic lymph node metastases, no ENE
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis[a]

[a]Lymph node metastasis outside the true pelvis in addition to visceral or bone sites.
ENE, Extranodal extension.
Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the *AJCC Cancer Staging System* (2020).

tool to select patients who either should or should not undergo lymphadenectomy. Patients with clinically node-negative disease, in addition to cross-sectional imaging of the abdomen, pelvis, and chest, might still receive surgical lymph node evaluation if they are in the high-risk group based on the presence of any of the following primary tumor pathological findings: (1) T2 or greater tumor,[47,48] (2) high-grade tumor,[49,50] or (3) presence of LVI or perineural invasion.[36,49] Both dynamic sentinel node biopsy and superficial or modified inguinal lymph node dissection (LND) (using either an open or minimally invasive approach (ie, laparoscopic and robotic-assisted approaches) can be used for surgical staging among patients with high-risk PSCC, whereas patients with low-risk disease can be spared and monitored with active surveillance.[51,52] Further surgical treatment for patients with high-risk disease is guided by the pathological results from the surgical staging. The reluctance to advocate automatic ilioinguinal lymphadenectomy in all patients with penile cancer stems from the substantial morbidity the procedure can produce. Postoperative complications have been reduced by improved preoperative and postoperative care and advances in surgical technique. The mortality from complete inguinal LND is rare and usually associated with septic complications.[53]

For men with evidence of palpable adenopathy upon clinical examination, baseline staging imaging using a computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomographic (PET)–CT to evaluate the extent of disease is considered standard per the European and American

guidelines. FNA for pathologic assessment can help with treatment planning because definitive surgical treatment is recommended for men with a positive FNA and no bulky, pelvic, or fixed lymphadenopathy upon imaging. In contrast, for men with low-risk disease (pTis, pTa, pT1a) with clinically suspicious adenopathy and a negative FNA result, we recommend confirmation with an excisional biopsy for definitive evaluation. For men with high-risk disease (≥T1b) with clinically suspicious adenopathy and a negative FNA result, confirmation with repeat excisional biopsy can be attempted but a superficial or modified inguinal LND with frozen section evaluation of the nodes is preferred to avoid delays. For patients with proven metastases via FNA or node biopsy, additional imaging studies, such as CT or MRI (that can show central necrosis or irregular nodal border)[44] or CT-PET scans, may be of value in predicting adverse nodal features, such as three or more positive nodes, extranodal extension, or pelvic metastases. Patients with these risk factors, those with a palpable lymph node (fixed or none fixed) larger than 4 cm inguinal, those with palpable fixed or bilateral metastatic LN that is 4 cm or smaller, and pelvic lymph node metastasis could benefit from multimodal therapy with neoadjuvant chemotherapy followed by surgical consolidation.

Computed Tomography Imaging

Patients with clinically palpable lymph nodes should undergo imaging to define the full extent of disease. MRI can be considered to evaluate tumor extent (invasion of the corpora or urethra) for patients with planned organ-sparing surgery as per the current EAU and NCCN guidelines.[54,55] Both CT and MRI scanning techniques depend primarily on lymph node enlargement for detection of metastases but are unable to define the internal architecture of normal-size nodes. Because CT and MRI have similar accuracy in detecting lymphadenopathy in other cancers, CT has often been the imaging modality chosen in penile cancer to examine the inguinal and pelvic areas as well as to rule out more distant metastases. CT scanning facilitates the examination of the inguinal region in obese patients and in those who have had prior inguinal surgery, for whom the physical examination may be unreliable. In addition, in patients with known inguinal metastases, CT-guided biopsy of enlarged pelvic nodes may provide important information for consideration of neoadjuvant chemotherapy. Otherwise, for patients with a normal inguinal examination, management recommendations should be based on the primary tumor risk factors with only intermediate- and high-risk patients requiring cross-sectional imaging.[54,55]

Positron Emission Tomography Imaging

The use of fluorodeoxyglucose (FDG) PET-CT in patients with PSCC with nonpalpable lymph nodes has been assessed by multiple studies, with the limitation of small sample size. Scher *et al*[56] examined 13 cN0 patients, and FDG PET-CT scans showed a sensitivity per lesion of 94% and 100% specificity. Leijte *et al*[57] published their effort in solely cN0 groin tumors, with 5 of 42 patients showing evidence of lymph node metastases, and PET-CT only identified 1, resulting in a sensitivity of only 20%, with 92% specificity. In 2012, a meta-analysis by Sadeghi *et al*[59] included seven studies, with the pooled sensitivity per groin for FDG PET-CT in cN0 patients reported as 56.5% (95% CI, 34.5%–76.8%). Based on this information, FDG PET-CT is not recommended to replace surgical staging for high-risk primary cancer with cN0 tumors, and surgical staging remains a necessity to identify small inguinal lymph node metastases.

TREATMENT

Local Control

Surgical amputation of the primary tumor remains the oncologic gold standard for rapid definitive treatment of the penile primary tumor; local recurrence rates range from 0% to 8%.[59] Amputation is often necessary for bulky stage T2 to T4 tumors, but it has been shown to decrease sexual quality of life.[60] It is generally accepted that patients with penile primary tumors exhibiting favorable histologic features (stages Tis, Ta, T1; grades 1 and 2 tumors) are at a lower risk for metastases. These patients are also best suited for organ-sparing or glans-sparing procedures, with the goal of preserving glans sensation where possible or at least to maximize penile shaft length. Such approaches include topical treatments (fluorouracil or imiquimod cream for Tis only), radiotherapy, Mohs surgery, limited excision strategies (eg, circumcision), and laser ablation.[61–65] MRI provides excellent soft tissue detail and can be a useful imaging strategy to assist in planning organ-sparing surgery.[66] Partial or total penectomy should be considered in patients exhibiting adverse features that defy adequate control by organ preservation strategies. These include tumors of size 4 cm or more, grade 3 lesions, and those invading deeply into the glans, urethra, or corpora cavernosa.

Therapeutic Lymph Node Dissection

The biology of penile cancer is such that it exhibits a prolonged locoregional phase before distant dissemination. Lymphadenectomy alone can be curative and should be incorporated into the treatment planning for

most patients. However, because of the morbidity of traditional lymphadenectomy, especially among those patients with clinically negative groins, contemporary controversial issues include the following: (1) the selection of patients for lymphadenectomy versus careful observation, (2) the types of procedures to correctly stage the inguinal region with low morbidity, and (3) multimodality strategies (eg, neoadjuvant chemotherapy, see further in the chapter) to improve survival among patients with bulky inguinal metastases.

The presence and the extent of metastasis to the inguinal region are the most important prognostic factors for survival in patients with SCC of the penis. The survival rates for therapeutic LND in patients with established regional lymph node metastases are variable, averaging about 60% (range, 0%–86%).[35,67] This variability in survival rates is directly attributable to the extent of nodal metastasis. Patients with pN1 or pN2 with a minimal number of lymph nodes involved have an average 5-year survival rate of 77% compared with only 25% when a greater degree of nodal involvement is present. In one study,[68] the 5-year survival rate of patients with extranodal involvement was only 6% (1 of 17 patients). The combined results of several small series suggest an average 5-year survival rate of 15% when pelvic lymph nodes are present. Taken together, these data suggest that the pathologic criteria that predict long-term survival (ie, 80% 5-year survival rate) after attempted curative surgical resection of inguinal metastases are (1) minimal nodal disease (up to two involved nodes in most series), (2) unilateral involvement, (3) no evidence of extranodal extension of cancer, and (4) absence of pelvic nodal metastases.

Chemotherapy for Stage IIIB/IV Penile Carcinoma

The first candidate drugs for the chemotherapeutic treatment of patients with stage IIIB/IV penile carcinoma included cisplatin, vincristine, methotrexate, fluorouracil, mitomycin, and bleomycin.[69] In a multicenter study conducted by the SWOG,[70] 26 patients with metastatic penile cancer received single-agent cisplatin at a dosage of 50 mg/m^2 on days 1 and 8 of each 28-day cycle. Only four patients (15%) experienced responses that persisted for 1 to 3 months.

The combination of bleomycin, methotrexate, and cisplatin (BMP) was studied in two phase II clinical trials, but the toxicity of the regimen was considerable, with multiple treatment-related deaths caused by bleomycin lung toxicity, other pulmonary causes, and infection.[71,72] The BMP regimen and bleomycin are no longer recommended for the treatment of patients with penile cancer because of the unacceptable toxicity.

Other cisplatin-based drug combinations demonstrated response rates of 8% to 50% (Table 46–3).[38,74–77] A regimen would be of interest if it has an overall response rate greater than 30% with acceptable toxicity. The study of irinotecan–cisplatin conducted by the European Organization for Research and Treatment of Cancer[74] was a prospective study with 26 evaluable patients but was interpreted as having a negative result by the authors because the response rate had an 80% confidence interval of 18.8% to 45.1%, extending well below 30%. In another study, paclitaxel, ifosfamide, and cisplatin (TIP) was given to patients with metastases limited to the inguinal and pelvic lymph nodes.[75] In this neoadjuvant study, patients with response or stable disease after four courses of TIP underwent surgery with curative intent. The response rate was 50%, and the safety profile of this regimen was a significant improvement over BMP, with no treatment-related deaths. In another study of taxane drugs for the treatment of metastatic penile cancer, docetaxel, 5-fluorouracil (5-FU), and cisplatin resulted in a response rate of 38.5%.[76] The response rate was not high enough to recommend this regimen in preference to 5-FU and cisplatin, and grade 3 and 4 toxicities were frequent.

5-FU and cisplatin were studied in a retrospective series of patients with metastatic penile cancer.[38] Partial responses had been seen in 8 of 25 evaluable patients (32%). Although there have been no randomized controlled trials to establish a single standard of chemotherapy treatment for metastatic penile cancer,

TABLE 46–3 Cisplatin-Based Chemotherapy Regimens Without Bleomycin

Reference	Regimen	Overall Response Rate (PR + CR) (%)	Median Overall Survival (Months)
Theodore et al[73] (2008)	Irinotecan Cisplatin	31	Not reported
Pagliaro et al[74] (2010)	Paclitaxel Ifosfamide Cisplatin	50[a]	17.1[a]
Di Lorenzo et al[38] (2012)	5-Fluorouracil Cisplatin	32	8
Nicholson et al[75] (2013)	Docetaxel Cisplatin 5-Fluorouracil	38.5	13.9
Houédé et al[76] (2015)	Gemcitabine Cisplatin	8	15

[a]Patients in this study had metastases confined to inguinal or pelvic lymph nodes (Tx N2–N3 M0) and underwent surgical consolidation when possible.
CR, complete response; PR, partial response.

either 5-FU plus cisplatin or paclitaxel, ifosfamide, and cisplatin have been endorsed by contemporary guidelines.[54,55]

Multimodality Therapy

Neoadjuvant Chemotherapy

As discussed in the section on therapeutic LND, the 5-year overall survival (OS) and disease-free survival (DFS) rates with surgery alone are as high as 80% for unilateral, superficial inguinal lymph node involvement with no more than two nodes (stage N1 or limited N2), only 10% to 20% for stages N2 and N3 (multiple, bilateral, or pelvic lymph node involved), and less than 10% in the presence of extranodal extension.[45,77] Nearly all recurrences are detected within 2 years of surgery, and an aggressive, multimodality approach to the treatment of high-risk patients could result in better OS.[37,74]

Neoadjuvant chemotherapy allows for timely delivery of systemic chemotherapy, results in potential volume reduction for enlarged lymphadenopathies, provides prognostic information, and facilitates subsequent surgical consolidation.[78,79] A group from the Netherlands reported on their retrospective analysis of 20 patients who had received preoperative chemotherapy to downstage unresectable disease.[80] Seventeen patients had bulky lymph node metastases (Tx, N3), and the other three had advanced primary tumors (T3–T4, N0–N1). The most commonly used regimens in the Dutch series, which spanned a 34-year period, were BMP (n = 10); bleomycin, vincristine, and methotrexate (n = 5); and single-agent bleomycin (n = 3). Severe toxicity occurred in four patients, including three treatment-related deaths. Twelve patients experienced an objective tumor response; nine of the 12 underwent surgery, and eight achieved long-term DFS. Two patients had no residual tumor in the surgical specimen. The finding of pathologic complete responses suggested that this could be used as a signal for efficacy, but the toxicity was deemed unacceptable with this specific chemotherapy regimen.

Neoadjuvant chemotherapy was next studied prospectively in a phase II clinical trial conducted at MD Anderson Cancer Center.[75] Thirty patients with clinical TX N2 to N3, M0 penile cancer received four courses of paclitaxel, ifosfamide, and cisplatin before a planned complete bilateral inguinal LND and uni- or bilateral pelvic LND. Fifteen patients (50%) experienced a partial or complete response to chemotherapy. Twenty-two patients (73%) were able to complete the neoadjuvant chemotherapy and surgery, of whom there were three patients (14%) with a pathologic complete response in the lymph nodes. Objective response to chemotherapy, absence of bilateral residual tumor, and absence of extranodal extension in residual tumor were associated with a higher rate of overall and progression-free survival (PFS) in a univariable analysis. The overall and PFS rates in N2 to N3 disease achieved with neoadjuvant paclitaxel, ifosfamide, and cisplatin are considered an improvement over the expected survival with surgery alone. Despite the absence of a randomized controlled trial, contemporary guidelines recommend neoadjuvant paclitaxel, ifosfamide, and cisplatin for patients presenting with bulky or high-risk regional lymph node metastases.[54,55]

Adjuvant Chemotherapy

Adjuvant chemotherapy has the advantage of allowing patient selection based on accurate pathologic staging. The development of neoadjuvant chemotherapy as standard treatment appears to be more achievable and has advantages of downstaging to facilitate surgery, better tolerance of chemotherapy in the preoperative setting, and earlier exposure of micrometastases to the chemotherapy agents. Tumor response can be detected in the neoadjuvant setting, but not in the adjuvant setting, and the histopathologic findings of postchemotherapy surgery provide an early indicator of the treatment effect and prognosis.[81] When patients have undergone surgery without neoadjuvant chemotherapy and are found to have multiple inguinal or any pelvic lymph nodes involved or extranodal extension, then a regimen such as paclitaxel, ifosfamide, and cisplatin can be administered as adjuvant therapy on the basis of extrapolation from the neoadjuvant data.[74]

Prospective data on adjuvant chemotherapy are not available, and only small retrospective studies have been reported. Recently, a large multicenter retrospective study assessed 141 patients with advanced pathological pelvic lymph node involvement and demonstrated a median OS improvement with the use of adjuvant chemotherapy.[82] This study showed a potential benefit of adjuvant chemotherapy use for patients with pelvic lymphadenopathy who did not receive neoadjuvant chemotherapy. This study has the inherent limitations of a retrospective study and incomplete information on the specific chemotherapy combinations used. Further prospective evaluation of adjuvant systemic chemotherapy in the management of locally advanced PSCC remains unavailable to define its specific role and benefit. The NCCN guidelines recommend using adjuvant chemotherapy if neoadjuvant chemotherapy was not given, with level 2A evidence, for patients with high pathological risk features (pathological N2, N3, or ECE).

Radiotherapy Combined with Surgery or Chemotherapy

Studies of radiotherapy in penile carcinoma have included penis-sparing treatment for small (T1–T2,

<4 cm) primary tumors, treatment of lymph node metastases, postoperative radiotherapy, and chemoradiotherapy. There are no published randomized trials of multimodality treatment with radiotherapy in penile cancer as there are in SCCs from other sites. For example, radiotherapy with surgical lymphadenectomy has been studied in women with cancer of the vulva, a disease site that has natural history and nodal drainage like those of the penis. Based on these studies, the standard of care for metastatic vulvar cancer is radiotherapy to the pelvis rather than pelvic LND.[83] The EAU penile cancer guideline group recently conducted a systematic review of the evidence and concluded that because of the heterogeneous and limited evidence showing clinical benefit, a routine recommendation of adjuvant radiotherapy is not yet warranted.[84] Pelvic LND remains the standard of care for penile cancer patients after definitive treatment of inguinal lymph node metastases.[39] Thus, a randomized trial in penile cancer would be informative concerning the optimal method for consolidation of pelvic lymph nodes.

International Randomized Trial

It has not been possible to conduct randomized controlled trials in penile cancer to answer basic questions. The International Penile Advanced Cancer Trial (InPACT) uses a Bayesian design for randomized treatment of patients with inguinal lymph node metastases from penile cancer. The trial has two independent randomizations, addressing key questions in the clinical pathway: (1) the role of neoadjuvant therapy prior to standard surgery, by randomizing to chemotherapy, chemoradiotherapy, or no neoadjuvant therapy, and (2), the role of prophylactic pelvic lymph node dissection after the standard surgery with therapeutic inguinal LND.[85] The primary outcome measure of the InPACT study is OS.[85]

CONCLUSION

The treatment of men with SCC of the penis has evolved considerably in recent years, along with our understanding of its molecular biology. Penis-sparing strategies for early-stage disease allow for better outcomes in terms of quality of life. Inguinal staging strategies to define microscopic inguinal metastases (including minimally invasive techniques) while decreasing morbidity continue to evolve. Neoadjuvant chemotherapy is now standard of care for patients presenting with bulky regional lymph nodes. An ambitious international randomized trial (InPACT) proposes to compare neoadjuvant and adjuvant as well as surgical and radiotherapeutic strategies in this clinical setting. Meanwhile, vaccination of both men and women against HPV offers to reduce the risk of cancer, particularly for uncircumcised men, who are already at increased risk. Viral antigens are a promising target for the immunotherapeutic treatment of patients with penile cancer and suggest a possible role in this disease for drugs that exert immune checkpoint blockade.[86]

MD ANDERSON PRACTICE TIPS

- We perform HPV/p16 testing among patients with penile cancer routinely because it can have prognostic value, information for counseling spouses and can provide further clinical trials options using HPV-directed novel therapies.
- We routinely perform penile-preserving strategies when appropriate to maximize penile length, function, and cosmetic appearance.
- We encourage patients with clinically evident lymph node metastases to enroll in the InPACT, a multicenter trial that aims to establish the standard of care for treatment of patients with penile cancer exhibiting regional metastases.
- We encourage genomic testing in patients with bulky advanced disease to identify potential therapy targets for enrollment of immune or targeted therapy trials.

REFERENCES

1. Nardi AC, Heyns CF, Pompeo A, eds. *Penile Cancer: Epidemiology and Natural History of Penile Cancer.* Montreal, Canada: Société Internationale d'Urologie (SIU); 2009:1-14.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018;68(1):7-30.
3. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424.
4. Arya M, Li R, Pegler K, et al. Long-term trends in incidence, survival and mortality of primary penile cancer in England. *Cancer Causes Control*. 2013;24(12):2169-2176.
5. Hansen BT, Orumaa M, Lie AK, et al. Trends in incidence, mortality and survival of penile squamous cell carcinoma in Norway 1956–2015. *Int J Cancer*. 2018;142(8):1586-1593.
6. Bermejo C, Busby JE, Spiess PE, et al. Neoadjuvant chemotherapy followed by aggressive surgical consolidation for metastatic penile squamous cell carcinoma. *J Urol*. 2007;177(4):1335-1338.
7. Alemany L, Cubilla A, Halec G, et al. Role of human papillomavirus in penile carcinomas worldwide. *Eur Urol*. 2016;69(5):953-961.
8. Holly EA, Palefsky JM. Factors related to risk of penile cancer: new evidence from a study in the Pacific Northwest. *J Natl Cancer Inst*. 1993;85(1):2-4.
9. Harish K, Ravi R. The role of tobacco in penile carcinoma. *Br J Urol*. 1995;75(3):375-377.
10. Dillner J, Von Krogh G, Horenblas S, Meijer CJLM. Etiology of squamous cell carcinoma of the penis. *Scand J Urol Nephrol*. 2000;34(suppl):189-193.
11. Daling JR, Madeleine MM, Johnson LG, et al. Penile cancer: importance of circumcision, human papillomavirus and smoking in in situ and invasive disease. *Int J Cancer*. 2005;116(4):606-616.
12. Miralles-Guri C, Bruni L, Cubilla AL, et al. Human papillomavirus prevalence and type distribution in penile carcinoma. *J Clin Pathol*. 2009;62(10):870-878.
13. Maden C, Sherman KJ, Beckmann AM, et al. History of circumcision, medical conditions, and sexual activity and risk of penile cancer. *J Natl Cancer Inst*. 1993;85(1):19-24.
14. Larke NL, Thomas SL, Dos Santos Silva I, Weiss HA. Male circumcision and penile cancer: a systematic review and meta-analysis. *Cancer Causes Control*. 2011;22(8):1097-1110.
15. Reddy CR, Devendranath V, Pratap S. Carcinoma of penis—role of phimosis. *Urology*. 1984;24(1):85-88.
16. Minhas S, Penile cancer: prevention and premalignant conditions. In Pompeo ACL, Heyns CF, Abrams P, eds. *Penile Cancer*. Internationale d'Urologie; 2009.
17. Olesen TB, Sand FL, Rasmussen CL, et al. Prevalence of human papillomavirus DNA and p16 INK4a in penile cancer and penile intraepithelial neoplasia: a systematic review and meta-analysis. *Lancet Oncol*. 2019;20(1):145-158.
18. Flaherty A, Kim T, Giuliano A, et al. Implications for human papillomavirus in penile cancer. *Urol Oncol Semin Orig Investig*. 2014;32(1):53.e1-53.e8.
19. Djajadiningrat RS, Jordanova ES, Kroon BK, et al. Human papillomavirus prevalence in invasive penile cancer and association with clinical outcome. *J Urol*. 2015;193(2):526-531.
20. Bleeker MC, Heideman DAM, Snijders PJF, et al. Penile cancer: epidemiology, pathogenesis and prevention. *World J Urol*. 2009;27(2):141-150.
21. Cubilla AL, Lloveras B, Alejo M, et al. Value of p16INK4a in the pathology of invasive penile squamous cell carcinomas. *Am J Surg Pathol*. 2011;35(2):253-261.
22. Gunia S, Erbersdobler A, Hakenberg OW, et al. p16 ^{INK4a} is a marker of good prognosis for primary invasive penile squamous cell carcinoma: a multi-institutional study. *J Urol*. 2012;187(3):899-907.
23. Chahoud J, Pickering CR, Pettaway CA. Genetics and penile cancer: recent developments and implications. *Curr Opin Urol*. 2019;29(4):364-370.
24. Mucci LA, Hjelmborg JB, Harris JR, et al. Familial risk and heritability of cancer among twins in Nordic countries. *JAMA*. 2016;315(1):68-76.
25. Schiffman M, Wentzensen N. Human papillomavirus infection and the multistage carcinogenesis of cervical cancer. *Cancer Epidemiol Biomarkers Prev*. 2013;22(4):553-560.
26. Chaux A, Cubilla AL. The role of human papillomavirus infection in the pathogenesis of penile squamous cell carcinomas. *Semin Diagn Pathol*. 2012;29(2):67-71.
27. Chellappan S, Kraus VB, Kroger B, et al. Adeno virus E1A, simian virus 40 tumor antigen, and human papillomavirus E7 protein share the capacity to disrupt the interaction between transcription factor E2F and the retinoblastoma gene product. *Proc Natl Acad Sci U S A*. 1992;89(10):4549-4553.
28. Lipinski MM, Jacks T. The retinoblastoma gene family in differentiation and development. *Oncogene*. 1999;18(55):7873-7882.
29. Busso-Lopes AF, Marchi FA, Kuasne H, et al. Genomic profiling of human penile carcinoma predicts worse prognosis and survival. *Cancer Prev Res*. 2015;8(2):149-156.
30. Feber A, Worth DC, Chakravarthy A, et al. CSN1 somatic mutations in penile squamous cell carcinoma. *Cancer Res*. 2016;76(16):4720-4727.
31. Chahoud J, McCormick BZ, Netto F, et al. Penile squamous cell carcinoma is genomically similar to other HPV-driven tumors. *J Clin Oncol*. 2019;37(7 suppl):505-505.
32 Jacob JM, Ferry EK, Gay LM, et al. Comparative genomic profiling of refractory and metastatic penile and nonpenile cutaneous squamous cell carcinoma: implications for selection of systemic therapy. *J Urol*. 2019;201(3):541-548.
33 Cabanas RM. Anatomy and biopsy of sentinel lymph nodes. *Urol Clin North Am*. 1992;19(2):267-276.
34 Cubilla AL. The role of pathologic prognostic factors in squamous cell carcinoma of the penis. *World J Urol*. 2009;27(2):169-177.
35 Heyns CF. Management of the lymph nodes in penile cancer. In: Pompeo ACL, Heyns CF, Abrams P, eds. *Penile Cancer*. Société Internationale d'Urologie; 2009.
36 Velazquez EF, Ayala G, Liu H, et al. Histologic grade and perineural invasion are more important than tumor thickness as predictor of nodal metastasis in penile squamous cell carcinoma invading 5 to 10 mm. *Am J Surg Pathol*. 2008;32(7):974-979.
37 Pettaway CA, Pagliaro L, Theodore C, Haas G. Treatment of visceral, unresectable, or bulky/unresectable regional metastases of penile cancer. *Urology*. 2010;76(2):S58-S65.
38 Di Lorenzo G, Buonerba C, Federico P, et al. Cisplatin and 5-fluorouracil in inoperable, stage IV squamous cell carcinoma of the penis. *BJU Int*. 2012;110(11b):E661-E666.
39 Hakenberg OW, Compérat EM, Minhas S, et al. EAU guidelines on penile cancer: 2014 update. *Eur Urol*. 2015;67(1):142-150.
40 Clark PE, Spiess PE, Agarwal N, et al. Penile cancer: clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2013;11(5):594-615.
41 Heyns CF, Mendoza-Valds A, Pompeo ACL. Diagnosis and staging of penile cancer. *Urology*. 2010;76(2 suppl 1):S15-S23.
42 Pettaway CA, Srigley JR, Brookland RK et al. Penis cancer. In: *AJCC Cancer Staging Manual*. 8th edition. Springer; 2017:701-715.
43 Paner GP, Stadler WM, Hansel DE, et al. Updates in the eighth edition of the tumor-node-metastasis staging classification for urologic cancers. *Eur Urol*. 2018;73(4):560-569.
44 Graafland NM, Teertstra HJ, Besnard AP, et al. Identification of high risk pathological node positive penile carcinoma: value of preoperative computerized tomography imaging. *J Urol*. 2011;185(3):881-887.

45 Djajadiningrat RS, Graafland NM, Van Werkhoven E, et al. Contemporary management of regional nodes in penile cancer—improvement of survival? *J Urol*. 2014;191(1):68-73.
46 Spiess PE, Horenblas S, Pagliaro LC, et al. Current concepts in penile cancer. *J Natl Compr Canc Netw*. 2013;11(5):617-624.
47 Solsona E, Iborra I, Ricos J V., et al. Corpus cavernosum invasion and tumor grade in the prediction of lymph node condition in penile carcinoma. *Eur Urol*. 1992;22(2):115-118.
48 Hall MC, Sanders JS, Vuitch F, et al. Deoxyribonucleic acid flow cytometry and traditional pathologic variables in invasive penile carcinoma: assessment of prognostic significance. *Urology*. 1998;52(1):111-116.
49 Ficarra V, Akduman B, Bouchot O, et al. Prognostic factors in penile cancer. *Urology*. 2010;76(2 Suppl 1):S66-73.
50 Ornellas AA, Kinchin EW, Nóbrega BLB, et al. Surgical treatment of invasive squamous cell carcinoma of the penis: Brazilian National Cancer Institute long-term experience. *J Surg Oncol*. 2008;97(6):487-495.
51. Horenblas S, Jansen L, Meinhardt W, et al. Detection of occult metastasis in squamous cell carcinoma of the penis using a dynamic sentinel node procedure. *J Urol*. 2000;163(1):100-104.
52. Master VA, Jafri SM, Moses KA, et al. Minimally invasive inguinal lymphadenectomy via endoscopic groin dissection: comprehensive assessment of immediate and long-term complications. *J Urol*. 2012;188(4):1176-1180.
53. Bevan-Thomas R, Slaton JW, Pettaway CA. Contemporary morbidity from lymphadenectomy for penile squamous cell carcinoma: the M.D Anderson Cancer Center experience. *J Urol*. 2002;167(4):1638-1642.
54. Hakenberg OW, Compérat E, Minhas S, et al. EAU guidelines: penile cancer. https://uroweb.org/guideline/penile-cancer
55. National Comprehensive Cancer Network. *Penile Cancer*. National Comprehensive Cancer Network; 2018.
56. Scher B, Seitz M, Reiser M, et al. 18F-FDG PET/CT for staging of penile cancer. *J Nucl Med*. 2005;46(9):1460-1465.
57. Leijte JAP, Graafland NM, Valdés Olmos RA, et al. Prospective evaluation of hybrid 18F-fluorodeoxyglucose positron emission tomography/computed tomography in staging clinically node-negative patients with penile carcinoma. *BJU Int*. 2009;104(5):640-644.
58. McDougal WS, Kirchner FK Jr, Edwards RH, Killion LT. Treatment of carcinoma of the penis: the case for primary lymphadenectomy. *J Urol*. 1986;136(1):38-41.
59. Sadeghi R, Gholami H, Zakavi SR, Kakhki VRD, Horenblas S. Accuracy of 18F-FDG PET/CT for diagnosing inguinal lymph node involvement in penile squamous cell carcinoma: systematic review and meta-analysis of the literature. Clin Nucl Med. 2012;37(5):436-441.
60. Opjordsmoen S, Fosså SD. Quality of life in patients treated for penile cancer. A follow-up study. *Br J Urol*. 1994;74(5):652-657.
61. Mohs FE, Snow LPO. Mohs micrographic surgery for penile tumors. *Urol Clin North Am*. 1992;19(2):291-304.
62. Minhas S, Kayes O, Hegarty P, et al. What surgical resection margins are required to achieve oncological control in men with primary penile cancer? *BJU Int*. 2005;96(7):1040-1043.
63. Windahl T, Skeppner E, Andersson SO, Fugl-Meyer KS. Sexual function and satisfaction in men after laser treatment for penile carcinoma. *J Urol*. 2004;172(2):648-651.
64. Alnajjar HM, Shabbir M, Watkin N. Penile-sparing approaches to primary penile tumours. In: *Penile Cancer: Diagnosis and Treatment*. Springer; 2013.
65. Crook J, Ma C, Grimard L. Radiation therapy in the management of the primary penile tumor: an update. *World J Urol*. 2009;27(2):189-196.
66. Krishna S, Shanbhogue K, Schieda N, et al. Role of MRI in staging of penile cancer. *J Magn Reson Imaging*. 2020;51(6):1612-1629.
67. Fraley EE, Zhang G, Manivel C, Niehans GA. The role of ilioinguinal lymphadenectomy and significance of histological differentiation in treatment of carcinoma of the penis. *J Urol*. 1989;142(6):1478-1482.
68. Ravi R. Correlation between the extent of nodal involvement and survival following groin dissection for carcinoma of the penis. *Br J Urol*. 1993;72(5):817-819.
69. Pagliaro LC, Crook J. Multimodality therapy in penile cancer: when and which treatments? *World J Urol*. 2009;27(2):221-225.
70. Gagliano RG, Blumenstein BA, Crawford ED, et al. cis-Diamminedichloroplatinum in the treatment of advanced epidermoid carcinoma of the penis: a Southwest Oncology Group Study. *J Urol*. 1989;141(1):66-67.
71. Corral DA, Sella A, Pettaway CA, et al. Combination chemotherapy for metastatic or locally advanced genitourinary squamous cell carcinoma: a phase II study of methotrexate, cisplatin and bleomycin. *J Urol*. 1998;160(5):1770-1774.
72. Haas GP, Blumenstein BA, Gagliano RG, et al. Cisplatin, methotrexate and bleomycin for the treatment of carcinoma of the penis: a Southwest Oncology Group study. *J Urol*. 1999;161(6):1823-1825.
73. Theodore C, Skoneczna I, Bodrogi I, et al. A phase II multicentre study of irinotecan (CPT 11) in combination with cisplatin (CDDP) in metastatic or locally advanced penile carcinoma (EORTC PROTOCOL 30992). *Ann Oncol*. 2008;19(7):1304-1307.
74. Pagliaro LC, Williams DL, Daliani D, et al. Neoadjuvant paclitaxel, ifosfamide, and cisplatin chemotherapy for metastatic penile cancer: a phase II study. *J Clin Oncol*. 2010;28(24):3851-3857.
75. Nicholson S, Hall E, Harland SJ, et al. Phase II trial of docetaxel, cisplatin and 5FU chemotherapy in locally advanced and metastatic penis cancer (CRUK/09/001). *Br J Cancer*. 2013;109(10):2554-2559.
76. Houédé N, Dupuy L, Fléchon A, Intermediate analysis of a phase II trial assessing gemcitabine and cisplatin in locoregional or metastatic penile squamous cell carcinoma. *BJU Int*. 2015;20.
77. Zhu Y, Ye DW, Yao XD, et al. New N staging system of penile cancer provides a better reflection of prognosis. *J Urol*. 2011;186(2):518-523.
78. Protzel C, Hakenberg OW. Chemotherapy in penile cancer. *Textb Penile Cancer*. 2017:235-243.
79. Necchi A. Systemic therapy for penile cancer. *Eur Urol Suppl*. 2018;17(6):160-163.
80. Leijte JA, Kerst JM, Bais E, et al. Neoadjuvant chemotherapy in advanced penile carcinoma. *Eur Urol*. 2007;52(2):488-494.
81. Dickstein RJ, Munsell MF, Pagliaro LC, Pettaway CA. Prognostic factors influencing survival from regionally advanced squamous cell carcinoma of the penis after preoperative chemotherapy. *BJU Int*. 2016;117(1):118-125.
82. Sharma P, Djajadiningrat R, Zargar-Shoshtari K, et al. Adjuvant chemotherapy is associated with improved overall survival in pelvic node–positive penile cancer after lymph node dissection: a multi-institutional study. *Urol Oncol Semin Orig Investig*. 2015;33(11):496.e17-496.e23.
83. Kunos C, Simpkins F, Gibbons H, et al. Radiation therapy compared with pelvic node resection for node-positive vulvar cancer: a randomized controlled trial. *Obstet Gynecol*. 2009;114(3):537-546.
84. Robinson R, Marconi L, MacPepple E, et al. Risks and benefits of adjuvant radiotherapy after inguinal lymphadenectomy in node-positive penile cancer: a systematic review by the European Association of Urology Penile Cancer Guidelines Panel. *Eur Urol*. 2018;74(1):76-83.
85. Canter DJ, Nicholson S, Watkin N, et al. The International Penile Advanced Cancer Trial (InPACT): rationale and current status. *Eur Urol Focus*. 2019;5(5):706-709.
86. Huang T, Cheng X, Chahoud J, et al. Effective combinatorial immunotherapy for penile squamous cell carcinoma. *Nat Commun*. 2020;11(1):2124.

47 Germ Cell Tumors

Joseph A. Moore
Shi-Ming Tu

KEY CONCEPTS

- Germ cell tumors (GCTs) are the most common new cancer diagnosis in young men and are divided into two types, seminoma and nonseminoma germ cell tumors (NSGCTs).
- In a young man without obvious testicular primary or unknown primary tumor, serum tumor markers, specifically human chorionic gonadotropinβ-, α-fetoprotein (AFP), and cytogenetic study, namely i(12p), have unique diagnostic and prognostic significance in GCTs.
- GCTs follow a distinct pattern of spread and metastasis—the right testicle drains to the interaortocaval lymph nodes, and the left testicle drains to the left paraaortic lymph nodes.
- Approximately half of testicular GCTs show histologic elements other than seminoma or produce serum elevation of AFP indicating nonseminoma. These cancers are collectively known as mixed NSGCTs, and they form a group of histologically and clinically diverse cancers.
- Optimal management of patients with high-risk or mixed NSGCTs requires a multidisciplinary approach, integrating chemotherapy and surgery, to achieve the highest cure rates.
- Patients who pose a unique diagnostic or therapeutic challenge should be considered for early referral to a large tertiary care center.

Testicular germ cell tumors (GCTs) account for the majority of testicular cancers and are highly curable. This chapter primarily discusses GCTs arising in the testicle, dividing this category into seminoma versus nonseminoma germ cell tumors (NSGCTs). In addition, the rare entity of extragonadal GCTs, which can arise in the mediastinum, retroperitoneum, or pineal body, is described.

OVERVIEW OF GERM CELL TUMORS

Epidemiology

The GCTs are the most common new cancer diagnosis in young men. Approximately 9600 new cases were expected to be diagnosed in 2020.[1] Highlighting the high curability of this cancer, GCTs only claimed approximately 440 lives in 2020 and carry a 5-year overall survival (OS) rate of approximately 95%.[1–3] The GCTs have a bimodal age distribution, with most men diagnosed between ages 15 and 25 years. There is a second peak of diagnosis around age 60 years, which largely represents seminoma histology and a lower mortality risk. Lifetime risk for the development of GCTs is approximately 0.5% or 1 in 200.[4]

Worldwide, GCTs are six times more common in developed countries, with the largest incidence reported in Denmark and Switzerland and the lowest in Japan, Finland, and Israel.[4] In the United States, the overall incidence of GCTs appears to be gradually increasing. The incidence has specifically increased among African Americans, with the greatest increase in seminoma histology. This does not appear to be related to screening or earlier diagnosis.[5] White men, although still representing the group most likely to be diagnosed, are more likely to be identified at an earlier stage than in the past.[6]

Risk Factors

Cryptorchidism is one of the few identifiable risk factors for the development of GCTs, representing at most about 10% of cases. When present, cryptorchidism imparts a relative risk between 3.5 and 17.1.[7] This increased risk includes the contralateral testicle, even if descended normally or via orchiopexy. It is unclear if

orchiopexy reduces the lifetime risk of GCTs, although data showing increased incidence even in the contralateral testicle support the theory that the etiology of GCTs lies in abnormal gonadal development rather than anatomic malposition.[8–10] Men with a prior history of GCTs also have an increased risk of GCTs in the contralateral testicle, suggesting a genetic predisposition, although men with a family history of GCTs account for only 1.5% of patients with new diagnosis.[11,12] A personal history of GCT carries an increased lifetime risk of secondary cancers, irrespective of histologic type.[13]

Tumor Biology

The most common genetic abnormality found in GCTs is an isochromosome of the short arm of chromosome 12, which has been identified in approximately 80% of GCTs and is pathognomonic.[14,15] This abnormality can be found in all histologic subtypes except spermatocytic seminoma.[16,17] Molecular characterization of 137 primary testicular GCTs demonstrated high aneuploidy, but somatic mutations are uncommon.[18] The most frequently mutated GCT gene is *KIT*, in which activating mutations are observed in 25% to 30% of seminomas, forming a distinct subtype of seminoma.[18–21] Significant differences in global DNA methylation and microRNA expression between GCT subtypes point to a likely role of epigenetic processes influencing final GCT histology.[18]

Germ cell neoplasia in situ (GCNIS), previously called intratubular germ cell neoplasia, has been identified as the precursor lesion in most GCTs. It is histologically described as atypical germ cells in the seminiferous tubules and is thought to arise from incompletely differentiated primordial germ cells. Such changes are found adjacent to most invasive GCTs, with the notable exception of spermatocytic seminoma.[22] The GCNIS cells express several proto-oncogenic proteins that play a role in tumorigenesis, including the receptor tyrosine kinase CD-117 or *c-kit*, a protein normally involved in germ cell migration and early differentiation.[23,24]

Histologic Classification

GCTs are divided into two types, seminoma and NSGCT, and each represents approximately 50% of all GCTs. Those that show exclusively seminoma histology constitute pure seminomas, and those containing any other histologic pattern are classified as NSGCTs, even if the dominant histologic pattern is seminoma. Thus, the term *seminoma* is used in two very different ways: as a histologic pattern and as a main subdivision of GCTs. NSGCTs can be divided into four main subtypes: embryonal carcinoma, yolk sac tumor, choriocarcinoma, and teratoma. The last can be further classified as mature, immature, or teratoma with malignant transformation. It is common to see more than one histologic subtype within a tumor, and these tumors are termed "mixed GCTs." The biology and clinical expression are dominated by the nonseminoma component, and thus the presence of any histologic component other than seminoma places the tumor in the category of NSGCT. Importantly, the clinical course can be largely inferred from the histology.

Clinical Presentation

Most patients with GCTs present with painless testicular swelling or a nodule. In some cases, testicular swelling can be accompanied by pain secondary to bleeding or infarction within the tumor. In the presence of pain or a history of injury, an appropriate differential diagnosis would include testicular torsion, epididymitis, orchitis, hydrocele, spermatocele, and hematoma. *It is extremely important that regardless of pain or other associated symptoms, all scrotal masses should be approached as if they were malignant*. In patients who present with gynecomastia, especially bilateral, GCTs should be considered.[25] Other symptoms can include fever, weight loss, lumbar back pain, cough, and hemoptysis (most often seen in patients presenting with high-volume disease).

Diagnosis

The importance of prompt diagnosis and treatment cannot be stressed enough because the extent of disease at presentation predicts overall prognosis. Awareness of GCT prevalence among young men is important for both general practitioners and the general public. Radiographic evaluation of a suspected primary should include high-resolution, transscrotal ultrasonography with color Doppler of both testicles, and any suspicious lesion should be definitively evaluated with radical orchiectomy.

Transscrotal biopsy is contraindicated in the diagnostic workup of a suspected testicular neoplasm because this procedure can disrupt regional lymphatics, potentially altering the otherwise-predictable nodal spread. Because the diagnosis of GCTs is rarely in question, the preferred diagnostic and therapeutic procedure for a testicular mass is radical inguinal orchiectomy. If a tissue diagnosis is believed to be necessary before orchiectomy, an open biopsy should be performed via an inguinal incision to allow for proper examination and tissue sampling with minimal risk of inguinal or scrotal contamination.

Serum Tumor Markers

Serum markers, specifically human chorionic gonadotropin (β-hCG), α-fetoprotein (AFP), and lactate dehydrogenase (LDH), have unique diagnostic and

prognostic significance in GCTs. These serum markers assist the clinician with diagnosis of GCTs, staging the patient and determining the optimal treatment based on risk stratification, assessing response to treatment, and monitoring surveillance.

Elevated in pregnancy, β-hCG is not normally detectable in males except in the setting of GCTs. It is the most commonly elevated tumor marker in testicular cancer. With a half-life of 18 to 36 hours, hCG can also be markedly elevated in gestational trophoblastic disease and occasionally in epithelial cancers.[26] It is composed of two subunits, α and β, which exist in multiple isoforms. The α subunit has sequence similarity to the α subunit of thyroid-stimulating hormone (TSH), follicle-stimulating hormone, and luteinizing hormone, which leads to "cross talk" between these hormones and hCG. For this reason, hCG assays measure the β subunit. This "cross talk" can be clinically significant in high-volume disease accompanied by high levels of hCG, where hCG causes hyperthyroidism by binding to the TSH receptor. *Extreme elevation of hCG in male patients should be considered pathognomonic for GCTs and, in selected cases of threatening disease, justifies initiation of therapy even before tissue confirmation.*

Normally produced by the fetal yolk sac, AFP also exists in multiple isoforms. It is elevated in GCT cells derived from the embryological yolk sac, including yolk sac tumor and embryonal carcinoma. AFP elevation is also found in other gastrointestinal (GI) malignancies, particularly hepatocellular carcinoma, as well as in conditions causing liver damage (cirrhosis, hepatitis, and so on). The serum half-life of AFP is approximately 5 to 7 days.[27] By definition, pure seminomas do not produce AFP, and in the setting of GCT, an elevated AFP implies a nonseminomatous histology.[28]

LDH is neither cancer specific nor germ cell specific. LDH concentrations are elevated in 40% to 60% of men with GCTs.[29] Of the LDH isoforms, LDH-1 is most specific for GCTs; however, there is no established routine use for the fractionation of LDH and precise measurement of LDH-1. Total LDH can be used to estimate the prognosis in advanced NSGCT at the time of diagnosis or to detect recurrent disease.[30]

Anatomic Progression

The GCTs follow a distinct pattern of spread and metastasis. The lymphatic drainage from the testicle reflects embryologic origin, and thus the right testicle drains to the interaortocaval lymph nodes, and the left testicle drains to the left paraaortic lymph nodes. These initial nodes of spread are termed the "landing zone." Epididymal lymphatics drain via the external iliac chain and scrotal lymphatics via the pelvic chain; therefore, locally advanced disease (involving the epididymis and scrotum) can present with involvement of these nodal basins. Distant metastasis involves the lungs principally followed by the liver, brain, and bones.

STAGING

Table 47–1 shows the American Joint Commission on Cancer (AJCC) TNM staging of testicular cancer.[31] This system uses primary tumor (T), lymph nodes (N), distant metastases (M), as well as elevated serum tumor markers (S) to categorize patients into prognostic stage groups I to III. It is important to note that for the purposes of staging, postorchiectomy serum tumor markers are used. In general, stage I disease is confined to the testis, stage II disease has nodal metastases confined to the retroperitoneum with markers in the good-prognosis range (S1), and stage III disease includes nodes that extend beyond the retroperitoneum, extranodal metastases, or elevation of tumor markers in the intermediate- or poor-prognosis range (S2–S3).

Fertility Considerations

The preservation of fertility is of particular importance to men with GCTs. Both the diagnosis and treatment of GCTs are associated with impaired fertility. It is recommended that if clinically feasible, the patient be counseled about and offered the opportunity to pursue sperm banking before starting chemotherapy. It is not recommended to delay chemotherapy in symptomatic poor-risk patients because poor physical condition often makes sperm donation difficult or even impossible.[32]

TESTICULAR SEMINOMA

Histology

Under microscopic visualization, classic seminoma has a "fried-egg" appearance, defined as a monotonous proliferation of large, rounded cells arranged in sheets or cords with large, centralized nuclei and nucleoli. These tumors can be difficult to distinguish from lymphoma if there is a background of lymphocytic infiltration. Further confirmation (ie, negativity for lymphocyte markers such as common leukocyte antigen) is often required. Although not specific, seminomas stain positive for placental alkaline phosphatase (PLAP) and are routinely negative for AFP and hCG. Figure 47–1 shows the histological appearance of classic seminoma.

On pathologic examination of the testis, seminoma tends to be a semisolid tumor that readily oozes onto the gross examination table. This

TABLE 47–1 Germ Cell Tumor: The American Joint Commission on Cancer Tumor, Node, Metastasis (TNM) Staging Classification of Testis Cancer

Pathological Primary Tumor (T)	
The extent of primary tumor is usually classified after radical orchiectomy, so a pathologic stage is assigned.	
pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor (eg, histologic scar in testis)
pTis	Germ cell neoplasia in situ
pT1	Tumor limited to testis (including rete testis invasion) without lymphovascular invasion
pT2	Tumor limited to the testis (including rete testis invasion) with lymphovascular invasion or Tumor invading hilar soft tissue or epididymis or penetrating visceral mesothelial layer covering the external surface of the tunica albuginea with or without lymphovascular invasion
pT3	Tumor invades spermatic cord soft tissue with or without lymphovascular invasion
pT4	Tumor invades scrotum with or without lymphovascular invasion
Clinical Regional Lymph Nodes (cN)	
cNX	Regional lymph nodes cannot be assessed
cN0	No regional lymph node metastasis
cN1	Metastasis with a lymph node mass ≤2 cm in greatest dimension or multiple lymph nodes, with none >2 cm in greatest dimension
cN2	Metastasis with a lymph node mass >2 cm but not >5 cm in greatest dimension or multiple lymph nodes, with any one mass >2 cm but not >5 cm in greatest dimension
cN3	Metastasis with a lymph node mass >5 cm in greatest dimension
Pathological Regional Lymph Nodes (pN)	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass ≤2 cm in greatest dimension and ≤5 nodes positive, with none >2 cm in greatest dimension
pN2	Metastasis with a lymph node mass >2 cm but not >5 cm in greatest dimension; >5 nodes positive, with none >5 cm; or evidence of extranodal extension of tumor
pN3	Metastasis with a lymph node mass >5 cm in greatest dimension
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonretroperitoneal nodal or pulmonary metastasis
M1b	Nonpulmonary visceral metastases
Serum Tumor Markers (S)	
SX	Marker studies not available or not performed
S0	Marker study levels within normal limits
S1	LDH <1.5 × ULN and
	hCG <5000 mIU/mL and
	AFP <1000 ng/mL

(*Continued*)

TABLE 47–1 Germ Cell Tumor: The American Joint Commission on Cancer Tumor, Node, Metastasis (TNM) Staging Classification of Testis Cancer (*Cont.*)

S2	LDH >1.5–10 × ULN or			
	hCG 5000–50,000 mIU/mL or			
	AFP 1000–10,000 ng/mL			
S3	LDH >10 × ULN or			
	hCG >50,000 mIU/mL or			
	AFP >10,000 ng/mL			
Stage Grouping				
Stage 0	pTis	N0	M0	S0
Stage I	pT1–pT4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
Stage IS	Any pT/TX	N0	M0	S1–S3
Stage II	Any pT/TX	N1–N3	M0	SX
Stage IIA	Any pT/TX	N1	M0	S0
	Any pT/TX	N1	M0	S1
Stage IIB	Any pT/TX	N2	M0	S0
	Any pT/TX	N2	M0	S1
Stage IIC	Any pT/TX	N3	M0	S0
	Any pT/TX	N3	M0	S1
Stage III	Any pT/TX	Any N	M1	SX
Stage IIIA	Any pT/TX	Any N	M1a	S0
	Any pT/TX	Any N	M1a	S1
Stage IIIB	Any pT/TX	N1–N3	M0	S2
	Any pT/TX	Any N	M1a	S2
Stage IIIC	Any pT/TX	N1–N3	M0	S3
	Any pT/TX	Any N	M1a	S3
	Any pT/TX	Any N	M1b	Any S

AFP, α-fetoprotein; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; ULN, upper level of normal.
Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the *AJCC Cancer Staging System* (2020).

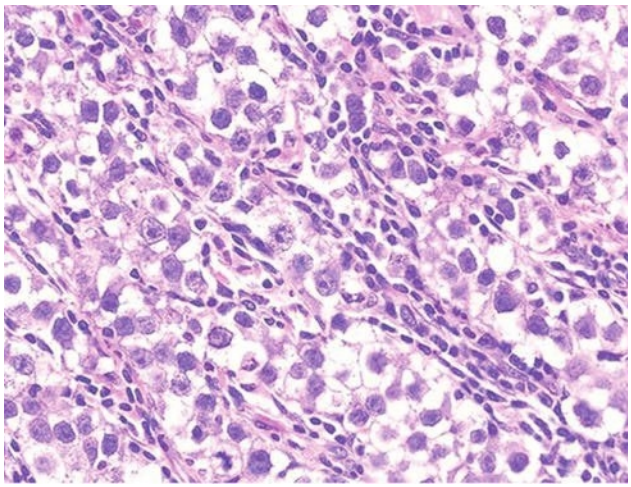


FIGURE 47–1 Histologic appearance of classic seminoma.

makes the presence of malignant cells on the surface of the spermatic cord and at the margins of resection a ubiquitous finding. Thus, the clinician must be careful not to be unduly influenced by reports of "margin positivity" and "involvement of the spermatic cord" in the pathology report.[33] Figure 47–2 shows the typical gross appearance of seminoma.

Even in the presence of significant metastatic disease, it is not uncommon to find only a scar in the testicle. This phenomenon is known as "burned-out" seminoma and can also occur in NSGCT. The biological basis for this spontaneous regression of the primary is unknown. Seminomas are typically associated with significant lymphocytic infiltration, and metastatic deposits characteristically leave a dense desmoplastic residual mass after treatment, often making them difficult to resect.

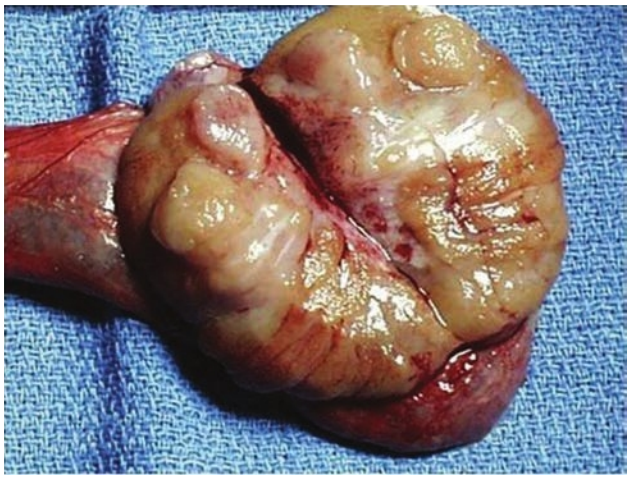


FIGURE 47–2 Gross appearance of seminoma.

Clinical Features

Pure seminoma is the most common GCT of the testicle, accounting for approximately 50% of GCTs. By definition, seminomas have no evidence of a nonseminoma component and do not produce AFP but may have modest elevation of β-hCG. Spermatocytic seminomas, a rare variant comprising only 10% of seminomas, are not associated with GCNIS. These tumors typically occur in men older than 50 years old, in stage I disease, and have a low metastatic rate. This subtype portends an excellent prognosis with resection alone (with or without radiotherapy).[34] Seminomas tend to spread via lymphatics initially, with late hematogenous spread, and are more likely to spread locally, as evidenced by positive margins and involvement of the spermatic cord on histology. The most common hematogenous spread is to the lungs, and metastatic seminomas rarely metastasize to the brain. Remarkably, bulky tumors rapidly respond, with dramatic loss of tumor bulk, but tumor lysis syndrome is never encountered.

Prognosis

The International Germ Cell Cancer Collaborative Group (IGCCCG) established a standard risk classification for both seminomas and NSGCTs (Table 47–2). Patients with metastatic seminoma are divided into either good- or intermediate-risk categories, with no definable "poor-risk" seminoma. The one characteristic that predicted worse outcome for seminoma was the presence of nonpulmonary visceral metastases (intermediate prognosis). The prechemotherapy tumor markers do not predict prognosis (unlike in NSGCTs, discussed further in the chapter). Ninety percent of patients with seminoma fall into the good-risk category, with a 5-year OS of 86%. Patients with seminoma in the intermediate-risk category have a 5-year OS of 72%.[2]

Management of Clinical Stage I Seminoma

Patients with clinical stage I seminoma, representing 70% of patients at diagnosis, have disease confined to the testicle with no evidence of nodal or distant metastasis. Most patients will be cured by radical orchiectomy alone, but approximately 20% recur without adjuvant

TABLE 47–2 International Germ Cell Cancer Collaborative Group Classification Prognostic Risk Stratification

Seminoma	Nonseminoma
Good Risk	
Any primary site	Testis or retroperitoneal primary
and	and
No nonpulmonary visceral metastases	No nonpulmonary visceral metastases
and	and
Normal AFP, any hCG, any LDH	AFP <1000 ng/mL
	hCG <5000 mIU/mL
	LDH <1.5 × ULN
82% 5-year PFS; 86% 5-year OS	89% 5-year PFS; 92% 5-year OS
Intermediate Risk	
Any primary site	Testis or retroperitoneal primary
and	and
Nonpulmonary visceral metastases	No nonpulmonary visceral metastases
and	and
Normal AFP, any hCG, any LDH	AFP 1000–10,000 ng/mL
	hCG 5000–50,000 mIU/mL
	LDH 1.5–10 × ULN
67% 5-year PFS; 72% 5-year OS	75% 5-year PFS; 80% 5-year OS
Poor Risk	
—	Mediastinal primary
	or
—	Nonpulmonary visceral metastases
	or
	AFP >10,000 ng/mL
—	hCG >50,000 mIU/mL
	LDH >10 × ULN
—	41% 5-year PFS; 48% 5-year OS

AFP, α-fetoprotein; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; OS, overall survival PFS, progression-free survival; ULN, upper limit of normal.

intervention. The disease-specific survival rate is nearly 100% with or without adjuvant treatment because patients who recur on surveillance are readily salvaged with standard treatment.

Active Surveillance

The benefits of active surveillance include avoidance of unnecessary treatment in patients who are likely to be already cured by orchiectomy. Mortensen et al[35] reported data on 1954 patients with clinical stage I seminoma managed with surveillance with a median follow-up time of 15 years. In total, 369 patients (19%) relapsed after a median 13.7 months. More than 70% of these patients relapsed during the first 2 years. In a pooled analysis of prognostic factors in 638 patients by Warde et al,[36] tumor size less than 4 cm maximum dimension and without invasion of rete testis had 5-year risk of relapse of only 12%. Patients with both risk factors had a risk of recurrence of 32%, but one of the two risk factors portends a 16% risk of relapse. Because of excellent outcomes of patients later treated for recurrent disease, active surveillance is considered a reasonable option for most patients, including those with both risk factors.

Radiotherapy

The recurrence rate after prophylactic radiotherapy for clinical stage I seminoma is about 4%, and most of those patients who recur after radiation survive with additional treatment (chemotherapy).[37] Treatment of paraaortic lymph nodes to a dose of 20 Gy was associated with excellent local control approaching 100%. A randomized trial of 20 Gy versus 30 Gy showed no difference in rate of recurrence.[38] Omission of ipsilateral iliac lymph nodes from the treatment field resulted in less toxicity (infertility, GI effects) and minimal loss of efficacy. Radiotherapy is contraindicated for patients with horseshoe kidney or inflammatory bowel disease.

Radiotherapy was once viewed favorably because it reduced the number of computed tomography (CT) scans that were necessary for follow-up, with a net reduction in the cost of treatment. There is, however, a risk of second malignant neoplasms related to treatment. Studies of testicular cancer survivors 25 or more years after treatment have revealed an increase in midline cancers, such as GI (colon, stomach, pancreas) and genitourinary (bladder, kidney) malignancies.[39,40] This added risk has brought about a reassessment of whether radiotherapy is warranted, especially considering that 80% of patients with clinical stage I seminoma will be treated unnecessarily, and that there is no survival benefit. At MD Anderson Cancer Center (MDACC), we no longer offer prophylactic radiation to men with stage I testicular seminoma.

Chemotherapy

A randomized controlled trial was conducted to compare a single infusion of carboplatin, with dose based on area under the curve of 7 versus radiotherapy for the adjuvant treatment of clinical stage I seminoma.[41] The median follow-up period was 6.5 years, and the relapse-free survival was similar in both treatment arms, 94.7% and 96.0%, respectively, showing noninferiority of the one cycle of single-agent carboplatin.[42] There are limited data comparing the long-term safety of carboplatin with that of radiotherapy, leading many practitioners to adopt surveillance as the preferred option. Figure 47–3 outlines an approach to therapy for stage I seminoma.

Management of Nonbulky, Good-Risk Seminoma (Stages IIA and IIB)

Patients with stage II seminoma are often divided into those with nonbulky versus bulky disease for treatment discussion. In general, nonbulky disease is defined as nodes less than 5 cm in cross-sectional dimension on CT or magnetic resonance imaging at MDACC. The primary mode of therapy for patients in this category is radiotherapy unless the patient has a contraindication or is unable to tolerate radiation treatment.

Radiotherapy

It is no longer recommended that patients with stages IIA and IIB seminoma receive high-dose radiation (30–35 Gy), mediastinal radiation, or left supraclavicular radiation. At MDACC, our current approach is to give 20 Gy to the paraaortic and ipsilateral iliac nodal fields with a 6-Gy boost to the paraaortic lymph nodes for patients with lymph nodes less than 3 cm.[43] For patients with lymph nodes greater than 3 cm but less than 5 cm, the MDACC approach is to give 20 Gy followed by a 10-Gy boost. Occasionally, radiographic evidence for residual disease is present postradiotherapy, but if the abnormality is less than 3 cm, observation is recommended.

Alternatives to Radiotherapy

A subset of patients exists who will not be able to receive radiation therapy for various reasons. These reasons may include patient refusal, inflammatory bowel disease, horseshoe or pelvic kidney, and history of abdominal surgery. In this setting, systemic chemotherapy could be offered. In a series published by Xiao et al,[44] patients with good-risk seminoma were included in the analysis and were treated with four cycles of etoposide and cisplatin (EP). Although this likely is overtreatment for stages IIA and IIB seminoma, it is a reasonable option for patients who

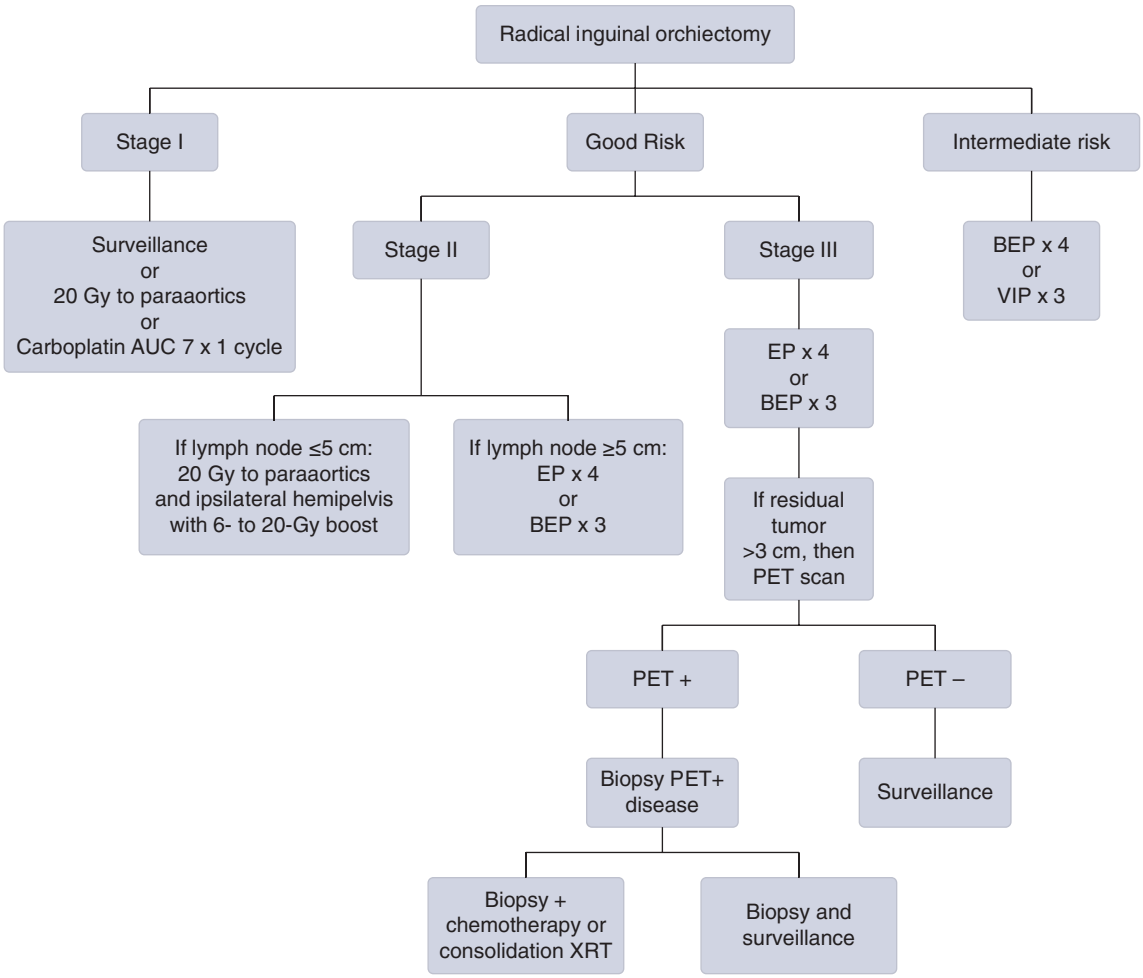


FIGURE 47–3 **Management of testicular cancer (seminoma). AUC, area under curve; BEP, bleomycin, etoposide, and cisplatin; EP, etoposide and cisplatin; PET, positron emission tomography; VIP, etoposide, ifosfamide, and cisplatin; XRT, radiation therapy.**

absolutely cannot receive radiation therapy. Alternatively, participation in a clinical trial investigating utility of laparoscopic retroperitoneal lymph node dissection as first-line treatment could be offered.

Management of Advanced, Good-Risk Seminoma (Stages IIC and III)

This treatment group includes patients with stage II with bulky lymphadenopathy (≥5 cm) and patients with stage III with good-risk disease. In this group of patients, the risk of recurrence remains high despite local therapy; therefore, the primary treatment recommendation is systemic chemotherapy.

Chemotherapy

The recommended systemic chemotherapy regimen for patients with good-risk advanced seminoma (stage IIC or III) is three cycles of bleomycin, etoposide, and cisplatin (BEP) or its equivalent. The evidence for use of three cycles of BEP versus four cycles was presented by de Wit et al.[45] These investigators showed that three cycles of BEP are equivalent to four cycles, with 2-year progression-free survival (PFS) of 90.4% and 89.4%, respectively.[45] Alternatively, patients who are unable or refuse to receive bleomycin or are older than 50 years can be successfully treated with four cycles of EP.

Residual Disease After Chemotherapy and the Role of Positron Emission Tomography

After completion of chemotherapy, restaging CT scans are performed. If a patient is found to have residual mass measuring 3 cm or less in size with normal tumor markers, active surveillance should be pursued. After chemotherapy, residual disease measuring greater than 3 cm can be further evaluated by positron emission tomography (PET) imaging. Evidence for the role of PET imaging in the setting of residual disease greater than 3 cm comes from the multicenter SEMPET study by De Santis et al.[46,47] In this evaluation of 56 patients with a median

follow-up time of 34 months, the positive predictive value of fluorodeoxyglucose (FDG) PET was 100%, with specificity and sensitivity of 100% and 80%, respectively, for the identification of residual disease in lesions larger than 3 cm. Since publication of the SEMPET study, there have been several conflicting studies with reported positive predictive value of PET ranging from 29% to 70%.[48–50]

Positron Emission Tomography–Negative Disease Postchemotherapy

If there is no evidence of avid uptake on PET after chemotherapy, the patient enters the active surveillance strategy. The negative predictive value of PET is greater than 90%.[47–49] If the patient is unable to have PET imaging, surgical biopsy can be considered for patients with residual disease measuring larger than 3 cm.

Positron Emission Tomography–Positive Disease Postchemotherapy

At MDACC, a positive PET scan result requires a confirmatory biopsy or resection of residual mass. If patient has a positive PET scan result in a location that is not amenable to biopsy, this is typically monitored at MDACC. If viable seminoma is confirmed with biopsy, several options can be considered. First, salvage radiation therapy to the residual mass can be offered, especially for smaller masses as seminomas may be more radiation sensitive than chemosensitive. Second, the patient can be offered salvage chemotherapy. Finally, the patient may undergo high-dose chemotherapy with autologous stem cell transplantation. See Figure 47–3 for the algorithm of our management strategy.

Management of Advanced, Intermediate-Risk Seminoma (Stage III)

Patients with stage III intermediate-risk seminoma have nonpulmonary visceral metastasis. The most common sites of disease are the liver and bone. These rare patients are offered systemic chemotherapy on presentation (see Fig. 47–3) with four cycles of BEP or four cycles of etoposide, ifosfamide, and cisplatin (VIP).

Salvage Therapy for Refractory or Recurrent Seminoma

The primary treatment for patients with recurrence after radiotherapy is salvage chemotherapy with treatment dictated by risk status. For patients with lung metastasis (good-risk category), the standard of care is administration of either three cycles of BEP or four cycles of EP. In patients with bone or liver metastasis (intermediate-risk category), salvage chemotherapy is pursued with four cycles of BEP or VIP.[51] Bleomycin should be avoided in men older than 50 years.

Clinical signs of chemotherapy-refractory disease should be approached with an aggressive change of strategy, including salvage chemotherapy and the option of high-dose chemotherapy with stem cell transplantation. These patients should be encouraged to enroll in a clinical trial if available, such as the ongoing TIGER trial, which randomizes patients to TIP or high-dose chemotherapy with autologous stem cell transplant.[52] Salvage TIP, Paclitaxel, Ifosfamide, Cisplatin is an option that can produce durable complete responses.[53] Usually reserved for BEP failures, the role of stem cell transplantation in refractory or recurrent advanced seminoma was addressed by Einhorn et al.[54] Nineteen percent of a series of 184 patients were patients with metastatic testicular seminoma. At a median follow-up period of 48 months, 26 of 35 patients with seminoma treated were in complete remission. Patients with relapsed refractory seminoma should be considered for referral to transplant centers if possible.

NONSEMINOMATOUS GERM CELL TUMORS

Histology

Embryonal Carcinoma

Embryonal carcinoma is the second most common pure presentation of GCT, accounting for approximately 2% of all testicular GCTs. It is a component of approximately 85% of all mixed GCTs.[55] It is rarely seen at the extremes of age, most commonly presenting in the 20- to 30-year age group, and presents with metastasis in one third of cases. Microscopically, embryonal carcinoma cells are the most undifferentiated of the

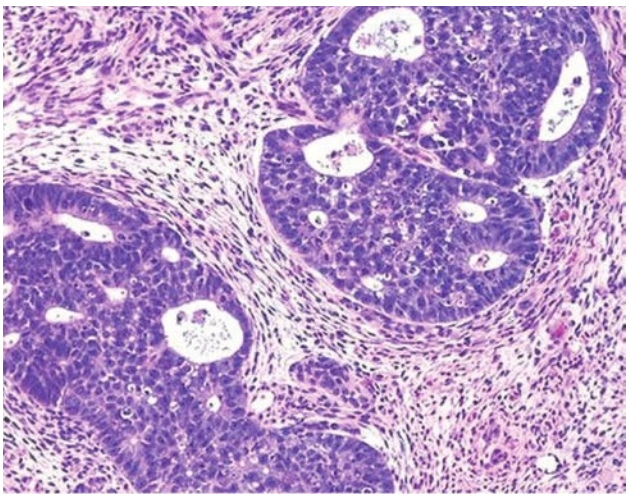


FIGURE 47–5 Histologic appearance of embryonal carcinoma.

Case 47–1: Seminoma Presenting with Renal Insufficiency

A 37-year-old man had a left inguinal orchiectomy for classic seminoma. Laboratory data at presentation to MDACC revealed serum creatinine of 1.8 mg/dL, calcium of 12.7 mg/dL, hemoglobin of 10.5 g/dL, human chorionic gonadotropin (hCG) of 113 mIU/mL, alkaline phosphatase of 194 IU/L, and lactate dehydrogenase (LDH) of 1773 IU/L (upper limit of normal, 618 IU/L). A computed tomography scan of the abdomen and pelvis revealed a large retroperitoneal mass with marked left hydronephrosis (Fig. 47–4A). The patient initially received one cycle of cyclophosphamide and carboplatin. Repeat laboratory data revealed serum creatinine of 1.1 mg/dL, calcium of 8.2 mg/dL, LDH of 483 IU/L, and undetectable hCG. He subsequently received three full cycles of etoposide and cisplatin (EP) with an excellent response. Repeat imaging shown in Figure 47–4B revealed marked improvement in the size of the mass (from 14 to 7 cm). Post-chemotherapy positron emission tomography imaging showed the residual mass to be metabolically inactive.

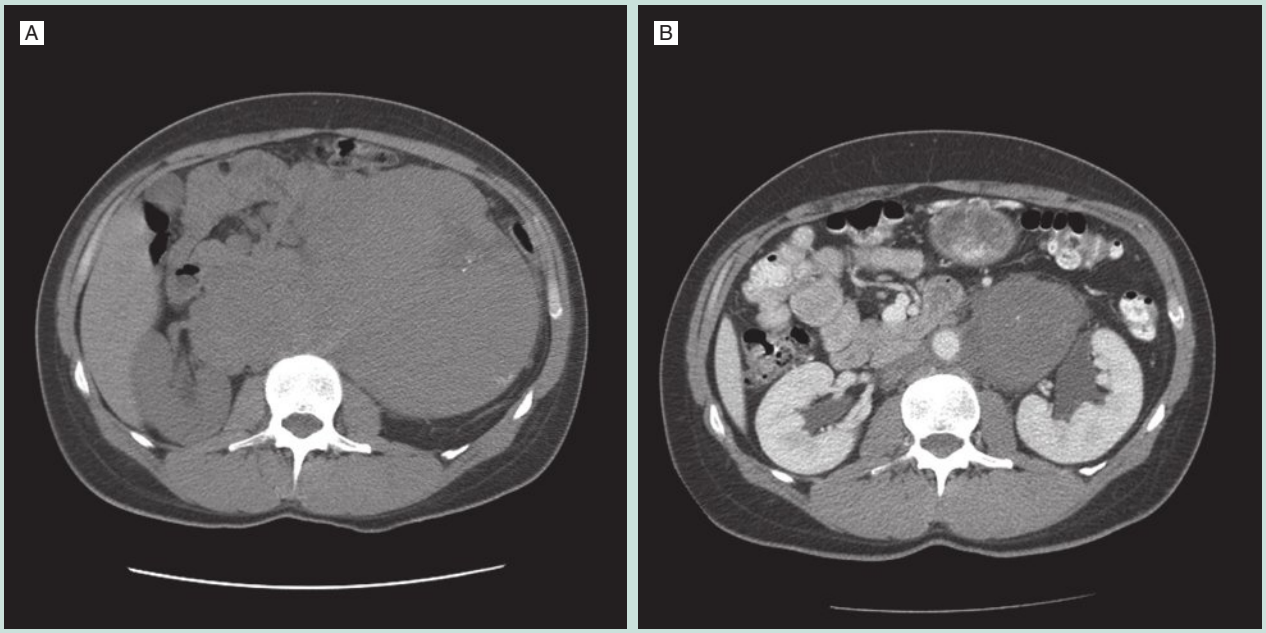


FIGURE 47–4 **A. Baseline imaging from the patient in Case 47–1 showing a large left retroperitoneal mass with left hydronephrosis. B. Repeat imaging from the patient in Case 47–1 showing marked improvement in mass after three cycles of chemotherapy.**

Comment: A patient with advanced seminoma presenting with hydronephrosis and renal insufficiency may receive induction chemotherapy with cyclophosphamide and carboplatin rather than placing nephrostomy tubes to allow administration of bleomycin, etoposide, and cisplatin (BEP) or EP in the first cycle. The patient can subsequently receive standard therapy after normalization of renal function.

GCT types and are characterized by pleomorphic cells with indistinct borders and scant cytoplasm, giving the appearance of overlapping nuclei. Tumor cells can be seen in sheets or arranged as papillary or tubular structures with a high mitotic rate. There is a propensity for vascular invasion. Phenotypic characterization can reveal positivity for cytokeratin, CD30, PLAP, OCT3/4, SOX2, AFP, and hCG. Modest elevations of both AFP and hCG are typical, but importantly, pure embryonal cancers can be marker negative in the serum. Figure 47–5 shows the typical histologic appearance of embryonal carcinoma.

Yolk Sac Tumors (or Endodermal Sinus Tumors)

Pure yolk sac tumors are extremely rare in adult patients but account for the majority of childhood GCTs. In adults, yolk sac elements are commonly seen as a component of mixed NSGCTs. Microscopically, yolk sac tumors are the most variable of GCTs and can manifest as macrocystic, papillary, solid, or a glandular and alveolar pattern with perivascular arrangements of epithelial cells known as glomeruloid or Schiller-Duval bodies. Very high serum AFP levels generally reflect the presence of a yolk sac component,

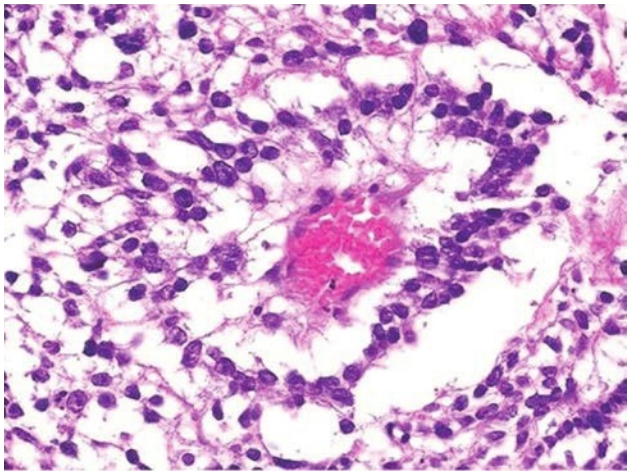


FIGURE 47–6 Histologic appearance of yolk sac tumor.

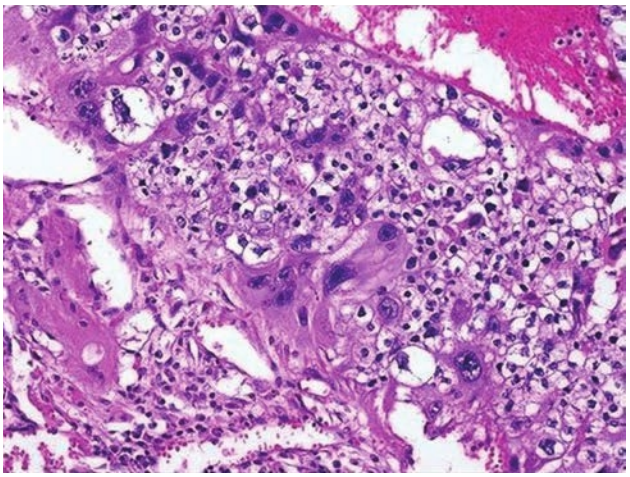


FIGURE 47–7 Histologic appearance of choriocarcinoma.

and serum levels of AFP immediately before the start of chemotherapy are important prognostically in the classification of good- (AFP <1000 ng/mL), intermediate- (1000-10,000 ng/mL), and poor-risk (>10,000 ng/mL) metastatic NSGCTs. Figure 47–6 shows the typical histologic appearance of a yolk sac tumor.

Choriocarcinoma

Also rare in the pure form in the adult population, choriocarcinoma frequently presents as a component of mixed NSGCTs. Choriocarcinomas comprise both syncytiotrophoblasts and cytotrophoblasts, typically arranged in sheets or nests. They are characterized by areas of hemorrhage and necrosis. Choriocarcinomas generally make copious amounts of hCG, and the level of this marker is also an indication of prognosis in metastatic NSGCTs. Levels of hCG greater than 50,000 mIU/mL are a marker of poor-prognosis NSGCT and are typical of metastatic choriocarcinoma. Half of choriocarcinomas are PLAP positive. Choriocarcinoma elements tend to dominate the clinical course and frequently metastasize to the brain. Symptoms of hyperthyroidism are common, owing to stimulation of the TSH receptor by hCG, and treatment such as a β-blocker is indicated while chemotherapy is initiated. Figure 47–7 shows the typical histologic appearance of choriocarcinoma.

Teratoma

Teratomas possess somatic cells from at least two germ cell layers (ectoderm, endoderm, and mesoderm). Variable degrees of differentiation allow for the subclassification of mature and immature forms. A mature teratoma consists of terminally differentiated tissues and can form cystic structures. Although histologically bland, this low-grade malignancy can grow to a threatening dimension and become unresectable. Only about 2% to 3% of all GCTs show mature teratoma as the only histologic component, but teratoma is commonly present as an element of a mixed GCT. A man presenting with teratoma as the only histologic pattern should be presumed to have a mixed GCT and be treated as such. An immature teratoma is less differentiated, although this distinction has no known clinical significance.

One of the unfortunate manifestations is somatic transformation or the development of somatic (non-GCT) malignancy within a teratoma. Sometimes known as "teratoma with malignant transformation," this entity typically displays the biology of whatever histology develops and can range from leukemias to sarcomas to carcinomas. In general, transformation to somatic malignancy carries a poor prognosis, and the best prevention is to surgically remove all residual teratoma whenever possible.[56] Figures 47–8 and 47–9 represent the typical histological and gross appearance of teratoma, respectively.

Clinical Features

As described previously, approximately half of testicular GCTs show histologic elements other than seminoma or produce serum elevation of AFP indicating nonseminoma. These cancers are collectively known as mixed GCTs or NSGCTs, and they form a group of histologically and clinically diverse cancers.[57] The NSGCTs are more likely than seminomas to spread hematogenously with increased risk of distant metastasis. Because of the unique and heterogeneous nature of NSGCTs, several clinical presentations warrant further discussion because of their significance to patient care and prognosis.

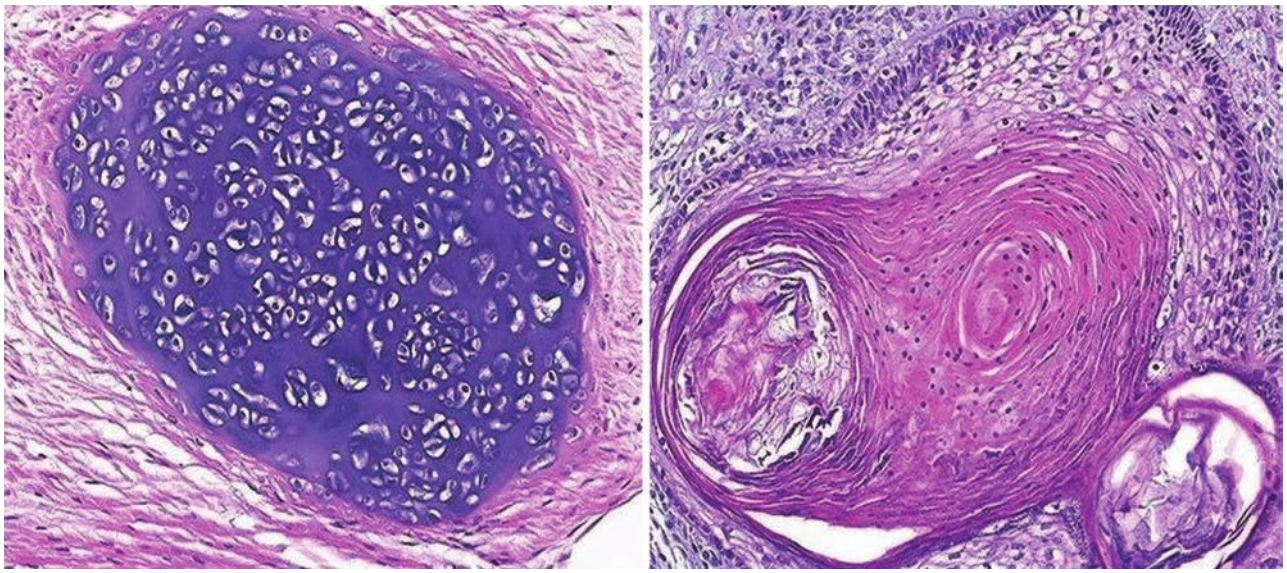


FIGURE 47–8 Histologic appearance of teratoma.

Growing Teratoma Syndrome

Residual teratoma is a low-grade, slow-growing malignancy that can be fatal by inexorable growth. This can take 10 or even 20 years to become threatening and thus can be missed without dedicated lifelong follow-up of patients with NSGCTs. Serum tumor markers are often normal in these patients. One of the most remarkable and clinically important features of teratomas is that they are often "pushing" and rarely invasive. Thus, at surgery, even very large masses are sometimes removed far more easily than would be expected on the basis of the preoperative imaging. It is important to consult a center where sufficient surgical experience is available before concluding that a residual teratoma is "unresectable."[58,59]



FIGURE 47–9 Gross appearance of teratoma.

Choriocarcinoma Syndrome

As the name implies, choriocarcinoma syndrome is seen in the setting of high-volume NSGCT that shows predominantly choriocarcinoma histology and is associated with very high (in some cases >1 million mIU/mL) levels of β-hCG. This syndrome is characterized by prominent constitutional symptoms that represent the effects of both a bulky cancer and secondary hyperthyroidism caused by cross-reaction of hCG with TSH receptors. Typically, patients are rapidly losing weight, tachycardic, anxious, and diaphoretic and have tender gynecomastia from secondary hyperprolactinemia. In addition, most patients have high-volume lung metastases with impending respiratory compromise from the burden of pulmonary metastasis. Hemorrhage can occur at any metastatic site. This is a medical emergency, and treatment should not be delayed for histologic confirmation because this is a pathognomonic constellation in a young man. Metastatic choriocarcinoma has a propensity for brain metastasis, although this is not always apparent on baseline imaging. At MDACC, low-dose induction chemotherapy is given first as fatal bleeding has been described with full-dose chemotherapy. In addition, several institutions have proposed using induction bleomycin, vincristine, and cisplatin (BOP) at low doses, which does not seem to compromise survival outcomes.[60,61] However, there are limited data on how to optimally administer induction chemotherapy.[62]

Prognosis

As described for seminoma, the IGCCCG developed a prognostic staging system for NSGCTs, with

extrapulmonary visceral metastasis found as a major factor in prognosis. Unlike seminoma, prechemotherapy tumor markers were identified as significant in the prognosis of these patients.[2] The prognostic categories are outlined in Table 47–2. In general, patients with mediastinal primary, nonpulmonary visceral metastasis and "poor-risk markers" as defined in the table are considered to have a poor prognosis and have a 5-year OS of 48% with standard treatment. Patients with testis or retroperitoneal primary and no extrapulmonary visceral metastasis are placed in the good-prognosis category based on tumor marker levels as described in the table. Patients with a good prognosis have a 5-year OS of 92%. All others are placed in the intermediate-risk group and have a 5-year OS of 80%.[2] Van Dijk et al[3] updated the 5-year OS data for NSGCTs in a pooled meta-analysis. The authors reported a 5-year OS of 94% for good prognosis, 83% for intermediate prognosis, and 71% for poor prognosis. This illustrates the improving survival rates in the high-risk group.

Management of Clinical Stage I Nonseminomatous Germ Cell Tumors

In general, individuals with clinical stage I NSGCT include patients with normal markers postorchiectomy and no evidence of disease outside the resected testis, epididymis, or cord. As with seminoma, radical inguinal orchiectomy is the initial therapy for early-stage NSGCT. Appropriate surgery will cure approximately 70% of patients in clinical stage I. The two identified risk factors in these patients include percentage of embryonal carcinoma histology and presence of lymphovascular invasion (LVI), with LVI the most predictive.[63] Patients are considered low risk for recurrence postorchiectomy if there is less than 50% embryonal component in the tumor and no evidence of LVI. The role of percentage of embryonal component is debatable because it is often seen together with LVI. In fact, European guidelines use only absence of LVI for determination of "low risk" for recommendation of observation.[64] Patients with either of these risk factors seem to have approximately 40% to 50% risk of recurrence.[65–67]

Observation

Observation is a reasonable strategy for the reliable low-risk patient, which in practice can be those with absence of LVI. The active surveillance schedule as outlined by the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology recommends that patients should have a physical examination and tumor marker measurements every 2 months during the first year, every 3 months during the second year, and every 4 to 6 months during the third year. Chest radiography is recommended at 4 and 12 months and then annually. Abdominal and pelvic CT is recommended approximately every 4 to 6 months during the first year, every 6 months during the second year, and annually for year 3.[68]

Observation is also acceptable for high-risk patients. The NCCN guidelines recommend more frequent imaging, with chest radiography every 2 months in the first year, every 3 months in the second year, and every 4 to 6 months in the third year. Also recommended are abdominal and pelvic CT every 4 months in the first year, every 4 to 6 months in the second year, and every 6 months in the third year.

Retroperitoneal Lymph Node Dissection

Retroperitoneal lymph node dissection (RPLND) is a surgical removal of the "landing zone" lymph nodes and is an accurate staging strategy. However, its role in primary prevention of recurrence in patients with stage I NSGCT is controversial. RPLND may be a reasonable option for patients with a teratoma-predominant tumor who are not comfortable with active surveillance and decline chemotherapy. Morbidity of RPLND includes sympathetic nerve damage that may lead to failure of ejaculation and infertility; however, use of a modified surgical template is a nerve-sparing approach that can preserve the sympathetic nerves and may facilitate anterograde ejaculation in 90% or more patients. RPLND (especially laparoscopic) should only be performed in high-volume centers to minimize morbidity. Stephenson et al[69] reported that RPLND in patients with clinical stage I yielded a 4-year progression-free probability of 96% and is an option for therapy in this patient population. Higher failure rates have been reported for patients with high-risk clinical stage I NSGCT. Patients who do not undergo prophylactic RPLND must undergo periodic CT scanning of the abdomen to rule out growing teratoma in the retroperitoneum.

Chemotherapy

Adjuvant chemotherapy for clinical stage I NSGCT consists of one or two cycles of BEP. In a randomized controlled trial, Albers et al,[70] in the German Testicular Cancer Study Group, compared RPLND with one cycle of BEP in 382 patients with a median follow-up period of 4.7 years. The 2-year recurrence-free survival rates were 99.46% in the chemotherapy group and 91.87% in the RPLND group, suggesting an advantage of one cycle of BEP chemotherapy. Tandstad et al,[71] in the Swedish and Norwegian Testicular Cancer Project (SWENOTECA) study, reported that one cycle of BEP reduced the risk of recurrence by 90% in patients with or without LVI. In practice, adjuvant chemotherapy should only be offered to patients with either LVI, embryonal carcinoma-predominant tumor, or both.

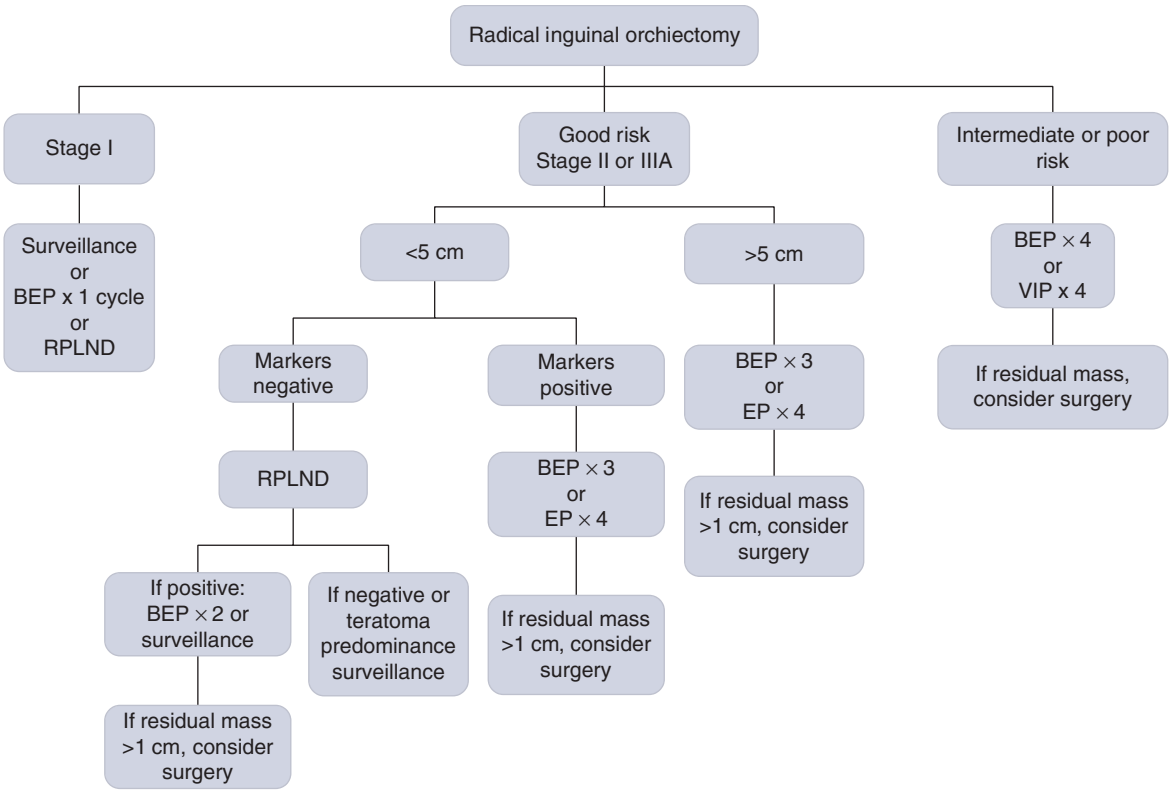


FIGURE 47–10 **Management of testicular cancer (nonseminoma). BEP, bleomycin, etoposide, and cisplatin; EP, etoposide and cisplatin; RPLND, retroperitoneal lymph node dissection; VIP, etoposide, ifosfamide, and cisplatin.**

Our algorithm for management of nonseminoma testicular cancer is shown in Figure 47–10.

Management of Clinical Stage IS Nonseminoma Germ Cell Tumors

Controversy exists regarding the optimal management strategy for clinical stage IS NSGCTs, which are stage I NSGCTs with persistent elevation of serum tumor markers after orchiectomy despite negative radiographic evidence of metastases. Current NCCN guidelines recommend treating these tumors like stage II and III tumors with immediate adjuvant chemotherapy with three cycles of BEP or four cycles of EP. These recommendations are based on small observational reports, and thus this practice remains controversial.[72–74] In a recent evaluation of stage IS patients with NSGCT in the National Cancer Database (NCDB) between 2004 and 2012, approximately 47% of the 781 patients received adjuvant therapy, and the remaining patients were placed on observation.[75] Of the patients who received adjuvant therapy, 80% were treated with chemotherapy, and 20% were treated with RPLND. The authors concluded there was no statistical difference in 5-year OS between the adjuvant therapy and observation cohorts, likely reflecting the high salvage rates with cisplatin-based chemotherapy in those patients initially observed. It is important to note that these data are retrospective and should be interpreted cautiously. At MDACC, patients with clinical stage IS are treated with adjuvant chemotherapy typically with three cycles of BEP, though this likely represents overtreatment.

Management of Good-Risk Clinical Stages IIA and IIB Nonseminoma Germ Cell Tumors

Patients with tumor marker-negative stages IIA or IIB NSGCTs present a unique clinical situation. Treatment options include primary RPLND or chemotherapy consisting of BEP for three cycles or EP for four cycles. At our institution, primary RPLND is favored for stage IIA patients. Patients with pathologic N1 (pN1) disease (see Table 47–1) have a relapse rate of 10% to 20%, and thus surveillance is generally favored if the patient is reliable.[76] The relapse rate for patients with pathologic N2 (pN2) disease is much higher; therefore, adjuvant chemotherapy with two cycles of EP is recommended. Inclusion of bleomycin in this setting is not necessary.[77] In addition, patients with exclusively teratoma

involvement in lymph nodes are observed given their observed resistance to chemotherapy. Patients with elevated serum tumor markers or retroperitoneal mass larger than 2 cm are typically treated with primary chemotherapy with BEP for three cycles or EP for four cycles. If residual mass greater than 1 cm is detected on follow-up staging, surgical resection is recommended.

Management of Good-Risk Stages IIC and III Nonseminoma Germ Cell Tumors

Patients with bulky retroperitoneal disease of greater than 5 cm or pulmonary metastasis with relatively low serum markers constitute those with advanced disease but still with a favorable prognosis. These patients may have either stage IIC or IIIA disease according to the AJCC criteria and are considered together in this discussion. The primary mode of treatment in this patient population is systemic chemotherapy. This may be administered before or after radical orchiectomy as long as surgical resection of the primary is performed after completion of therapy. Again, three cycles of BEP chemotherapy are considered standard of care, and four cycles of EP are considered a reasonable alternative for patients with a contraindication to receive bleomycin. Resection of residual disease present on restaging should be performed.

Pathology of the resected tumor after salvage chemotherapy is different from after primary chemotherapy. After primary chemotherapy, viable GCT, fibrosis, and teratoma are found in approximately 20%, 40%, and 40% of pathological specimens, respectively, compared with 50%, 10%, and 40% after salvage chemotherapy, respectively.[78,79] Patients with greater than 10% viable GCT in the residual pathology specimen after primary chemotherapy should receive an additional two cycles of platinum-based chemotherapy (see Fig. 47–10) based on NCCN recommendations.[68] However, it is unclear whether additional chemotherapy provides a survival advantage, and some experts may opt for surveillance, especially if microscopic disease was present.[80,81]

Management of Intermediate- and Poor-Risk Advanced-Stage IIIB and IIIC Nonseminoma Germ Cell Tumors

Patients with advanced NSGCTs who present with intermediate- or poor-risk features are managed with systemic chemotherapy consisting of four cycles of BEP or VIP. In selected cases, the treatment may be started based on clinical diagnosis before radical orchiectomy. We consider VIP for patients who are not candidates for bleomycin, such as those with underlying lung disease. Patients with persistent elevation of tumor markers after four courses of first-line chemotherapy in most cases should go on to receive salvage chemotherapy or high-dose chemotherapy with autologous stem cell transplantation.

Personalized Strategy Based on Tumor Marker Decline

Failure of either AFP or hCG to normalize is a well-recognized feature of chemotherapy resistance.[82] The rate of tumor marker decline has also been studied as a predictor of poor outcome. For patients presenting with stage IIIC NSGCT, it is possible to identify a subgroup of about 25% who, based on favorable marker decline, will do comparatively well and a larger group of about 75% whose outcome with standard therapy is poor.[83] This observation led to a phase III clinical trial in which patients with stage IIIC NSGCT received BEP in the first cycle, and at completion of the first cycle, those with normalization or favorable decline in both tumor markers remained on BEP (four courses total), and the rest were randomized (1:1) to BEP or an intensified regimen. Final results of this study confirmed superior PFS and OS in the group with favorable decline compared with unfavorable decline (treated with BEP) and demonstrated a statistically significant improvement in 3-year PFS for patients randomized to intensified treatment versus BEP.[84] However, intensified regimens have not shown improvement in OS and thus are not considered standard of care.

Management of Recurrent and Refractory Nonseminoma Germ Cell Tumors

Several chemotherapy regimens with clinical activity in the salvage setting have been reported, and these include VIP, TIP, VeIP (vinblastine, ifosfamide, and cisplatin), or gemcitabine–oxaliplatin. In general, many patients respond, and some are even cured with salvage chemotherapy and surgical consolidation, especially those with a small or moderate volume of disease. There is clinical equipoise regarding high-dose chemotherapy with autologous stem cell transplant versus conventional-dose chemotherapy in the salvage setting.[85–88] If possible, relapsed or refractory patients should be enrolled in the ongoing phase III TIGER trial, which randomizes patients to TIP or high-dose chemotherapy with autologous stem cell transplant.[52]

High-Dose Chemotherapy

High-dose induction chemotherapy with autologous peripheral-blood stem cell transplantation has been

studied in first recurrence and later recurrence of GCT.[54] Einhorn et al[89] retrospectively reviewed 365 patients (285 patients with advanced NSGCT) with a median follow-up period of 3.3 years. Patients with advanced NSGCT treated with high-dose chemotherapy and subsequent autologous stem cell transplantation had 2-year PFS rate of 52%. The authors advocated the use of this aggressive treatment as second-line therapy, suggesting that it is more advantageous than when it is used in the third-line setting. Based on this study and despite the absence of a randomized trial, patients with recurrent or refractory advanced-stage NSGCT may be considered for this aggressive, yet effective, treatment strategy.

Special Considerations

Pitfalls in Tumor Marker Elevation

Mild elevation of β-hCG (usually <20 mIU/mL) may occur secondary to hypogonadism or marijuana use and therefore should not always be attributed to residual or recurrent tumor. It is also possible to have β-hCG entrapped or sequestered in necrotic tumor after chemotherapy.[90] Modest elevation of AFP may be present with residual teratoma and normalizes after surgical resection, but it may also be constitutionally elevated or indicate the presence of liver disease. In addition, elevated tumor markers may indicate unidentified central nervous system disease or residual primary testicular tumor (sanctuary sites).

Role of Desperation Surgery

Some patients with NSGCTs have rising tumor markers despite optimal systemic therapy. In these instances, "desperation surgery" to resect all visible disease may be the only option. It is estimated that up to 20% of patients who fit these criteria can be cured with surgical resection. Patients with isolated retroperitoneal lymph node disease, those with AFP-only elevation, and those who undergo a complete resection of residual disease have the most favorable outcomes.[91,92] Referral to a center with high surgical expertise in this setting is recommended because potentially large en bloc resections may be required to achieve the desired outcome of complete resection.

Treatment of Late Relapse

Late relapse is defined as disease recurrence after 24 months from chemotherapy treatment. Teratoma and embryonal carcinoma are the most common histologies in this setting, with pure teratoma conferring a better prognosis. Surgery is the preferred initial treatment in these cases if the tumor is anatomically resectable.

Case 47–2: The Challenge of Managing Intercurrent Illness

A 35-year-old man who was a heavy smoker and marijuana user underwent a left orchiectomy for a 3.5-cm mixed nonseminoma germ cell tumors (NSGCT) and presented 2 months later to MDACC with left groin pain and left thigh numbness. Tumor markers were α-fetoprotein (AFP), 6575; human chorionic gonadotropin, 1059; and lactate dehydrogenase, 2441. Computed tomography scans revealed bilateral lung nodules, a large (14.7-cm) retroperitoneal mass, left hydronephrosis, and multiple other enlarged abdominal and pelvic lymph nodes. During the first bleomycin, etoposide, and cisplatin (BEP) chemotherapy cycle, he had an inferior myocardial infarction (MI) secondary to an occluding atherosclerotic plaque in the right coronary artery. After coronary stenting and optimal medical therapy, the patient was able to complete four cycles of BEP on schedule and at full dose, without delay or significant complications, except for moderate peripheral neuropathy. His tumor markers declined as follows:

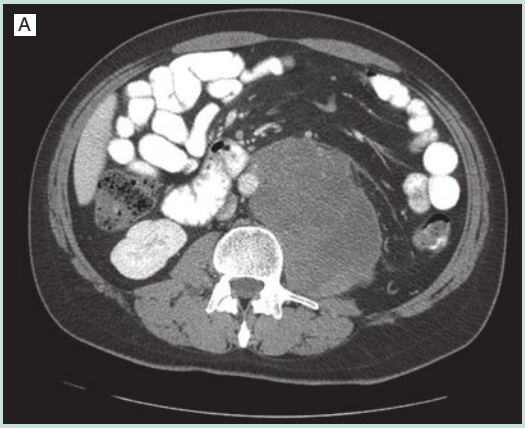
- s/p cycle 1 AFP = 3,853 ng/mL, hCG = 34.7 mIU/mL
- s/p cycle 2 AFP = 542 ng/mL, hCG = 5.2 mIU/mL
- s/p cycle 3 AFP = 88.1 ng/mL, hCG = 4.6 mIU/mL
- s/p cycle 4 AFP = 42 ng/mL, hCG = 4.7 mIU/mL

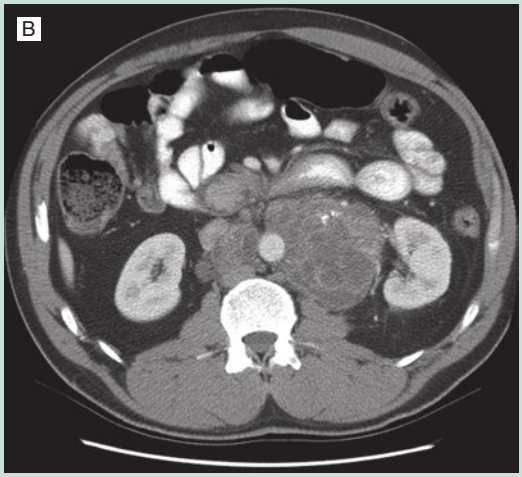
The patient received intramuscular testosterone injection for a low serum testosterone level, and 3 weeks later, serum hCG was less than 1.0 mIU/mL. Six months after his MI, the patient had resection of the large left retroperitoneal mass, left kidney, left adrenal gland, segmental resection of the left psoas muscle, as well as retroperitoneal lymph node dissection . Pathology of the specimen revealed 98% necrosis and only two microscopic foci of residual viable yolk sac tumor in transition to adenocarcinoma. The patient has been recurrence free for 3 years.

Comments: This case illustrates three points. The first is the importance of pursuing chemotherapy while managing an intercurrent illness. The second point is to remember that there are causes of elevated tumor markers other than tumor. The third point is that we do not treat foci of malignant transformation of teratoma.

Case 47–3: Desperation Surgery

A 46-year-old man presented with back pain and was found to have an 11-cm retroperitoneal mass, biopsy of which revealed high-grade germ cell tumor (GCT) (Fig. 47–11A). He underwent a left radical orchiectomy for a 2.8-cm mixed GCT (99% seminoma, 1% teratoma). Postoperatively, serum α-fetoprotein (AFP) was greater than 10,000 ng/mL. He received six cycles of etoposide and cisplatin (EP) followed by one cycle of vinblastine, ifosfamide, cisplatin (VeIP) but never achieved tumor marker normalization (Fig. 47–11B). At presentation to MDACC, his serum AFP was 604 ng/mL. The patient received multiple additional cycles of rotating salvage chemotherapy, including actinomycin-D, cyclophosphamide, and etoposide (ACE); TIP, Paclitaxel, Ifosfamide, Cisplatin, vincristine, methotrexate, and bleomycin (POMB); doxorubicin, paclitaxel, and gemcitabine (ATG); and cisplatin, cyclophosphamide, and doxorubicin (CisCA) (Fig. 47–11C). The patient developed renal insufficiency, recalcitrant anemia, and grade 3 peripheral neuropathy and had transient normalization of serum tumor markers while awaiting surgical resection. At the time of surgery, serum AFP was 46.9 ng/mL. The patient underwent retroperitoneal lymph node dissection with excision of retroperitoneal masses, left radical nephrectomy, and excision of retrocrural lymph node masses. Pathology demonstrated metastatic mixed GCT, including areas of embryonal carcinoma (EST), mature teratoma, and focal areas suspicious for embryonal carcinoma and choriocarcinoma. He remains disease free past 5 years from the time of his salvage surgery.





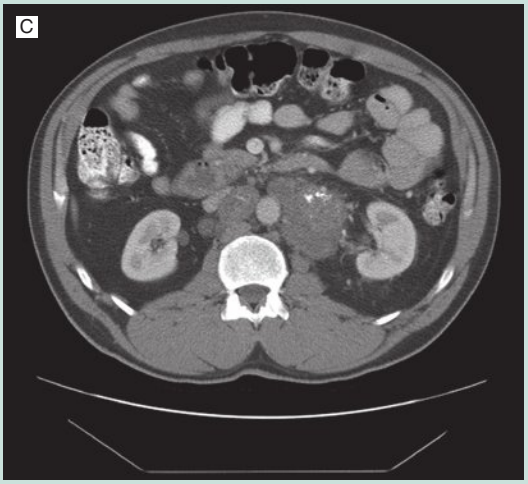


FIGURE 47–11 A. Baseline imaging of the patient described in Case 47–4 with a large retroperitoneal mass. B. Repeat imaging of the patient in Case 47–4 after six cycles of etoposide and cisplatin. C. Imaging of the patient from Case 47–4 showing residual disease despite multiple lines of salvage chemotherapy before desperation surgery.

Comments: Four cycles of bleomycin, etoposide, and cisplatin (BEP) and not EP is the standard for patients with intermediate- and poor-risk nonseminoma germ cell tumor. In rare cases, when the tumor markers do not normalize, even after exhausting all chemotherapeutic options, patients may be salvaged surgically. Patients who have primarily AFP elevation and EST or teratoma benefit the most from such an approach.

Late Complications of Therapy

Although rare, specific complications are associated with treatment of GCTs that are especially important in this patient population because curability may lead to a normal life expectancy. Secondary leukemias occur in fewer than 0.5% of patients and are associated with use of etoposide. Bleomycin toxicity can appear early and is most associated with dose greater than 200 IU. Patients may also have increased risk of vascular side effects, including Raynaud syndrome and hypertension. Up to 20% of patients may develop metabolic syndrome.[93] Additional complications include renal insufficiency, chemotherapy-induced peripheral neurotoxicity, sensorineural hearing loss, chronic electrolyte abnormalities, hypogonadism, and neuropsychiatric abnormalities.[94]

EXTRAGONADAL GERM CELL TUMORS

Extragonadal GCTs (EGCTs) are classified as such if there is no evidence of a primary tumor in the testis or ovary. Typically arising in the midline, the most common sites for EGCTs are the anterior mediastinum, pineal, and suprasellar regions. Mediastinal EGCTs appear as large anterior masses on radiographs. Mediastinal seminomas constitute approximately one third of mediastinal GCTs.[95] Patients with pure seminoma arising in the mediastinum have similar prognosis as patients with testicular seminomas and are treated with four cycles of EP at our institution, provided they do not have extrapulmonary visceral metastasis.

Case 47–4: Germ Cell Tumors with Occult Primary

A 29-year-old man presented with weight loss and left supraclavicular lymphadenopathy (Fig. 47–12A) but had negative testicular examination and ultrasound results. Imaging studies confirmed a 5-cm left supraclavicular lymph node and showed a small left pleural effusion. A biopsy of the supraclavicular lymph node demonstrated poorly differentiated adenocarcinoma. Embryonal carcinoma could not be excluded. Immunostains for placental alkaline phosphatase and Ki-1 were positive but were negative for α-fetoprotein and inconclusive for human chorionic gonadotropin. Laboratory evaluation revealed azoospermia but normal serum chemistries and tumor markers. The patient was treated with three cycles of bleomycin, etoposide, and cisplatin (BEP) and achieved a complete remission; he is now disease free for 5 years without surgical consolidation (Fig. 47–12B).

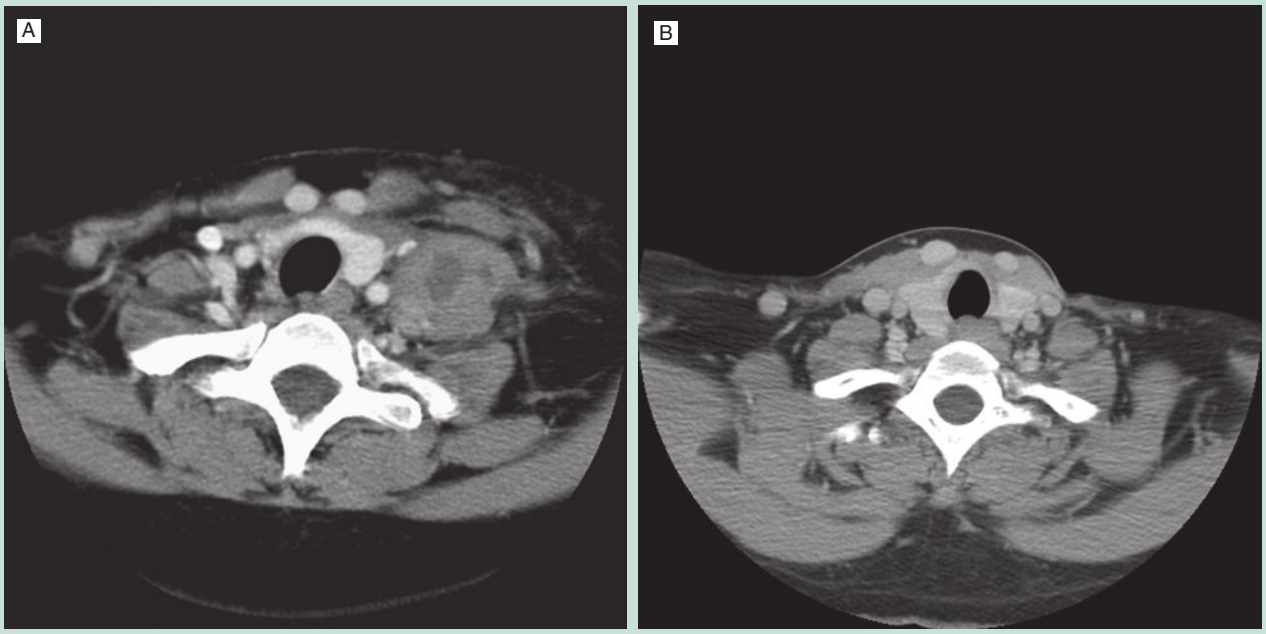


FIGURE 47–12 A. Baseline imaging of the patient described in Case 47–5 showing bulky left supraclavicular adenopathy. B. Imaging after three cycles of chemotherapy.

Comments: The case of unknown primary carcinoma in a young man, even if tumor marker results are negative, should raise the diagnosis of germ cell tumor and should be treated as such. Surgical consolidation is not always necessary when a clinical complete response is achieved with chemotherapy.

Extragonadal NSGCTs represent a distinct subset of GCTs and carry a poor prognosis with 5-year OS rates of about 40% to 50%.[2,96–99] The most common origin is the mediastinum, but they can also arise in the retroperitoneum or pineal region. Rare cases involve the vagina, prostate, liver, and orbit. Extragonadal NSGCTs are characterized by prominence of yolk sac tumor and teratoma histology compared with primary testicular GCTs.[100] Initial diagnosis may be aided by elevations of AFP or hCG. Klinefelter syndrome is associated with increased risk of primary mediastinal NSGCTs.[101] Additional associations include acute megakaryoblastic and myelogenous leukemia, myelodysplastic syndrome, and malignant histiocytosis. Some of these cases represent malignant transformation of immature teratoma elements.

The aggressive nature of mediastinal NSGCTs is coupled with the surgical difficulty of resection of residual disease after therapy. Early diagnosis and aggressive resection of mediastinal NSGCTs may improve the outcome. At our institution, the treatment strategy for patients with this rare entity includes presurgical chemotherapy to optimum response and then consolidation surgery. Four cycles of VIP, rather than four cycles of BEP, are preferred at MDACC because these patients typically undergo thoracic surgery and may require prolonged exposure to high partial pressures of oxygen during surgery, which can provoke bleomycin-related pneumonitis.[102]

CONCLUSION

The GCTs represent the paradigm of curable solid tumors. Optimal management of patients with GCTs requires a multidisciplinary approach, integrating chemotherapy and surgery, to achieve the highest cure rates. Patients who pose a unique diagnostic or therapeutic challenge should be considered for early referral to a large tertiary care center.

MD ANDERSON PRACTICE TIPS

- All scrotal masses should be approached as if they are malignant. Appropriate workup includes transscrotal ultrasonography with color Doppler of both testicles, and any suspicious lesion should be definitively evaluated with radical orchiectomy.
- Extreme elevation of hCG in men should be considered pathognomonic for GCTs and, in selected cases of threatening disease, justifies initiation of therapy even before tissue confirmation.
- Beware of common pitfalls in serum tumor marker elevation, including hypogonadism, marijuana use, or hepatitis.
- Clinical signs of chemotherapy-refractory disease should be approached with an aggressive change of strategy, including salvage chemotherapy and the option of high-dose chemotherapy with stem cell transplantation. These patients should be encouraged to enroll in a clinical trial if available, such as the ongoing TIGER trial, which randomizes patients to TIP or high-dose chemotherapy with autologous stem cell transplant.
- RPLND (especially laparoscopic) should only be performed in high-volume centers to minimize morbidity.
- The treatment strategy for extragonadal NSGCTs typically includes presurgical chemotherapy to optimum response and then consolidation surgery. Special attention should be paid to patients with growing teratoma syndrome, as well as those with indolent or chemotherapy-resistant tumors who may benefit from early surgical intervention.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin.* 2020;70(1):7-30.
2. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. *J Clin Oncol.* 1997;15(2):594-603.
3. van Dijk MR, Steyerberg EW, Habbema JD. Survival of non-seminomatous germ cell cancer patients according to the IGCC classification: an update based on meta-analysis. *Eur J Cancer.* 2006;42(7):820-826.
4. Bray F, Ferlay J, Devesa SS, et al. Interpreting the international trends in testicular seminoma and nonseminoma incidence. *Nat Clin Pract Urol.* 2006;3(10):532-543.
5. McGlynn KA, Devesa SS, Graubard BI, Castle PE. Increasing incidence of testicular germ cell tumors among black men in the United States. *J Clin Oncol.* 2005;23(24):5757-5761.
6. McGlynn KA, Devesa SS, Sigurdson AJ, et al. Trends in the incidence of testicular germ cell tumors in the United States. *Cancer.* 2003;97(1):63-70.
7. Dieckmann KP, Pichlmeier U. Clinical epidemiology of testicular germ cell tumors. *World J Urol.* 2004;22(1):2-14.
8. Moller H, Cortes D, Engholm G, Thorup J. Risk of testicular cancer with cryptorchidism and with testicular biopsy: cohort study. *BMJ.* 1998;317(7160):729.
9. Giwercman A, Bruun E, Frimodt-Moller C, Skakkebaek NE. Prevalence of carcinoma in situ and other histopathological abnormalities in testes of men with a history of cryptorchidism. *J Urol.* 1989;142(4):998-1001: discussion 1001-1002.
10. Akre O, Pettersson A, Richiardi L. Risk of contralateral testicular cancer among men with unilaterally undescended testis: a meta analysis. *Int J Cancer.* 2009;124(3):687-689.
11. Dieckmann KP, Pichlmeier U. The prevalence of familial testicular cancer: an analysis of two patient populations and a review of the literature. *Cancer.* 1997;80(10):1954-1960.
12. Fossa SD, Chen J, Schonfeld SJ, et al. Risk of contralateral testicular cancer: a population-based study of 29,515 U.S. men. *J Natl Cancer Inst.* 2005;97(14):1056-1066.
13. Travis LB, Curtis RE, Storm H, et al. Risk of second malignant neoplasms among long-term survivors of testicular cancer. *J Natl Cancer Inst.* 1997;89(19):1429-1439.
14. Bosl GJ, Ilson DH, Rodriguez E, et al. Clinical relevance of the i(12p) marker chromosome in germ cell tumors. *J Natl Cancer Inst.* 1994;86(5):349-355.
15. Ottesen AM, Skakkebaek NE, Lundsteen C, et al. High-resolution comparative genomic hybridization detects extra chromosome arm 12p material in most cases of carcinoma in situ adjacent to overt germ cell tumors, but not before the invasive tumor development. *Genes Chromosomes Cancer.* 2003;38(2):117-125.
16. Atkin NB, Baker MC. Specific chromosome change, i(12p), in testicular tumours? *Lancet.* 1982;2(8311):1349.
17. Rodriguez E, Mathew S, Reuter V, et al. Cytogenetic analysis of 124 prospectively ascertained male germ cell tumors. *Cancer Res.* 1992;52(8):2285-2291.
18. Shen H, Shih J, Hollern DP, et al. Integrated molecular characterization of testicular germ cell tumors. *Cell Rep.* 2018;23(11):3392-3406.
19. Summersgill B, Goker H, Weber-Hall S, et al. Molecular cytogenetic analysis of adult testicular germ cell tumours and identification of regions of consensus copy number change. *Br J Cancer.* 1998;77(2):305-313.
20. Kemmer K, Corless CL, Fletcher JA, et al. KIT mutations are common in testicular seminomas. *Am J Pathol.* 2004;164(1):305-313.
21. McIntyre A, Summersgill B, Grygalewicz B, et al. Amplification and overexpression of the KIT gene is associated with progression in the seminoma subtype of testicular germ cell tumors of adolescents and adults. *Cancer Res.* 2005;65(18):8085-8089.
22. Huyghe E, Soulie M, Escourrou G, et al. Conservative management of small testicular tumors relative to carcinoma in situ prevalence. *J Urol.* 2005;173(3):820-823.
23. Horie K, Fujita J, Takakura K, et al. The expression of c-kit protein in human adult and fetal tissues. *Hum Reprod.* 1993;8(11):1955-1962.
24. Hoei-Hansen CE, Rajpert-De Meyts E, Daugaard G, Skakkebaek NE. Carcinoma in situ testis, the progenitor of testicular germ cell tumours: a clinical review. *Ann Oncol.* 2005;16(6):863-868.
25. Braunstein GD. Clinical practice. Gynecomastia. *N Engl J Med.* 2007;357(12):1229-1237.
26. Wehmann RE, Nisula BC. Metabolic and renal clearance rates of purified human chorionic gonadotropin. *J Clin Invest.* 1981;68(1):184-194.
27. Light PA. Tumour markers in testicular cancer. *J R Soc Med.* 1985;78 Suppl 6:19-24.
28. Yuasa T, Yoshiki T, Ogawa O, et al. Detection of alpha-fetoprotein mRNA in seminoma. *J Androl.* 1999;20(3):336-340.
29. Gilligan TD, Seidenfeld J, Basch EM, et al. American Society of Clinical Oncology Clinical Practice Guideline on uses of serum tumor markers in adult males with germ cell tumors. *J Clin Oncol.* 2010;28(20):3388-3404.
30. Mencel PJ, Motzer RJ, Mazumdar M, et al. Advanced seminoma: treatment results, survival, and prognostic factors in 142 patients. *J Clin Oncol.* 1994;12(1):120-126.
31. Brimo F SJ, Ryan CJ, et al. Testis. In: Amin M, ed. *AJCC Cancer Staging Manual*. 8th edition. Springer International Publishing; 2017.
32. Jeruss JS, Woodruff TK. Preservation of fertility in patients with cancer. *N Engl J Med.* 2009;360(9):902-911.
33. Nazeer T, Ro JY, Kee KH, Ayala AG. Spermatic cord contamination in testicular cancer. *Mod Pathol.* 1996;9(7):762-766.
34. Chung PW, Bayley AJ, Sweet J, et al. Spermatocytic seminoma: a review. *Eur Urol.* 2004;45(4):495-498.
35. Mortensen MS, Lauritsen J, Gundgaard MG, et al. A nationwide cohort study of stage I seminoma patients followed on a surveillance program. *Eur Urol.* 2014;66(6):1172-1178.
36. Warde P, Specht L, Horwich A, et al. Prognostic factors for relapse in stage I seminoma managed by surveillance: a pooled analysis. *J Clin Oncol.* 2002;20(22):4448-4452.
37. Mead GM, Fossa SD, Oliver RT, et al. Randomized trials in 2466 patients with stage I seminoma: patterns of relapse and follow-up. *J Natl Cancer Inst.* 2011;103(3):241-249.
38. Jones WG, Fossa SD, Mead GM, et al. Randomized trial of 30 versus 20 Gy in the adjuvant treatment of stage I Testicular Seminoma: a report on Medical Research Council Trial TE18, European Organisation for the Research and Treatment of Cancer Trial 30942 (ISRCTN18525328). *J Clin Oncol.* 2005;23(6):1200-1208.
39. Groot HJ, Lubberts S, de Wit R, et al. Risk of solid cancer after treatment of testicular germ cell cancer in the platinum era. *J Clin Oncol.* 2018;36(24):2504-2513.
40. Kvammen O, Myklebust TA, Solberg A, et al. Causes of inferior relative survival after testicular germ cell tumor diagnosed 1953-2015: a population-based prospective cohort study. *PLoS One.* 2019;14(12):e0225942.
41. Oliver RT, Mason MD, Mead GM, et al. Radiotherapy versus single-dose carboplatin in adjuvant treatment of stage I seminoma: a randomised trial. *Lancet.* 2005;366(9482):293-300.
42. Oliver RT, Mead GM, Rustin GJ, et al. Randomized trial of carboplatin versus radiotherapy for stage I seminoma: mature results on relapse and contralateral testis cancer rates in MRC TE19/EORTC 30982 study (ISRCTN27163214). *J Clin Oncol.* 2011;29(8):957-962.

43. Classen J, Schmidberger H, Meisner C, et al. Radiotherapy for stages IIA/B testicular seminoma: final report of a prospective multicenter clinical trial. *J Clin Oncol.* 2003;21(6):1101-1106.
44. Xiao H, Mazumdar M, Bajorin DF, et al. Long-term follow-up of patients with good-risk germ cell tumors treated with etoposide and cisplatin. *J Clin Oncol.* 1997;15(7):2553-2558.
45. de Wit R, Roberts JT, Wilkinson PM, et al. Equivalence of three or four cycles of bleomycin, etoposide, and cisplatin chemotherapy and of a 3- or 5-day schedule in good-prognosis germ cell cancer: a randomized study of the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group and the Medical Research Council. *J Clin Oncol.* 2001;19(6):1629-1640.
46. De Santis M, Bokemeyer C, Becherer A, et al. Predictive impact of 2-18fluoro-2-deoxy-D-glucose positron emission tomography for residual postchemotherapy masses in patients with bulky seminoma. *J Clin Oncol.* 2001;19(17):3740-3744.
47. De Santis M, Becherer A, Bokemeyer C, et al. 2-18fluoro-deoxy-D-glucose positron emission tomography is a reliable predictor for viable tumor in postchemotherapy seminoma: an update of the prospective multicentric SEMPET trial. *J Clin Oncol.* 2004;22(6):1034-1039.
48. Muller J, Schrader AJ, Jentzmik F, Schrader M. [Assessment of residual tumours after systemic treatment of metastatic seminoma: (1)(8)F-2-fluoro-2-deoxy-D-glucose positron emission tomography - meta-analysis of diagnostic value]. *Urologe A.* 2011;50(3):322-327.
49. Bachner M, Loriot Y, Gross-Goupil M, et al. 2-(1)(8)fluoro-deoxy-D-glucose positron emission tomography (FDG-PET) for postchemotherapy seminoma residual lesions: a retrospective validation of the SEMPET trial. *Ann Oncol.* 2012;23(1):59-64.
50. Cathomas R, Klingbiel D, Bernard B, et al. Questioning the value of fluorodeoxyglucose positron emission tomography for residual lesions after chemotherapy for metastatic seminoma: results of an International Global Germ Cell Cancer Group registry. *J Clin Oncol.* 2018:JCO1800210.
51. Vuky J, Tickoo SK, Sheinfeld J, et al. Salvage chemotherapy for patients with advanced pure seminoma. *J Clin Oncol.* 2002;20(1):297-301.
52. McHugh DJ, Feldman DR. Conventional-dose versus high-dose chemotherapy for relapsed germ cell tumors. *Adv Urol.* 2018;2018:7272541.
53. Kondagunta GV, Bacik J, Donadio A, et al. Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. *J Clin Oncol.* 2005;23(27):6549-6555.
54. Einhorn LH, Williams SD, Chamness A, et al. High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. *N Engl J Med.* 2007;357(4):340-348.
55. Mostofi FK, Sesterhenn IA, Davis CJ Jr. Developments in histopathology of testicular germ cell tumors. *Semin Urol.* 1988;6(3):171-188.
56. Spiess PE, Pisters LL, Liu P, et al. Malignant transformation of testicular teratoma: a chemoresistant phenotype. *Urol Oncol.* 2008;26(6):595-599.
57. Bosl GJ, Geller N, Cirrincione C, et al. Interrelationships of histopathology and other clinical variables in patients with germ cell tumors of the testis. *Cancer.* 1983;51(11):2121-2125.
58. Logothetis CJ, Samuels ML, Trindade A, Johnson DE. The growing teratoma syndrome. *Cancer.* 1982;50(8):1629-1635.
59. Paffenholz P, Pfister D, Matveev V, Heidenreich A. Diagnosis and management of the growing teratoma syndrome: a single-center experience and review of the literature. *Urol Oncol.* 2018;36(12):529 e523-529 e530.
60. Fizazi K, Prow DM, Do KA, et al. Alternating dose-dense chemotherapy in patients with high volume disseminated non-seminomatous germ cell tumours. *Br J Cancer.* 2002;86(10):1555-1560.
61. Shamash J, Mee M, Sarker SJ, et al. Dose dense chemotherapy for untreated poor prognosis and relapsed germ cell tumours—an 18 year experience with GAMEC chemotherapy. *BJU Int.* 2019.
62. Honecker F, Aparicio J, Berney D, et al. ESMO Consensus Conference on testicular germ cell cancer: diagnosis, treatment and follow-up. *Ann Oncol.* 2018;29(8):1658-1686.
63. Albers P, Siener R, Kliesch S, et al. Risk factors for relapse in clinical stage I nonseminomatous testicular germ cell tumors: results of the German Testicular Cancer Study Group Trial. *J Clin Oncol.* 2003;21(8):1505-1512.
64. Krege S, Beyer J, Souchon R, et al. European consensus conference on diagnosis and treatment of germ cell cancer: a report of the second meeting of the European Germ Cell Cancer Consensus group (EGCCCG): part I. *Eur Urol.* 2008;53(3):478-496.
65. Sturgeon JF, Moore MJ, Kakiashvili DM, et al. Non-risk-adapted surveillance in clinical stage I nonseminomatous germ cell tumors: the Princess Margaret Hospital's experience. *Eur Urol.* 2011;59(4):556-562.
66. Kollmannsberger C, Tandstad T, Bedard PL, et al. Patterns of relapse in patients with clinical stage I testicular cancer managed with active surveillance. *J Clin Oncol.* 2015;33(1):51-57.
67. Daugaard G, Gundgaard MG, Mortensen MS, et al. Surveillance for stage I nonseminoma testicular cancer: outcomes and long-term follow-up in a population-based cohort. *J Clin Oncol.* 2014;32(34):3817-3823.
68. Gilligan T, Lin DW, Aggarwal R, et al. Testicular cancer, version 2.2020, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw.* 2019;17(12):1529-1554.
69. Stephenson AJ, Bosl GJ, Bajorin DF, et al. Retroperitoneal lymph node dissection in patients with low stage testicular cancer with embryonal carcinoma predominance and/or lymphovascular invasion. *J Urol.* 2005;174(2):557-560; discussion 560.
70. Albers P, Siener R, Krege S, et al. Randomized phase III trial comparing retroperitoneal lymph node dissection with one course of bleomycin and etoposide plus cisplatin chemotherapy in the adjuvant treatment of clinical stage I Nonseminomatous testicular germ cell tumors: AUO trial AH 01/94 by the German Testicular Cancer Study Group. *J Clin Oncol.* 2008;26(18):2966-2972.
71. Tandstad T, Dahl O, Cohn-Cedermark G, et al. Risk-adapted treatment in clinical stage I nonseminomatous germ cell testicular cancer: the SWENOTECA management program. *J Clin Oncol.* 2009;27(13):2122-2128.
72. Culine S, Theodore C, Terrier-Lacombe MJ, Droz JP. Primary chemotherapy in patients with nonseminomatous germ cell tumors of the testis and biological disease only after orchiectomy. *J Urol.* 1996;155(4):1296-1298.
73. Davis BE, Herr HW, Fair WR, Bosl GJ. The management of patients with nonseminomatous germ cell tumors of the testis with serologic disease only after orchiectomy. *J Urol.* 1994;152(1):111-113; discussion 114.
74. Saxman SB, Nichols CR, Foster RS, et al. The management of patients with clinical stage I nonseminomatous testicular tumors and persistently elevated serologic markers. *J Urol.* 1996;155(2):587-589.
75. Kamran SC, Seisen T, Markt SC, et al. Contemporary treatment patterns and outcomes for clinical stage IS testicular cancer. *Eur Urol.* 2018;73(2):262-270.
76. Rabbani F, Sheinfeld J, Farivar-Mohseni H, et al. Low-volume nodal metastases detected at retroperitoneal lymphadenectomy for testicular cancer: pattern and prognostic factors for relapse. *J Clin Oncol.* 2001;19(7):2020-2025.
77. McHugh DJ, Funt SA, Silber D, et al. Adjuvant chemotherapy with etoposide plus cisplatin for patients with pathologic stage II nonseminomatous germ cell tumors. *J Clin Oncol.* 2020;38(12):1332-1337.

78. Oldenburg J, Alfsen GC, Lien HH, et al. Postchemotherapy retroperitoneal surgery remains necessary in patients with nonseminomatous testicular cancer and minimal residual tumor masses. *J Clin Oncol.* 2003;21(17):3310-3317.
79. Albers P, Weissbach L, Krege S, et al. Prediction of necrosis after chemotherapy of advanced germ cell tumors: results of a prospective multicenter trial of the German Testicular Cancer Study Group. *J Urol.* 2004;171(5):1835-1838.
80. Fizazi K, Tjulandin S, Salvioni R, et al. Viable malignant cells after primary chemotherapy for disseminated nonseminomatous germ cell tumors: prognostic factors and role of postsurgery chemotherapy—results from an international study group. *J Clin Oncol.* 2001;19(10):2647-2657.
81. Fizazi K, Oldenburg J, Dunant A, et al. Assessing prognosis and optimizing treatment in patients with postchemotherapy viable nonseminomatous germ-cell tumors (NSGCT): results of the sCR2 international study. *Ann Oncol.* 2008;19(2):259-264.
82. Murphy BA, Motzer RJ, Mazumdar M, et al. Serum tumor marker decline is an early predictor of treatment outcome in germ cell tumor patients treated with cisplatin and ifosfamide salvage chemotherapy. *Cancer.* 1994;73(10):2520-2526.
83. Pagliaro LC, Logothetis CJ. Cancer of the testis. In: *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology.* 10th edition. Wolters Kluwer Health Adis (ESP); 2015.
84. Fizazi K, Pagliaro L, Laplanche A, et al. Personalised chemotherapy based on tumour marker decline in poor prognosis germ-cell tumours (GETUG 13): a phase 3, multicentre, randomised trial. *Lancet Oncol.* 2014;15(13):1442-1450.
85. Lorch A, Kollmannsberger C, Hartmann JT, et al. Single versus sequential high-dose chemotherapy in patients with relapsed or refractory germ cell tumors: a prospective randomized multicenter trial of the German Testicular Cancer Study Group. *J Clin Oncol.* 2007;25(19):2778-2784.
86. Pico JL, Rosti G, Kramar A, et al. A randomised trial of high-dose chemotherapy in the salvage treatment of patients failing first-line platinum chemotherapy for advanced germ cell tumours. *Ann Oncol.* 2005;16(7):1152-1159.
87. Daugaard G, Skoneczna I, Aass N, et al. A randomized phase III study comparing standard dose BEP with sequential high-dose cisplatin, etoposide, and ifosfamide (VIP) plus stem-cell support in males with poor-prognosis germ-cell cancer. An intergroup study of EORTC, GTCSG, and Grupo Germinal (EORTC 30974). *Ann Oncol.* 2011;22(5):1054-1061.
88. Motzer RJ, Nichols CJ, Margolin KA, et al. Phase III randomized trial of conventional-dose chemotherapy with or without high-dose chemotherapy and autologous hematopoietic stem-cell rescue as first-line treatment for patients with poor-prognosis metastatic germ cell tumors. *J Clin Oncol.* 2007;25(3):247-256.
89. Adra N, Abonour R, Althouse SK, et al. High-dose chemotherapy and autologous peripheral-blood stem-cell transplantation for relapsed metastatic germ cell tumors: the Indiana University experience. *J Clin Oncol.* 2017;35(10):1096-1102.
90. Mohler JL, Siami PF, Flanigan RC. False positive beta-human chorionic gonadotropin in testicular cancer. *Urology.* 1987;30(3):252-254.
91. Ong TA, Winkler MH, Savage PM, et al. Retroperitoneal lymph node dissection after chemotherapy in patients with elevated tumour markers: indications, histopathology and outcome. *BJU Int.* 2008;102(2):198-202.
92. Beck SD, Foster RS, Bihrle R, et al. Outcome analysis for patients with elevated serum tumor markers at postchemotherapy retroperitoneal lymph node dissection. *J Clin Oncol.* 2005;23(25):6149-6156.
93. Willemse PM, Burggraaf J, Hamdy NA, et al. Prevalence of the metabolic syndrome and cardiovascular disease risk in chemotherapy-treated testicular germ cell tumour survivors. *Br J Cancer.* 2013;109(1):60-67.
94. Kerns SL, Fung C, Monahan PO, et al. Cumulative burden of morbidity among testicular cancer survivors after standard cisplatin-based chemotherapy: a multi-institutional study. *J Clin Oncol.* 2018;36(15):1505-1512.
95. Moran CA, Suster S, Przygodzki RM, Koss MN. Primary germ cell tumors of the mediastinum: II. Mediastinal seminomas—a clinicopathologic and immunohistochemical study of 120 cases. *Cancer.* 1997;80(4):691-698.
96. Logothetis CJ, Samuels ML, Selig DE, et al. Chemotherapy of extragonadal germ cell tumors. *J Clin Oncol.* 1985;3(3):316-325.
97. Toner GC, Geller NL, Lin SY, Bosl GJ. Extragonadal and poor risk nonseminomatous germ cell tumors. Survival and prognostic features. *Cancer.* 1991;67(8):2049-2057.
98. Moran CA, Suster S, Koss MN. Primary germ cell tumors of the mediastinum: III. Yolk sac tumor, embryonal carcinoma, choriocarcinoma, and combined nonteratomatous germ cell tumors of the mediastinum—a clinicopathologic and immunohistochemical study of 64 cases. *Cancer.* 1997;80(4):699-707.
99. Bokemeyer C, Nichols CR, Droz JP, et al. Extragonadal germ cell tumors of the mediastinum and retroperitoneum: results from an international analysis. *J Clin Oncol.* 2002;20(7):1864-1873.
100. Moran CA, Suster S. Primary germ cell tumors of the mediastinum: I. Analysis of 322 cases with special emphasis on teratomatous lesions and a proposal for histopathologic classification and clinical staging. *Cancer.* 1997;80(4):681-690.
101. Nichols CR, Heerema NA, Palmer C, et al. Klinefelter's syndrome associated with mediastinal germ cell neoplasms. *J Clin Oncol.* 1987;5(8):1290-1294.
102. Ranganath P, Kesler KA, Einhorn LH. Perioperative morbidity and mortality associated with bleomycin in primary mediastinal nonseminomatous germ cell tumor. *J Clin Oncol.* 2016;34(36):4445-4446.

Section X Neurologic Tumors

Section Editor: John de Groot

48 Tumors of the Central Nervous System

This page intentionally left blank

48 Tumors of the Central Nervous System

Shiao-Pei Weathers
Barbara O'Brien
Ashley Aaroe
Debra Yeboa
Sujit Prabhu
John de Groot

KEY CONCEPTS

- Brain tumors are a heterogeneous group of lesions divided into two main categories: (1) primary brain and spinal tumors arising from the cells of the central nervous system (CNS) and (2) brain metastases from systemic cancer, which are significantly more common. Neurologic deficits are determined by the location and extent of CNS involvement, as opposed to histology. Brain tumors of all kinds can predispose to seizure and high intracranial pressure.
- The most common systemic malignancy that gives arise to brain metastases is lung cancer followed by breast cancer, melanoma, renal cancer, and colorectal cancer. Of these solid tumors, melanoma is known to have the highest tropism to colonize the brain. Tumors classically associated with hemorrhagic brain metastases include melanoma, renal cell carcinoma, thyroid carcinoma, and choriocarcinoma.
- Gliomas are the most frequently occurring primary brain tumors and include astrocytomas (including glioblastoma), oligodendrogliomas, and ependymomas. Primary brain glial tumors are graded according to the most malignant portion of the tumor. Grade is inversely correlated with prognosis. Increasingly, molecular features are being used to define and classify glial tumors because these features yield additional insight about the anticipated behavior of the tumor and response to therapy.
- Mutation of isocitrate dehydrogenase (IDH) is thought to represent an early step in gliomagenesis and is nearly ubiquitous in low-grade gliomas. It therefore distinguishes secondary glioblastoma that has evolved from a low-grade tumor from primary glioblastoma that arises de novo. IDH mutation has been established as a positive prognostic factor in glioblastoma (GBM). The most common IDH mutation is R132H, which can be detected by immunohistochemistry, though other noncanonical mutations in IDH1 and IDH2 can be identified through next-generation sequencing. IDH inhibition is under investigation as a possible therapeutic strategy.
- Hypermethylation of the promotor region of the O6-methylguanine-DNA methyltransferase (MGMT) gene is another prognostic alteration in glioblastoma. Promotor methylation decreases MGMT transcription, thereby also decreasing production of a DNA repair enzyme that reverses damage induced by alkylating chemotherapy.
- The development of brain metastases and leptomeningeal carcinomatosis is predicated on complex interactions between tumor cells and the adjacent microenvironment, sometimes referred to as the "seed and soil" hypothesis. Emerging therapeutic options for brain metastases include molecularly targeted therapies and immunotherapy used either in addition to or in lieu of conventional treatment depending on the clinical scenario.
- Patients with brain tumors experience unique physical and cognitive symptoms that can have a significant impact on functional status and quality of life such as weakness, aphasia, memory impairment, hemispatial neglect, vision changes, dysphagia, mood dysregulation, and personality change. Care should be taken to identify and manage such symptoms in addition to treating the underlying disease process.

OVERVIEW

Brain tumors are a heterogeneous group of lesions that range from benign, slow-growing tumors found only incidentally on autopsy to malignant, rapidly growing tumors that cause death within months. The most common intracranial tumors are brain metastases from systemic cancer, estimated at 200,000 new cases per year in the United States, based on a 10% to 15% incidence.[1] In comparison, the incidence of primary

brain and spinal cord tumors for 2020 was estimated at 23,890 new cases (https://www.cancer.org/cancer/brain-spinal-cord-tumors-adults/about/key-statistics.html).

Because of their histologic heterogeneity, as well as the unique microenvironment within the blood–brain barrier (BBB), management of patients with brain tumors is complex and benefits from a multidisciplinary team using an individualized approach. Accurate characterization of the tumor pathology can have a significant impact on treatment selection, often necessitating confirmation at a specialized cancer center. Optimal outcomes involve the coordination of neurosurgery, radiation oncology, and neuro-oncology specialists.

Despite advances in neurosurgical techniques, radiation therapy, and chemotherapy, the prognosis for patients with high-grade gliomas such as glioblastoma, the most common form of glioma, remains dismal. Large clinical trials have reported a median survival of only 14 to 16 months with a 26% to 33% 2-year survival rate.[2,3] A review of eight consecutive phase II chemotherapy trials for recurrent glioblastoma demonstrated only a 6% response rate (complete response [CR] and partial response [PR]), with a 6-month progression-free survival (PFS) rate of 15% and a 1-year survival rate of 21%.[4] It is therefore important to consider patients with brain tumors—specifically, those with high-grade gliomas—for entry into clinical trials, which exist for all stages of disease from initial diagnosis to salvage therapy at relapse. This chapter provides basic principles that can be used for diagnosing and treating patients with brain tumors along with an introduction to the molecular mechanisms underlying gliomagenesis.

CLASSIFICATION

Brain tumors are either primary tumors that arise de novo or secondary metastases, the latter of which is far more common. Most commonly, brain metastases result from lung cancer followed by breast, melanoma, renal, and colorectal cancers. Most patients with brain metastases die from progression of their systemic cancer, but because of improvements in systemic therapy, brain metastases are now seen more frequently and with increasing morbidity and mortality. Advances in treating brain metastasis with surgery and radiotherapy (RT) have improved overall survival (OS) when systemic disease is controlled.

Primary brain tumors are classified by the World Health Organization (WHO) grading system (Table 48–1), which is based on the pattern of cell differentiation in the tumor, molecular characteristics (eg, isocitrate dehydrogenase [IDH] or 1p19q status), and histologic features associated with biological aggressiveness (ie, mitotic figures, necrosis, and vascular proliferation). Tumor grade is inversely correlated with prognosis, with grade I the least aggressive and grade IV the most. The most common primary brain tumors are meningiomas, gliomas, nerve sheath tumors, and pituitary tumors'.[5]

Molecular features are an increasingly significant factor in the WHO classification system because we have learned that some of these may better distinguish between distinct entities than histologic characterization alone. The Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW) was founded in 2016 and has sought to elucidate the im pact that such features have on tumor behavior and response to treatment. The upcoming WHO 2020-2021 classification is expected to incorporate several interim recommendations from the cIMPACT-NOW working groups that pertain to classification of IDH-mutant astrocytoma, identification of IDH wild-type astrocytomas with molecular features of glioblastoma, and definition of other types of glioma. These updates are further discussed in later sections.

EPIDEMIOLOGY

Brain Metastases

Brain metastases occur far more commonly than primary brain tumors. Nearly any type of primary cancer can metastasize to the brain, including hematologic malignancies. Most commonly, brain metastases originate from lung cancer, which represents the second most common systemic cancer in men and women.[6] The next most common pathology to metastasize to the brain is breast cancer followed by melanoma, renal cancer, and colorectal cancer.[7] Among solid tumors, melanoma has the highest propensity to metastasize to the brain. Based on autopsy findings, 40% to 60% of patients with melanoma develop brain metastases.[8]

Most brain metastases, particularly melanoma, present with multiple lesions, although when renal cancer metastasizes to the brain, it often results in a single lesion. Approximately 10% of metastatic lesions present as an intraparenchymal hemorrhage. Hemorrhagic metastases are most commonly seen in patients with melanoma, renal cell carcinoma, thyroid carcinoma, and choriocarcinoma. The pattern of distribution of metastases in the brain varies depending on the primary cancer. For example, posterior fossa metastases primarily originate from abdominal or pelvic primaries.

The incidence of brain metastases appears to be rising, which may be a consequence of increasingly sensitive imaging modalities such as magnetic resonance imaging (MRI), increased frequency of surveillance,

TABLE 48–1 Major Entities in the 2016 World Health Organization Classification of Tumors of the Central Nervous System

Diffuse Astrocytic and Oligodendroglial Tumors	
Diffuse astrocytoma (IDH-mutant, IDH wild-type, NOS)	Diffuse midline glioma, H3K27M-mutant
Anaplastic astrocytoma (IDH-mutant, IDH wild-type, NOS)	Oligodendroglioma (IDH-mutant and 1p/19q codeleted, NOS)
Glioblastoma (IDH-mutant, IDH wild-type, NOS)	Anaplastic oligodendroglioma (IDH-mutant and 1p/19q codeleted
Ependymal Tumors	
Subependymoma	Anaplastic ependymoma
Myxopapillary ependymoma	
Ependymoma (papillary, clear cell, tanycytic)	
Ependymoma, RELA fusion positive	
Neuronal and Mixed Neuronal-Glial Tumors	
Dysembryoplastic neuroepithelial tumor	Rosette-forming glioneuronal tumor
Gangliocytoma	Diffuse leptomeningeal glioneuronal tumor
Ganglioglioma	Central neurocytoma
Embryonal Tumors	
Medulloblastomas (can be genetically or histologically defined)	Embryonal tumor with multilayered rosettes (C19MC-altered, NOS)
CNS neuroblastoma	Atypical teratoid/rhabdoid tumor
Other Astrocytic Tumors	
Pilocytic astrocytoma	Pleomorphic xanthoastrocytoma
Subependymal giant cell astrocytoma	Anaplastic pleomorphic xanthoastrocytoma
Choroid Plexus Tumors	
Choroid plexus papilloma	
Choroid plexus carcinoma	
Tumors of the Pineal Region	
Pineocytoma	Pineoblastoma
Pineal parenchymal tumor of intermediate differentiation	Papillary tumor of the pineal region

CNS, central nervous system; IDH, isocitrate dehydrogenase; NOS, not otherwise specified.

and the improving survival of patients with metastatic disease. The development of brain metastases usually occurs in the context of systemic relapse, although relapses can be isolated to the central nervous system (CNS). The impermeability of the BBB, which often limits chemotherapy penetration into the CNS, may be the culprit in circumstances of isolated CNS relapse.

Primary Brain Tumors

Of the primary brain tumors, meningiomas arising from the arachnoid cap cells of the meninges represent the most common histologic entity, comprising 38% of all tumors and 53% of nonmalignant tumors.[5] The second most common group is glioma, which describes tumors arising from the glial support cells of the CNS and includes astrocytomas, oligodendrogliomas, and ependymomas. Combined, gliomas account for approximately 25% of all primary brain tumors and more than 80% of all malignant CNS tumors. As previously noted, glioblastoma is the most aggressive type of glioma and, representing 57% of this group, is also the most common. It is also the most common malignant primary brain tumor. The most recent data from the Central Brain Tumor Registry of the United States reported an incidence of all primary benign and malignant CNS tumors of 23.41 cases per 100,000 between 2012 and 2016.[5]

The incidence of primary brain tumors differs by age. Glioblastomas typically peak in incidence between ages 65 and 74 years, anaplastic gliomas peak between ages 45 and 54 years, and low-grade gliomas are most typically seen between ages 20 and 34 years.[5] In addition to the disparities of age, gender differences are seen in the incidence of primary brain tumors. Overall,

41.9% of all tumors diagnosed between 2012 and 2016 occurred in males (169,868 tumors) and 58.1% in females (235,872 tumors), and specific tumor types are noted to be more common in certain genders; for example, glioblastoma is more common in males and meningioma more common in females, potentially related to estrogen exposure.[5]

Primary CNS lymphoma (PCNSL), concordant with AIDS, has decreased since its peak in the early 1990s, when it reached 10.2 per 1 million person-years. By 1998, the incidence decreased to 5.1 per 1 million person-years, which was attributed to the treatment of human immunodeficiency virus (HIV) with highly active antiretroviral therapy in men younger than the age of 60 years.[9] An increased incidence in PCNSL is seen not only in HIV/AIDS but also in iatrogenic immunosuppression, such as organ transplant, autoimmune disease, and cancer. The rate for persons older than 60 years of age, however, has remained stable since 1994, at approximately 16 per 1 million person-years.[9]

Risk Assessment and Reduction

Although many factors have been considered as putatively involved in gliomagenesis, moderate- to high-dose ionizing radiation is the strongest established causative agent underlying the development of brain tumors, as was seen notably in atomic bomb survivors. Children are particularly radiosensitive, and it has been demonstrated that children given prophylactic cranial irradiation for acute lymphoblastic leukemia have an increased risk for both gliomas and meningiomas.[10] Increased risk of brain tumors has been seen after therapeutic irradiation for pituitary tumors as well. Even low doses of radiation previously used to treat scalp ringworm increased the risk of developing nerve sheath tumors, meningiomas, and gliomas.[11] Fortunately, diagnostic radiation does not appear to be strongly associated with the development of gliomas.[12] Although one recent review found an excess relative risk (1.29) of developing a brain tumor in children exposed to one or more head computed tomography (CT) scans, this association does not necessarily imply causation.[13] Judicious use of ionizing diagnostic radiation is nevertheless recommended in patients with underlying susceptibility to develop brain tumors, such as those with Li-Fraumeni syndrome.

Although a link between brain tumors and chemical exposure has been suggested, no specific agent has been identified with a link to brain tumors that can be validated with an exposure-disease correlation. No consistent link has been proven to underlie for the occurrence of cancer in agricultural workers. Positive correlations have been drawn between the occurrence of brain tumors and occupations involving exposure to synthetic rubber, vinyl chloride, and petroleum refining.[14] Whereas smoking is implicated in an increased risk for many cancers, it is not associated with an increased risk of brain tumors. Exposure to cured foods and nitrites has also been studied, with mixed results.[15] No correlation between alcohol intake or cosmetic use and brain tumors has been found.[16] There has been concern, particularly in the popular press, about the relationship between exposure to cell phones and the risk for brain tumors. Thus far, several case-control studies and a cohort study have failed to establish such a link.

Other than the increased incidence of PCNSL in patients with HIV infection, associations between viral exposures and brain tumors have not been consistent. Human cytomegalovirus (CMV) has recently garnered increasing attention in regard to its role in gliomagenesis. There is sufficient evidence that CMV sequences and viral gene expression exist in most gliomas and that CMV could modulate the malignant phenotype in glioblastoma, but a specific role of CMV in glioma development has yet to be defined.[17]

A protective effect of allergies (asthma, eczema, and hay fever) was noted in a meta-analysis of more than 3000 patients, with a relative risk of glioma incidence of 0.61,[18] supporting a role for immune modulation in brain tumor genesis. A retrospective case-control series demonstrated a decreased incidence of glioma in patients who reported histories of chickenpox, shingles, herpes simplex virus, and Epstein-Barr virus,[19] and as a surrogate for exposure to infections in early life, birth order was correlated with increased risk for the development of glioma in adulthood.[20]

Genetic Predisposition

Relatively few brain tumors are attributable to heredity; studies have cited from 1% to 5%.[21] Brain tumors can arise as a component of familial tumor syndromes, such as neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), Li-Fraumeni syndrome, and others.

NF1 is caused by a mutation of the *NF-1* gene on chromosome 17q11.2 that encodes the tumor suppressor protein neurofibromin that normally downregulates the RAS-MAPK (mitogen-activated protein kinase) pathway. Patients with NF1 are at increased risk for the development of gliomas originating predominantly in the optic pathway and brainstem. These neoplasms are typically pilocytic astrocytomas with a tendency toward a more indolent course compared with their sporadic counterparts. Optic gliomas are present in approximately 20% of patients with NF1 and cause symptoms in approximately one third of patients.[22] In addition to gliomas, NF1 is also associated with peripheral neurofibromas, café-au-lait macules, iris hamartomas, and other malignancies,

including leukemia and pheochromocytoma. Cancer is the second leading cause of death in patients with NF1.

NF2 is marked by a mutation of the *NF-2* gene on chromosome 22q12 that encodes the protein merlin. NF2 is associated with bilateral vestibular schwannomas, meningiomas, and gliomas, including an increased risk for ependymomas, particularly of the spinal cord at the cervicomedullary junction. Meningiomas occur in approximately 80% of patients with NF2 and are largely low grade with benign behavior.[23]

Several other notable genetic syndromes confer an increased risk of developing brain tumors. Li-Fraumeni syndrome results from an autosomal dominant mutation of the *p53* tumor suppressor gene, located on chromosome 17p. This *p53* mutation results in many types of malignancies, including glioma and medulloblastoma, as well as sarcoma, breast cancer, leukemia, and adrenocortical cancer. Gorlin syndrome results from mutations in tumor suppressor gene *PTCH1* on chromosome 9 and is associated with increased risks of meningioma and medulloblastoma. Turcot syndrome is an autosomal dominant disease characterized by multiple polyps of the gastrointestinal tract as well as brain tumors. Two separate mutations have been identified in Turcot syndrome. One involves the adenomatous polyposis coli gene, which is associated with medulloblastoma, and mutation of the *hMLH1* DNA mismatch repair gene is associated with glioblastoma.

BIOLOGY AND MOLECULAR GENETICS

The understanding of cancer relies on uncovering the underlying molecular biologic mechanisms and signaling pathways that drive tumorigenesis. Delineating such mechanisms is complicated by the tremendous degree of intertumoral and intratumoral heterogeneity. Newer drugs target specific extracellular receptors or block intracellular signal transduction systems.

Glial Tumors

Pathway Alterations

Malignant glial tumors often exhibit significant histologic heterogeneity, which is reflected at the molecular level. Large-scale profiling efforts have accelerated our understanding of gliomas. The landscape of somatic genomic alterations has been comprehensively characterized by The Cancer Genome Atlas (TCGA). In the 2013 TCGA publication, alterations in three core overlapping pathways were described: receptor tyrosine kinase–RAS–phosphatidylinositol 3 kinase (RTK-RAS-PI3K [phosphoinositide 3-kinase]) signaling (altered in 90% of glioblastomas), p53 signaling (altered in 86% of glioblastomas), and retinoblastoma (*RB*) signaling (altered in 79% of glioblastomas). The alterations affecting the p53 pathway (*MDM2, MDM4,* and *TP53*), the Rb pathway (*CDK4, CKD6, CCND2, CDKN2A/B,* and *RB1*), and the PI3K pathway (*PIK3CA, PIK3R1, PTEN, EGFR, PDGFRA*, and *NF1*) were found to be mutually exclusive.[24] Of the 251 glioblastomas analyzed, at least one RTK was found altered: *EGFR* (57.4%), *PDGFRA* (13.1%), *MET* (1.6%), and *FGFR2/3* (3.2%). Mutations of PI3K were found in 25.1% of glioblastomas and were found to be mutually exclusive for *PTEN* mutations and deletions. The p53 pathway was found to be altered in 85.3% of tumors through mutations and deletion of *TP53* (27.9%), amplification of *MDM1/2/4* (15.1%), or deletion of *CDKN2A* (57.8%).[24] TCGA analysis also identified mutations in genes for which targeted therapies have been developed, including *BRAF*[25] and *FGFR1/FGFR2/FGFR3*.[26]

The epidermal growth factor (EGF) pathway was found to be altered in 57.4% of glioblastoma (GBMs) in the most recent TCGA data. An alternate mutation in the external domain generates a truncated receptor, the EGFRvIII mutant, which is constitutively activated in gliomas.[27] Growth factors such as EGF and platelet-derived growth factor (PDGF) activate multiple signal transduction pathways that lead to cell survival and proliferation. The *EGFR* can activate the PI3K pathway, which is also frequently mutated in glioma. When the PI3K pathway is activated, the activation of *AKT* (protein kinase B) is triggered, in turn activating multiple prosurvival pathways, such as nuclear factor κB (NF-κB), forkhead, and glycolysis. The activation of the PI3K pathway has been associated with the reduced survival of patients with glioma.[28] Growth factors can also stimulate the *ras* pathway, which initiates a signal cascade through *Raf-MEK-Erk* and promotes cell survival and tumorigenesis.[29] PTEN (phosphatase and tensin homolog) has phosphatase activity that inhibits the PI3K pathway. The deletion of *MMAC/PTEN* leads to *AKT* pathway activation. The activation of *p53* can result in either apoptosis or cell cycle arrest and initiation of DNA repair mechanisms. The abrogation of *p53* activity would be expected to increase proliferation and mutations, leading to genetic instability, the prodrome of tumorigenesis.

Cell cycle regulation is a key target of carcinogenesis. Cell cycle checkpoints are affected by multiple proteins, acting either as accelerators or inhibitors of cell regulation. Important molecules in this process include *p53, p21,* and *MDM*. Another cell cycle regulation pathway important for glial tumors involves the *RB* gene. When the *RB* gene is phosphorylated, the E2F transcription factor is released and activates cellular proliferation. The regulation of *RB* activity is complex and involves multiple cyclins (cyclin D), cyclin-dependent kinases (CDK4/6), and CDK inhibitors (p16), whose activities are under investigation.[30]

Gliomagenesis

The majority of glioblastomas (~90%) are primary, characterized by rapid development in the absence of any clinical or histologic evidence of a lower-grade lesion, in contrast to secondary glioblastomas, which are IDH mutated and progress from a low-grade astrocytoma or anaplastic astrocytoma. Primary and secondary glioblastomas arise from distinctly different genetic pathways. Primary glioblastomas are postulated to develop quickly from glial progenitor cells over a period of a few months, potentially acquiring mutations in *EGFR, TP53*, or *PTEN*. In contrast, secondary glioblastomas are believed to arise from a stepwise accumulation of mutations.

IDH mutations are believed to be a very early event in gliomagenesis that persist during progression to secondary glioblastomas. The *IDH1/2* mutations likely occur before the acquisition of a *TP53* mutation, a driving force toward astrocytic differentiation, and before the acquisition of 1p/19q loss which believed to be the driving force toward oligodendroglial differentiation. Codeletion of 1p/19q has been classified as the genetic signature of oligodendrogliomas. Recent exomic sequencing has revealed that mutations in the *CIC* gene at 19q13.2 and *FUBP1* gene at 1p are also frequently observed in oligodendrogliomas. In addition to the acquisition of *TP53* mutations, *ATRX* mutations are often noted in WHO grade II and III astrocytomas and secondary glioblastomas.[31]

Predictive and Prognostic Factors

In glioma, allelic losses of chromosomes 1p and 19q (1p19q loss) emerged as markers of chemotherapeutic response and longer survival,[31] qualifying 1p19q loss as a prognostic factor. Studies have also confirmed that 1p/19q LOH is also predictive of response to chemotherapy. In independent seminal studies by the European Organization for Research and Treatment of Cancer (EORTC) and Radiation Therapy Oncology Group (RTOG), patients with anaplastic oligodendrogliomas harboring 1p/19q LOH did significantly better when treated with a combination of radiation and chemotherapy compared with treatment with radiation alone. Tumors without 1p/19q LOH did not incur a survival benefit.[32–34] 1p19q loss was subsequently determined to be a defining characteristic of oligodendroglioma histology, allowing for elimination of the previous diagnostic entity "mixed oligoastrocytoma."

O6-methylguanine-DNAmethyltransferase(MGMT) is a DNA repair protein that reverses DNA damage induced by alkylating agents such as temozolomide and has been implicated as a major mechanism of resistance to alkylating agents. Hypermethylation of the promoter region of the *MGMT* gene, which inactivates *MGMT* gene transcription, has been associated with response to alkylating agents and increased survival in patients with glioma.[35]

IDH mutations were first reported in 2008[36] and quickly became a seminal discovery. The *IDH* mutations now definitively distinguish primary from secondary glioblastomas and have been established as a positive prognostic factor with an increase in OS noted in patients harboring an *IDH* mutation over those with wild-type *IDH*.[37] In low-grade glioma, anaplastic glioma, and glioblastoma, *IDH*-mutation status appears to be the most important prognostic factor.[36,38] In a study of 382 patients with high-grade gliomas, *IDH1* mutation was found to be of greater prognostic relevance than histologic diagnosis according to the 2007 WHO classification system. The sequence of more favorable to poorer outcome was[1] anaplastic astrocytoma with *IDH1* mutation,[2] glioblastoma with *IDH1* mutation,[3] anaplastic astrocytoma without *IDH1* mutation, and[4] glioblastoma without *IDH1* mutation.[38]

Given the information from recent studies, a logical flow to identification of diffuse gliomas has been established in the WHO 2016 classification. After a diffusely infiltrative glioma has been identified on histopathology, testing for IDH1 and IDH2 is undertaken by either immunohistochemistry or next-generation sequencing.

If an IDH mutation is identified, then evaluation for combined loss of chromosome arms 1p and 19q through balanced translocation may be required in tumors that are suspicious for oligodendroglioma. If needed, it is done via fluorescence in situ hybridization. This is done in this sequence as 1p19q loss is essentially only found in IDH-mutated tumors. Loss of 1p19q defines oligodendroglioma (and anaplastic oligodendroglioma), whereas intact 1p19q defines IDH-mutant astrocytomas (including diffuse astrocytoma, anaplastic astrocytoma, and glioblastoma, though the latter may be renamed to IDH-mutated astrocytoma, grade IV, to better distinguish it from IDH wild-type glioblastoma). It has also been noted that CDKN2A and CKDN2B loss is associated with poor prognosis in IDH-mutant astrocytoma, and this feature may be incorporated into subsequent classification schema.[39]

If 1p and 19q are intact or there is only loss of one arm, additional tests may help to clarify. ATRX mutation (or "loss" of normal expression) and TP53 mutation characterize astrocytoma, whereas as previously noted CIC, TERT promoter, and FUBP1 mutations are typically found in oligodendroglioma. CIC mutations are associated with worse OS. It is important to note that TERT promoter mutations are common in both oligodendroglioma and glioblastoma; therefore, first classifying by IDH and 1p19q status is essential. TERT promoter mutations are also prognostically significant, and detection of these mutations was found to be

associated with better prognosis in oligodendroglioma and oligoastrocytoma in historical studies of glioma.

In IDH wild-type glioma, several molecular features have been identified that confer a worse prognosis. A recent publication by the cIMPACT-NOW working group recommends that IDH wild-type glioma with EGFR amplification, or combined gain of chromosome 7 and loss of chromosome 10, or TERT promoter mutation should be classified as "diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV." This means that even histologically "lower-grade" tumors are expected to behave more similar to glioblastoma than other grade II or grade III entities.[40]

Meningiomas

Germline mutations of the NF2 gene result in neurofibromatosis type 2, as described earlier, though somatic mutations are also frequently noted, and disruption is seen in approximately half of meningiomas.[41,42] Merlin, as noted, functions as a tumor suppressor and is a member of a family of cytoskeleton-associated proteins linked to RTK activity and ECM interactions.[43]

In one study, whole-genome or whole-exome sequencing was performed on 17 sporadic meningiomas. The majority of meningiomas harbored simple genomes, with fewer mutations, rearrangements, and copy number alterations than observed in other adult tumors. Focal *NF2* inactivation was confirmed in 43% of tumors.

A subset of meningiomas lacking *NF2* alterations exhibited recurrent oncogenic mutations in *AKT1* and *SMO* with immunohistochemical (IHC) evidence of activation of their pathways. Mutations involving *SMO* were observed in 3 of 17 tumors, and *AKT*1 mutations were noted in 5 of 17 samples. Interestingly, these mutations were seen in the more therapeutically challenging tumors involving the skull base and were of higher grade.[44] Hyperactive Hedgehog signaling has been linked to many other cancers and is under active investigation in meningiomas highlighting SMO as a potential therapeutic target.[45] Inhibitors of PI3K/AKT/mTOR (mammalian target of rapamycin) are also under active investigation for meningiomas harboring *AKT1* mutations.

Of note, other inherited syndromes are associated with meningioma to be aware of, including schwannomatosis (mutation in SMARCB), Gorlin syndrome (PTCH1), and Coffin-Siris syndrome (SMARCE1).

Brain Metastases

The development of brain metastases is an intricate sequential process. In addition to proliferating, tumor cells must migrate and enter the systemic circulation, survive, travel, or transport through the blood to the brain; adhere to and extravasate through the endothelium, invade the brain parenchyma; and proliferate, which requires the recruitment of a secondary blood supply. Failure at any of these steps will halt the metastatic process. Each of these steps requires complex interactions between the tumor cell and its changing microenvironment.

An understanding of the biological processes of brain metastases and the role of the BBB provides potential targets for intervention to improve treatment. There are multiple complex regulators of cell adhesion, including molecules such as integrins, cadherins, selectins, and heparin sulfate proteoglycans.[46] In addition, integrins can recruit intracellular signaling molecules such as focal adhesion kinase and src, which can lead to a cascade of cellular signaling that affects cell cycle control and proliferation. Integrins also play a part in regulating angiogenesis and tumor invasion. Other molecules that mediate invasion include the MMP family, serine proteases, and heparinase.[47]

Tumor cells must generate their own blood supply if they are to grow successfully and remain viable. Important activators of angiogenesis include vascular endothelial growth factor (VEGF), angiopoietin, hypoxia-inducible transcription factor, cyclooxygenase 2, PDGF, integrins, matrix metalloproteinases, and others. Important inhibitors of angiogenesis include angiostatin, endostatin, tissue inhibitors of matrix metalloproteinases (TIMPs), interferons, and platelet factor 4.[48] Upregulation of activators or downregulation of inhibitors favors angiogenesis. As tumors grow, they begin to produce increasing numbers of angiogenic molecules that can participate in metastasis.[48] Because a multitude of pathways are involved in tumor growth and invasion, it is likely that if one pathway is inhibited, cells may escape through alternate pathways.

Effective drug delivery through the BBB to tumor cells is a significant obstacle to chemotherapy, both for brain metastases and primary brain tumors. The P-glycoprotein family of transporters actively exports drugs such as anthracyclines, vinca alkaloids, taxanes, and etoposide.[49] The BBB can be breached by circulating cancer cells, which migrate across the BBB without degrading its permeability and proliferate. When the tumor reaches a size that requires recruitment of new vessels, the BBB is disrupted, which allows imaging of brain tumors with contrast agents. In experimental models, whereas brain metastases smaller than 0.25 mm in diameter are associated with an intact BBB, larger tumors demonstrate BBB permeability.[50] Despite the presence of the BBB, studies of drug levels in brain tumors from systemic delivery have demonstrated pharmacologically relevant concentrations of drugs such as etoposide, cisplatin, cytarabine, and

methotrexate. Measurements of drug levels in cerebrospinal fluid (CSF) are not accurate indicators of tissue drug levels and vary widely depending on the agent.[51] Finding novel ways to circumvent the issues presented by the BBB is an area of active research. Current strategies under development include the use of focused ultrasound to open the BBB, the use of immunotherapy (checkpoint inhibitors, for example, are not required to enter the CNS to exert their effects on the immune system), and the increasing use of BBB-penetrant small-molecule drugs such as alectinib, which can have both systemic and CNS effects. These approaches are discussed in further detail later in this chapter.

Similarly, the development of leptomeningeal disease depends on tumor cells adapting to the harsh, relatively oxygen and micronutrient-poor environment in the CSF. Tumor cells are thought to enter the leptomeningeal space through hematogenous dissemination, direct invasion from a tumor adjacent to the cranial or peripheral nerves, or venous spread.

CLINICAL PRESENTATION, DIAGNOSIS, AND PATHOLOGY

Clinical Presentation

Brain tumors are usually diagnosed after presentation with symptoms such as seizure, headache, or focal neurologic deficits. We commonly see high-grade, malignant tumors presenting with headache, which reflects elevated intracranial pressure, and focal neurologic signs, such as weakness or aphasia. Low-grade glial tumors often come to attention with seizure, possibly caused by *IDH* mutation, resulting in accumulation of 2-hydroxyglutarate, which mimics an excitatory neurotransmitter. Other slow-growing tumors, such as meningioma, may be clinically silent and incidentally detected during imaging for an unrelated problem.

Diagnosis

Universally, the first step in diagnosis is imaging. We use contrast-enhanced MRI, the diagnostic standard, for brain tumor imaging. In addition to its superior sensitivity compared with CT, MRI provides more detailed anatomic as well as physiologic information that can contribute to a differential diagnosis. Although contrast-enhanced CT can detect high-grade lesions that cause BBB breakdown, low-grade lesions may be detectable only on MRI using sequences sensitive for edema, ischemia, and tissue changes. Even in the case of known systemic primary cancer, contrast-enhanced CT may miss small foci of metastatic disease that are visible on MRI (Figs. 48–1 to 48–8). In special cases, advanced brain tumor imaging techniques such as MR spectroscopy, positron emission tomography (PET), or perfusion may be indicated, which is discussed further later.

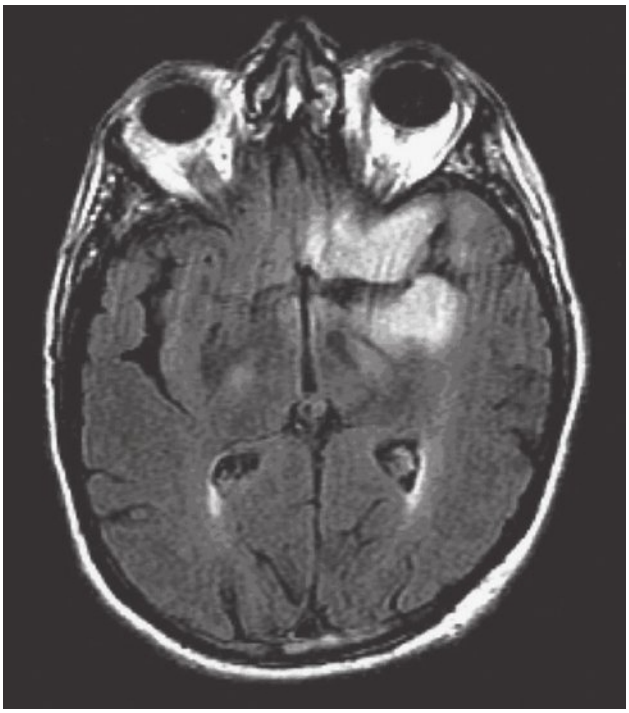


FIGURE 48–1 Low-grade glioma.

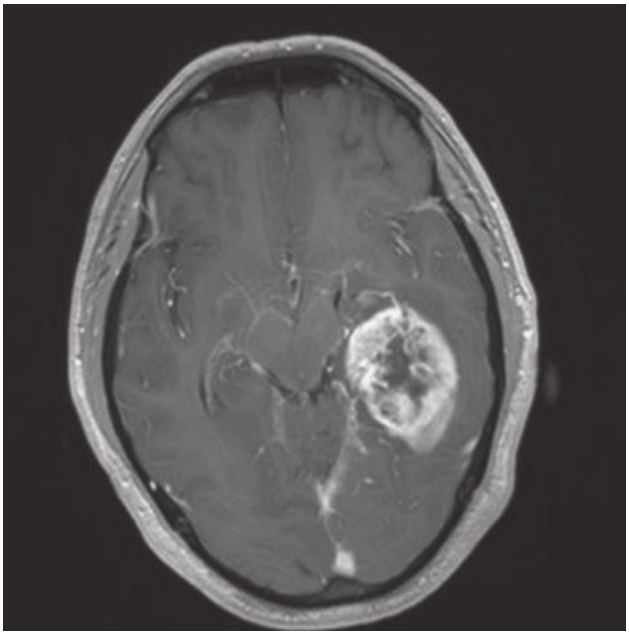


FIGURE 48–2 Glioblastoma.

Noncancerous brain lesions that may be mistaken for malignancy on imaging include infection, demyelinating disease, vascular malformations, and stroke. A particular variant of demyelinating disease (tumefactive

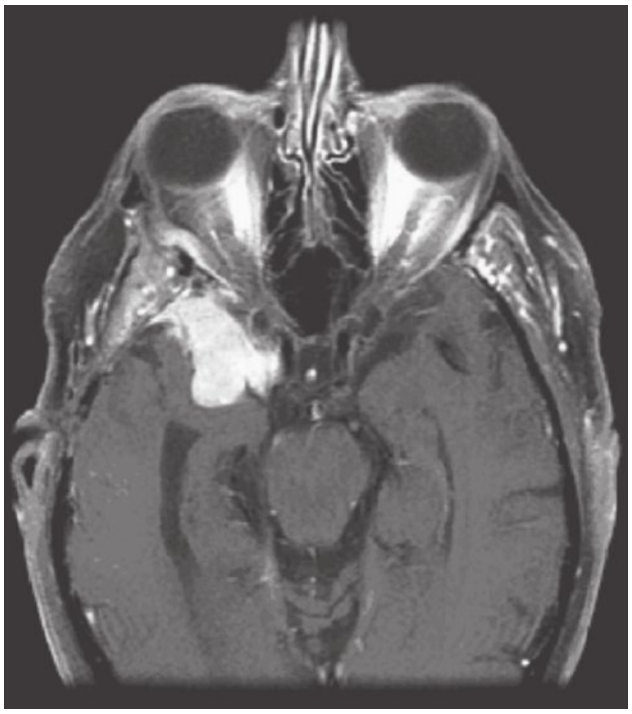


FIGURE 48–3 Meningioma.

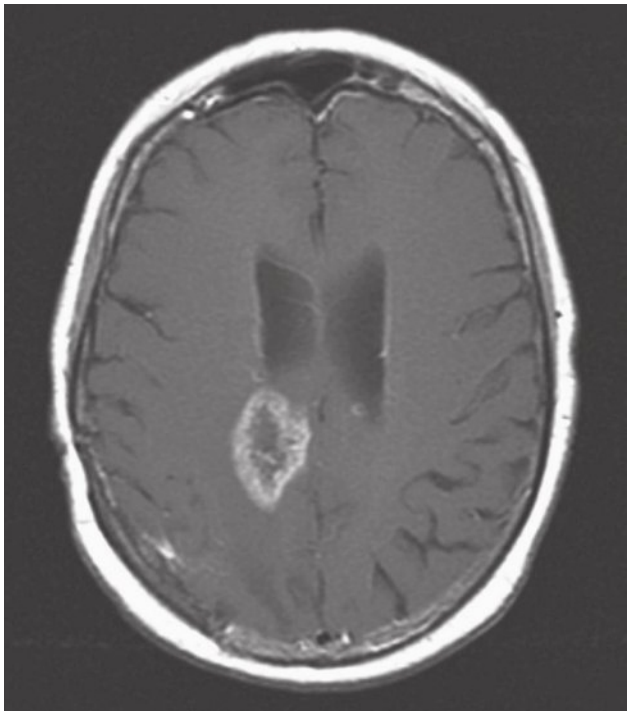


FIGURE 48–4 Radiation necrosis.

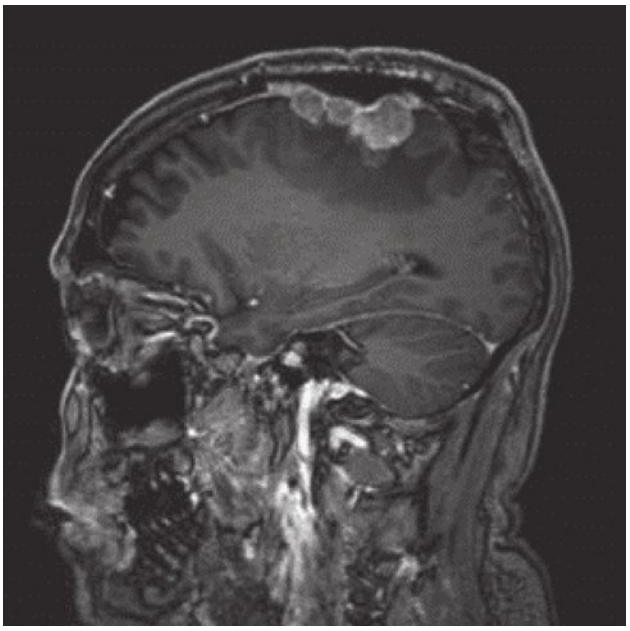


FIGURE 48–5 Anaplastic meningioma.

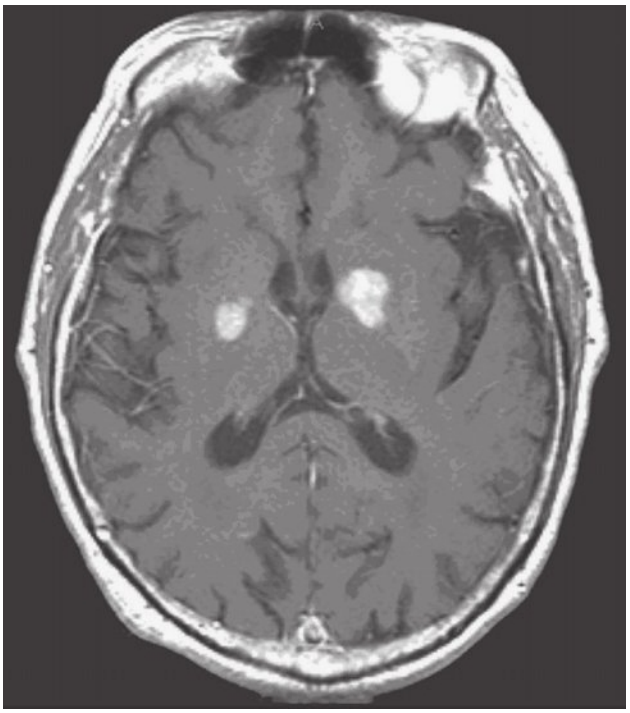


FIGURE 48–6 Central nervous system lymphoma.

multiple sclerosis) with large focal tumorlike lesions is known to resemble a malignant brain tumor. Unfortunately, some of these lesions have been irradiated, under the presumptive diagnosis of glioblastoma, which only increases the severity of the demyelination. Conversely, patients with primary brain tumors are sometimes initially diagnosed with stroke or demyelinating disease. Further complicating the picture are patients who have brain tumors in addition to stroke, which is far more prevalent with increasing age. Patients with systemic cancer, often in remission,

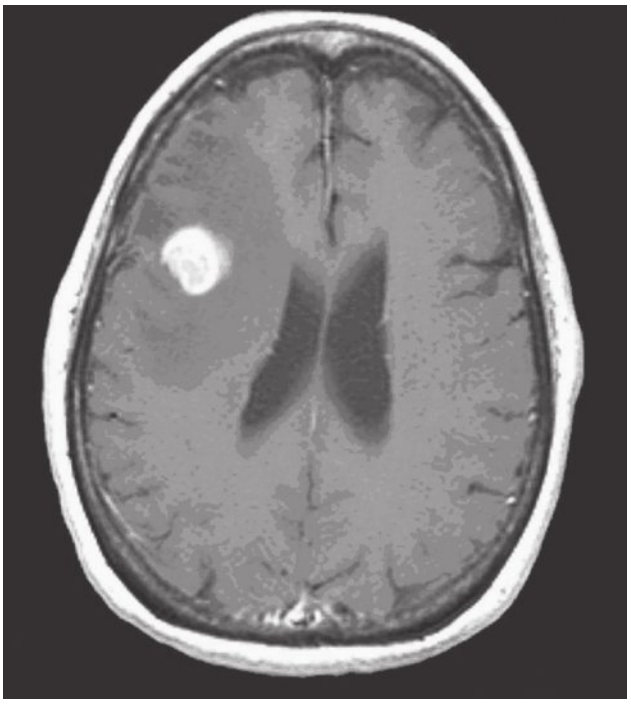


FIGURE 48–7 Single brain metastasis, lung adenocarcinoma.

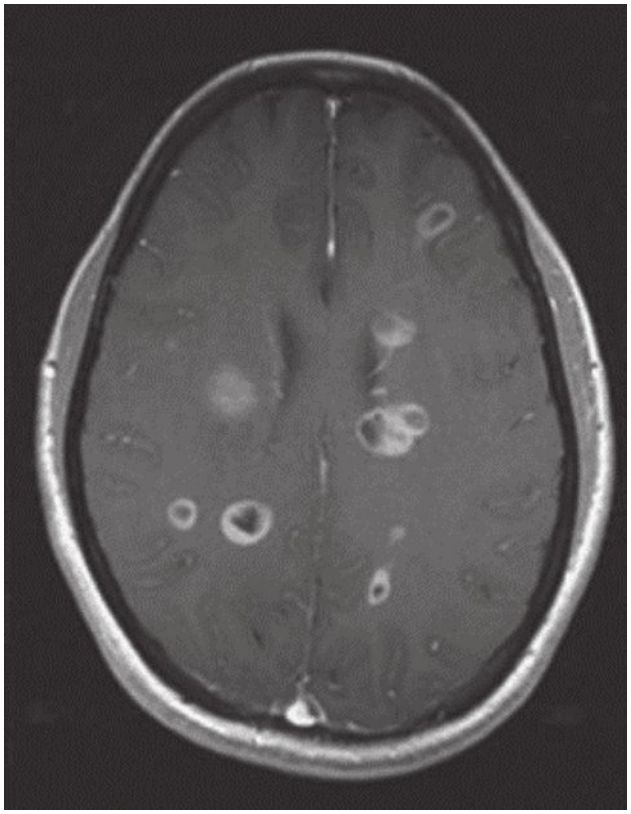


FIGURE 48–8 Multiple brain metastases, breast.

or in stable condition, can present with brain lesions that are suspected to be brain metastases but turn out to be a primary brain tumor. These types of cases often benefit from an interpretation by a specialized neuroradiologist who has been provided with a relevant patient history. A history of immunosuppression and multiple subcortical enhancing lesions may prompt the suspicion of a PCNSL or infection with toxoplasmosis. Further testing with brain thallium single-photon emission computed tomography (SPECT) scanning or fluorodeoxyglucose (FDG) imaging may serve to distinguish between the two possibilities.

Several classic radiographic appearances of brain tumors suggest malignancy. An irregular enhancing lesion with extensive edema following white matter pathways suggests a malignant glioma. Non–contrast-enhancing lesions with increased diffuse signals on FLAIR (fluid-attenuated inversion recovery) imaging suggest a low-grade astrocytoma. Recently, an imaging characteristic called "T2–FLAIR mismatch"—wherein a lesion is hyperintense on T2-weighted imaging but predominantly hypointense with a small hyperintense rim on FLAIR—has been shown to be a highly specific finding in IDH-mutant, 1p19q intact tumors.[52] As a general rule for glial tumors, the presence of contrast enhancement suggests a high-grade malignancy. The WHO grade IV tumors nearly always enhance, as opposed to grade II tumors, which are typically nonenhancing. Two notable exceptions include pilocytic astrocytoma (WHO grade I) and pleomorphic xanthoastrocytoma (WHO grade II), which typically have an enhancing nodule and associated cyst. Meningiomas are typically homogeneously enhancing dural-based lesions associated with calcification. The appearance of multiple enhancing subcortical lesions with homogeneous enhancement suggests PCNSL. However, the same lesions, if associated with a known primary malignancy, may indicate brain metastases.

The brain tumor imaging characteristics seen on MRI are helpful in making a diagnosis. However, confirmation of the diagnosis with pathology is necessary in nearly all cases. It should be noted that testing of the CSF for tumor markers, cytology, and cell-free DNA is an emerging modality for diagnostic pathology of brain tumors. One recent report showed that tumor-derived DNA was detected in CSF in 49.4% of patients with infiltrative glioma, particularly in patients with significant disease burden, and correlated well with certain early, foundational mutations (eg, IDH) in the primary tumor.[53] The significance of other mutations in the CSF is less clear. At this point, CSF sampling does not obviate the need for surgical biopsy or resection of a parenchymal lesion in most situations.

The discovery of a brain lesion should therefore trigger prompt referral to a neurosurgeon. A referral to a specialized neuropathologist may be necessary for

diagnosis of uncommon or rare tumors and in cases when there is only limited biopsy tissue available. Biopsies must be of adequate quality and be representative of the overall tumor to allow accurate diagnosis. Our institution insists on reviewing patient diagnostic slides before rendering a treatment recommendation, and it is not uncommon for our neuropathologists to disagree with the diagnosis provided by the referring physician. One study found diagnostic discrepancy in up to 42% of cases reviewed by neuropathologists at our institution, with 8.8% of disagreements being categorized as "serious" such that they would impact treatment.[54] Primary brain glial tumors are graded according to the most malignant portion of the tumor. A brain lesion that is predominantly grade III astrocytoma but has a few regions that meet the criteria for grade IV astrocytoma (glioblastoma) should be graded as a glioblastoma. The tumor grade may be underestimated if the most malignant portion of the tumor is not sampled. Typically, the most malignant region corresponds to an area of contrast enhancement. If a patient is suspected of having PCNSL, the use of corticosteroids should be avoided. Primary CNS lymphoma can be sensitive to steroids that are lymphocytolytic, and the preoperative use of even small doses of corticosteroids can lead to a nondiagnostic biopsy. These patients usually require repeat biopsy after steroid discontinuation. Patients may present with deep central lesions involving the brainstem or thalamus. These cases may require referral to a specialized neurosurgical center to evaluate whether open biopsy, resection, or stereotactic-guided biopsy is appropriate. In these cases, close coordination with a department of neuropathology is critical in obtaining adequate tissue for diagnosis.

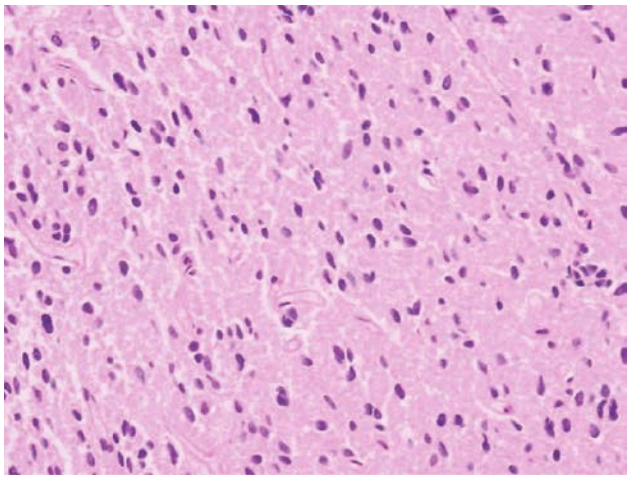


FIGURE 48–9 Low-grade astrocytoma, World Health Organization grade II (×200). (Used with permission from Dr. Gregory N. Fuller.)

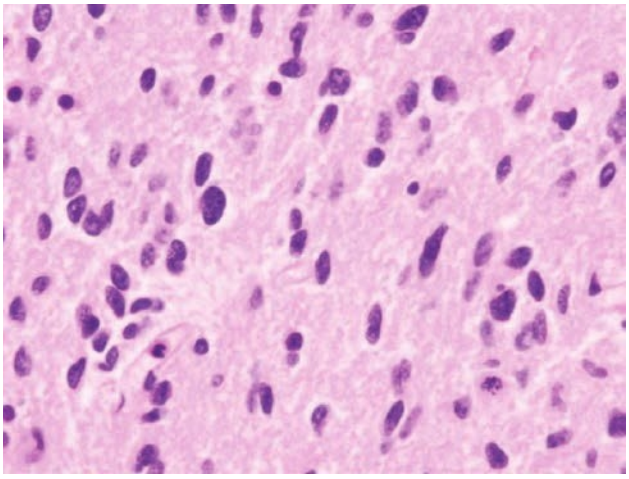


FIGURE 48–10 Low-grade astrocytoma, World Health Organization grade II (×400). (Used with permission from Dr. Gregory N. Fuller.)

Pathology

Diffuse astrocytomas are characterized by well-differentiated astrocytes—fibrillary, gemistocytic, or rarely protoplasmic—with mildly increased cellularity. The cellular morphology of the tumor cells may differ within the same tumor sample and show great variability between tumors. Necrosis and microvascular proliferation are absent. Rare mitotic figures may occur, and nuclear atypia may be present but not sufficiently to characterize the tumor as an anaplastic astrocytoma. The typical MIB-1 labeling index is less than 4% (Figs. 48–9 and 48–10).

Oligodendrogliomas are characterized by moderately cellular tumor cells with rounded, homogeneous nuclei, giving a "fried egg" artifactual appearance that is referred to as "classical oligodendroglioma" As noted earlier, after several studies including an RTOG trial found that 80% of tumors with classical oligodendroglial morphology were associated with 1p/19q deletion compared with only 13% of 1p and 19q deletions seen in nonclassical oligodendrogliomas; 1p19q codeletion is now a defining feature of oligodendroglioma. Microcalcifications, microcyst formation, extracellular mucin deposition, and a dense network of branching capillaries are other oligodendroglial features. Nuclear atypia may be seen, but significant mitotic activity or microvascular proliferation is suggestive of an anaplastic tumor. The MIB-1 index is typically less than 5% (Figs. 48–11 and 48–12).

Anaplastic oligodendrogliomas are characterized by oligodendroglial cells, with signs of increased cellularity, nuclear atypia, and mitotic activity. Cellular pleomorphism may be present, with formation of multinucleated giant cells or spindle cells. Gliofibrillary

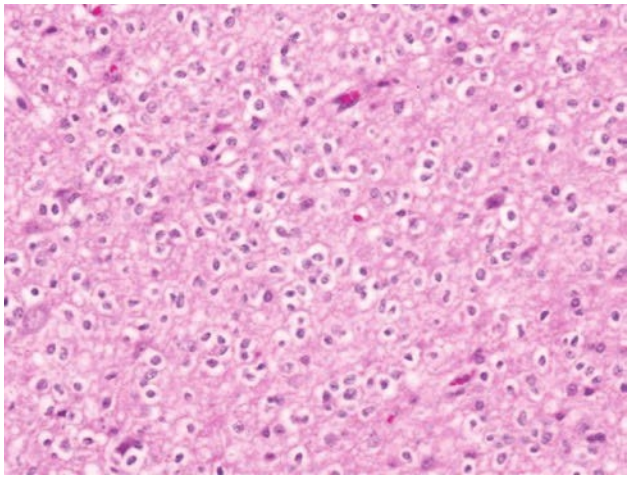


FIGURE 48–11 Oligodendroglioma, World Health Organization grade II (×200).

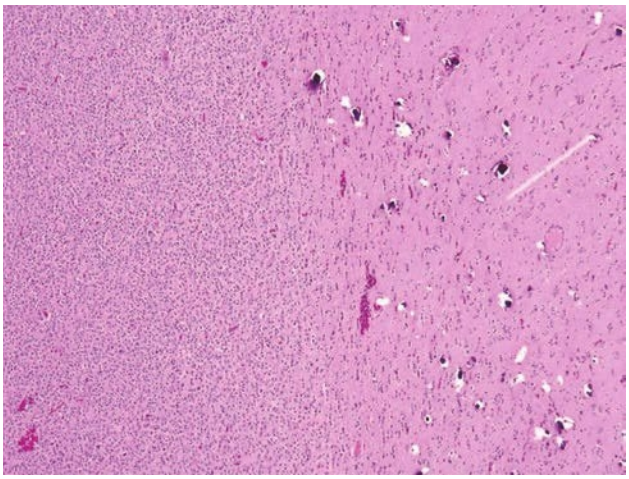


FIGURE 48–13 Anaplastic oligodendroglioma, World Health Organization grade III (×40).

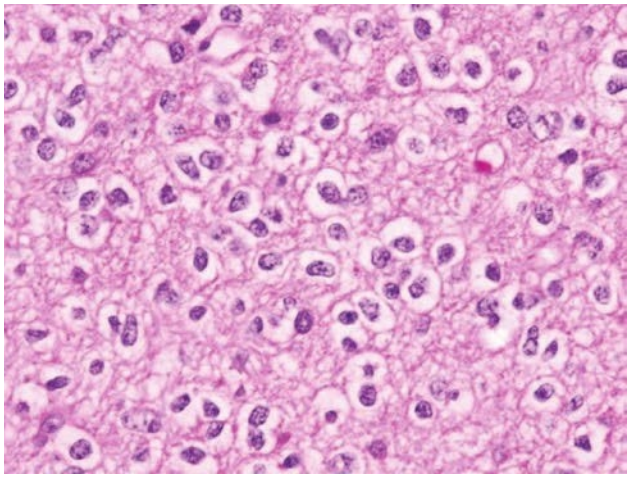


FIGURE 48–12 Oligodendroglioma, World Health Organization grade II (×400).

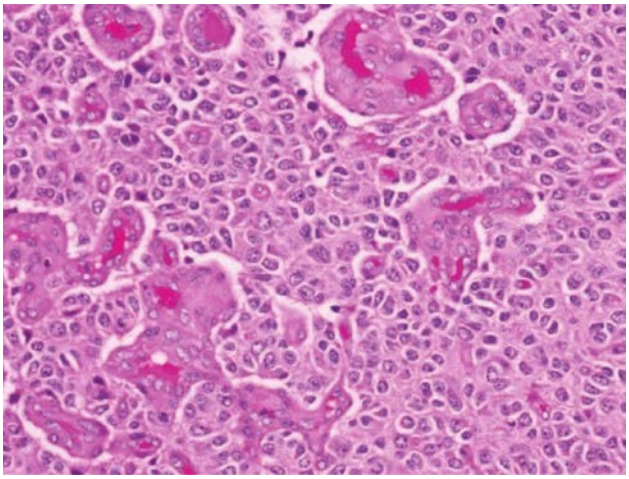


FIGURE 48–14 Anaplastic oligodendroglioma, World Health Organization grade III (×200).

oligodendrocytes and minigemistocytes are common. Although microvascular proliferation and necrosis may be present, their presence does not change the diagnosis to glioblastoma. There is currently no designation for a WHO grade IV oligodendroglioma. The MIB-1 ratio is usually greater than 5% (Figs. 48–13 to 48–15.)

Anaplastic astrocytoma is characterized by diffusely infiltrating astrocytes with increased cellularity, nuclear atypia, and mitotic activity. They are more cellular than low-grade astrocytomas, and the nuclear atypia include formation of nuclear inclusions, multinucleated cells, and abnormal mitoses. Microvascular proliferation is absent; if present, it would upgrade the tumor to glioblastoma. The typical MIB-1 labeling index ranges from 5% to 10% and can occasionally overlap with index values for low-grade astrocytoma and glioblastoma (Figs. 48–16 and 48–17).

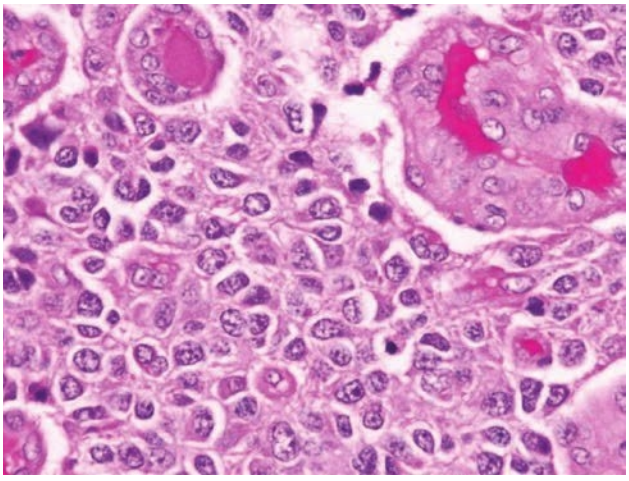


FIGURE 48–15 Anaplastic oligodendroglioma, World Health Organization grade III (×400).

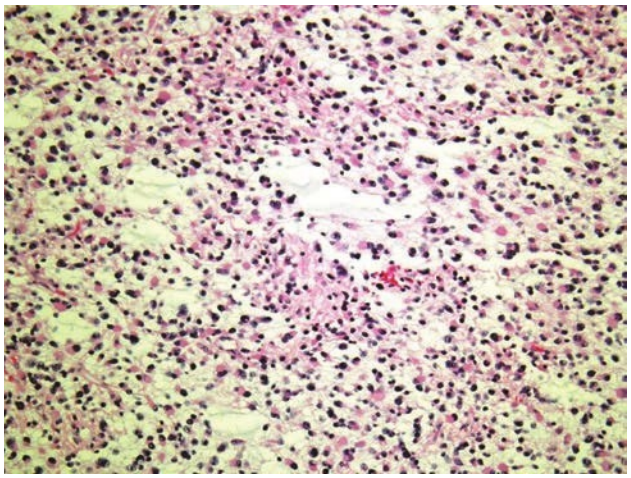


FIGURE 48–16 Anaplastic astrocytoma, World Health Organization grade III (×100).

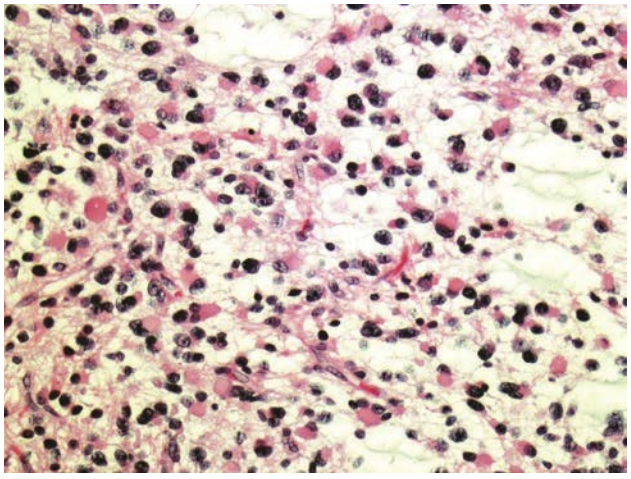


FIGURE 48–17 Anaplastic astrocytoma, World Health Organization grade III (×200).

Glioblastoma and glioblastoma multiforme are synonymous; "multiforme" was dropped from the name in the 2007 WHO classification book, although glioblastoma is still commonly referred to as GBM or glioblastoma multiforme. Glioblastoma is an anaplastic cellular tumor with marked nuclear atypia and mitotic activity, often with marked regional heterogeneity and cellular polymorphism. The presence of either microvascular proliferation or necrosis differentiate this lesion from anaplastic astrocytoma. Other features associated with glioblastoma include formation of epithelial "adenoid" structures, multinucleated giant cells, granular cells, lipidized cells, perivascular lymphocytes, and metaplasia. Glioblastoma is associated with a high proliferative rate, and MIB-1 labeling typically ranges from 15% to 20% (Figs. 48–18 to 48–20).

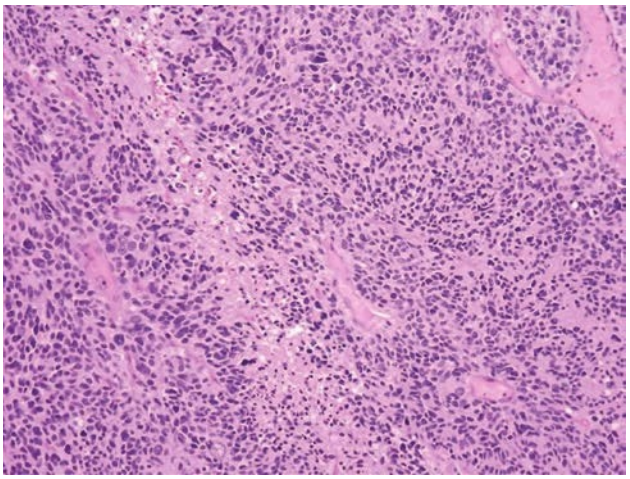


FIGURE 48–18 Glioblastoma, World Health Organization grade IV (×100).

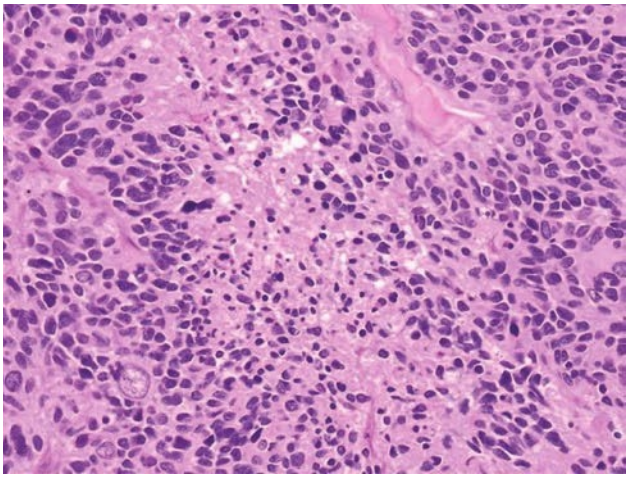


FIGURE 48–19 Glioblastoma, World Health Organization grade IV (×200).

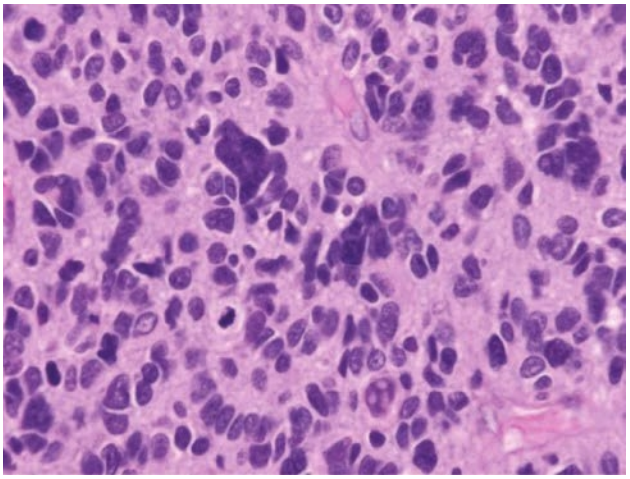


FIGURE 48–20 Glioblastoma, World Health Organization grade IV (×400).

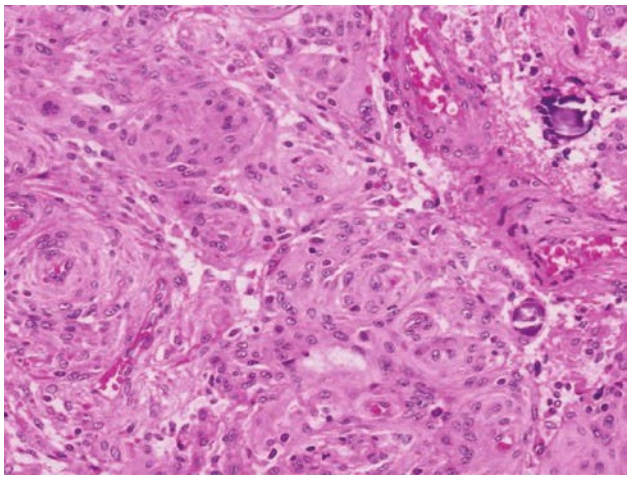


FIGURE 48–21 Meningioma (×100).

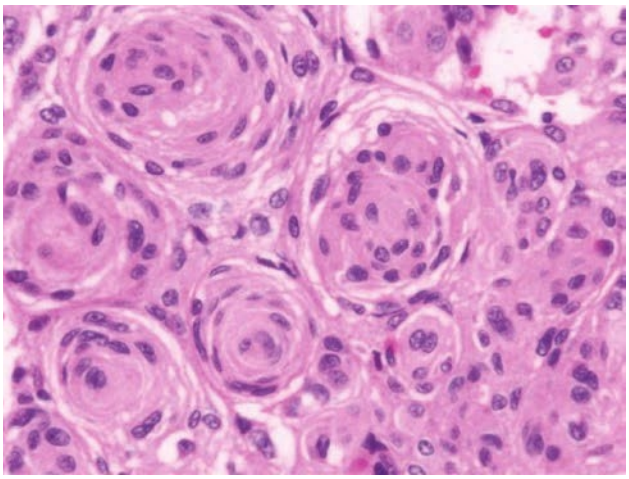


FIGURE 48–22 Meningioma (×200).

As noted in the earlier discussion of molecular genetics, molecular profiling is becoming an increasingly important tool in classification of different tumors. At our institution, molecular classification of diffuse gliomas has become standard. IDH and 1p/19q status are now routinely reported as part of an integrated diagnosis in addition to other pathologic features, including morphologic characteristics such as oligodendroglial or astrocytic phenotype, the results of other relevant IHC stains or diagnostic molecular tests (eg, p53, ATRX, *EGFR* amplification, proliferation indices), and the method of molecular feature determination (eg, fluorescence in situ hybridization, IHC, comparative genomic hybridization).55 This comprehensive format helps inform clinical decision making and patient counseling.

Meningiomas can have a wide range of appearances and are subtyped according to their appearance. Most meningiomas are grade I. The transitional variant has numerous concentric "onion bulb" structures. The psammomatous variant has calcified psammoma bodies. Pleomorphic nuclei and occasional mitoses are allowed, although four or more mitoses per 10 high-power field (hpf) would qualify in diagnosing atypical meningioma, grade II. Increased cellularity, high nuclear-to-cytoplasmic ratio, prominent nucleoli, and foci of necrosis also upgrade these to a grade II. Anaplastic meningiomas, grade III, have more than 20 mitoses per 10 hpf or obviously malignant cytology resembling carcinoma, melanoma, or high-grade sarcoma56 (Figs. 48–21 and 48–22).

TREATMENT AND PROGNOSIS

Low-Grade Glioma

Diffuse astrocytomas are infiltrative low-grade brain tumors. Patients commonly present with new-onset seizures. Their peak incidence is in the third decade of life followed by the second decade. Overall, these low-grade tumors represent 4% of glial tumors.[5] Variation in length of survival depends on patient age, performance status at diagnosis, and total versus partial tumor (as visualized on MRI) resection.[57,58]

Oligodendrogliomas are diffusely infiltrative, well-differentiated tumors composed of oligodendrocytes. These tumors comprise 3% to 4% of all primary brain tumors and approximately 7% of glial tumors, with an incidence of 0.3 per 100,000 per year. The peak incidence is from the ages of 30 to 50 years. Tumors with oligodendroglial differentiation behave more indolently than astrocytomas. The oligodendrogliomas appear to be more sensitive to both chemotherapy and radiation therapy than astrocytomas, and the benefit from these therapies is more pronounced and durable.

Clinical Management

When a diagnosis of low-grade glioma is suspected, we recommend proceeding with a biopsy or resection to differentiate between a low-grade glioma and a nonenhancing anaplastic glioma (Tables 48–2 and 48–3). As previously noted, histologic grade does not convey the full story. Within the category of a grade II infiltrating glioma, for example, it is important to distinguish

TABLE 48–2 Initial Brain Tumor Workup

Contrast-enhanced MRI
Magnetic resonance spectroscopy may help diagnose nonenhancing tumors
Referral to neurosurgery for resection vs biopsy for tissue diagnosis
Confirmation of pathologic diagnosis
Postoperative MRI obtained within 3 days of surgery

MRI, magnetic resonance imaging.

TABLE 48–3 Evaluation by Tumor Type

Astrocytoma, oligodendroglioma, anaplastic astrocytoma, anaplastic oligodendroglioma, glioblastoma
MRI of the brain (with and without contrast)
MRI of the spine (with and without contrast), only if patient is symptomatic
Primary CNS lymphoma
MRI of the brain and spine (with and without contrast)
Lumbar puncture
Ophthalmology evaluation, including slit-lamp examination
CT of the chest, abdomen, and pelvis
Consider bone marrow biopsy

CNS, central nervous system; CT, computed tomography; MRI, magnetic resonance imaging.

TABLE 48–4 Management of Low-Grade Gliomas

Confirmation of diagnosis with biopsy or resection is preferred, although observation is acceptable with close follow-up.
Maximal safe resection should be considered.
Observation for low-risk patients is reasonable.
For high-risk patients (age older than 40 or subtotal resection), consider radiation therapy followed by chemotherapy.
Radiation therapy (focal brain irradiation) is the current standard of treatment.
Formal serial neuropsychologic testing is helpful in assessing cognitive function.
Consider use of psychostimulants to improve cognitive function and quality of life.
Consider biopsy or resection of progressive tumor to confirm diagnosis and consider the same salvage regimens as for malignant glioma.

IDH-mutant from IDH wild-type disease because the latter represents a more aggressive entity. It is also important to distinguish an oligodendroglioma from an astrocytoma if the histologic features are unclear because these entities are also treated differently.

If gross total resection or a major resection is possible without significant morbidity, neuro-oncologists generally recommend a complete resection, which may decrease the risk of malignant transformation from residual tumor cells. In multiple retrospective series, total resection of nonenhancing tumor improves survival.[57] A volumetric analysis of the preoperative tumor, in addition to analysis of postoperative residual tumor, showed a correlation with time to recurrence and the likelihood of malignant transformation.[59] There are several low-grade tumors—such as pilocytic astrocytoma, ependymoma and subependymoma, pleomorphic xanthoastrocytoma, ganglioglioma, and dysembryoplastic neuroepithelial tumor—that may be definitively treated by complete surgical resection alone. These patients may benefit from treatment at a specialized neurosurgical center that treats a large volume of patients with brain tumors (Table 48–4).

If a complete resection is not recommended, therapeutic options range from observation to treatment with focal brain irradiation, chemotherapy, or both. Older studies of low-grade astrocytomas suggested that radiation improved survival. The 5-year survival rates ranged from 49% to 68% for irradiated tumors compared with 32% for nonirradiated tumors.[60] The EORTC 22845 trial randomized patients to either up-front RT (54 Gy in 6 weeks) or delayed radiation therapy at progression. The PFS was 5.3 years in the early radiation group and 3.4 years in the control group. OS, however, was 7.4 years in the up-front radiation group versus 7.2 years in the control group.[2] No data were collected on quality of life. These data suggest that it is acceptable to delay radiation therapy until there are signs of tumor progression, especially for asymptomatic patients and patients who have had a complete tumor resection.

Patients with low-grade glioma should be carefully assessed to determine whether their symptoms are caused by the tumor. Formal neuropsychological testing may reveal cognitive deficits that are not apparent in the simple mental status screening used for dementia. In addition, these tests can be repeated to detect subtle cognitive decline, which may lead to a decision to alter a prescribed therapy. Patients who are symptomatic from their tumor from seizures, who have altered mental status because of tumor bulk or location, or who have other focal neurologic signs would be expected to improve with treatment of the tumor.

The etiology of cognitive decline in patients with a primary brain tumor is multifactorial. The causes include direct tumor effects from invasion and destruction as well as side effects from radiation therapy, chemotherapy, and anticonvulsants.[61] We have found the use of psychostimulants such as methylphenidate to be helpful in improving cognitive function, mood, and fatigue.[62] Other supportive care considerations are discussed in a later section.

Although there are concerns about the long-term effects of brain irradiation, radiation therapy is the standard of care.[61] The dose of RT currently used by the RTOG for low-grade glioma is 54 Gy to localized treatment fields as defined by the tumor appearance on T2-weighted MRI and including a 2-cm margin. A European trial involving 379 patients with low-grade glioma did not demonstrate a benefit for higher radiation dose when comparing 45 Gy with 59.4 Gy.[63] A second prospective study that randomized 203 patients with low-grade glioma to radiation therapy with either 50.4 or 64.8 Gy found a slightly lower survival (64% vs 72% at 5 years) and higher incidence of radiation

necrosis in the group receiving the higher dose of 64.8 Gy.[64] Current National Comprehensive Cancer Network guidelines recommend that patients with grade II gliomas be treated with 45 to 54 Gy in 1.8- to 2.0-Gy fractions but with the caveat that patients with IDH wild-type gliomas—which, as previously noted, will soon be reclassified to reflect their more aggressive behavior—may be treated with higher doses.[65]

Chemotherapy is also used in low-grade glioma. A small study of patients with incompletely resected tumors randomized to RT alone or RT with CCNU (lomustine) demonstrated a median survival time of 4.5 years with no difference between the two treatment arms.[66] An RTOG trial (RTOG 98-02) randomized patients with low-grade glioma and a high risk of recurrence (age 40 years or older or subtotal resection or biopsy) to either radiation therapy alone or radiation therapy followed by six cycles of procarbazine, CCNU, and vincristine (PCV). The early results of this trial were first presented at the American Society of Clinical Oncology (ASCO) meeting in 2014. The combination of PCV and radiation therapy prolonged both OS and PFS compared with radiation therapy alone in patients with high-risk grade 2 glioma, defined as patients with less than a subtotal resection and age older than 40 years.[67] Subsequent analysis published in the *New England Journal of Medicine* confirmed that addition of PCV to radiation doubled the median survival period from 7.8 years to 13.3 years and increased the 10-year survival rate by from 40% to 60%.[68] This benefit was initially predominantly seen in IDH-mutant, 1p19q-co-deleted tumors, though recently published genomic analysis confirms that there is also a benefit in 1p19q-intact tumors (ie, IDH-mutant astrocytoma).[69] The standard of care for low-grade gliomas that are not thought appropriate for observation is therefore radiation followed by adjuvant chemotherapy. For high-risk low-grade astrocytomas (IDH-mutant, 1p19q-intact), the adjuvant chemotherapy of choice in clinical practice is temozolomide. For high-risk low-grade oligodendrogliomas (IDH-mutant, 1p19q-co-deleted), the PCV regimen is preferred.

The utility of chemotherapy as an initial treatment for patients with low-grade gliomas without high-risk features is unproven. It has been postulated that perhaps in some low-risk patients, chemotherapy might delay the need for radiation therapy (which, although it can prolong PFS, can have long-term cognitive sequelae).[70] Several limited studies have demonstrated an encouraging radiographic response by low-grade gliomas (primarily oligodendrogliomas but also astrocytomas) after treatment with temozolomide or PCV.[34,71,72] Another strategy to mitigate the long-term risk of cognitive effects is the emerging use of proton radiation. In contrast to conventional photon-based radiation, the mass of protons limits their ability to penetrate normal tissue surrounding the tumor and allows for better dose conformity. Evidence suggests that patients with low-grade glioma treated with proton radiation have largely stable cognitive function on limited longitudinal follow-up.[73]

Malignant Gliomas

Anaplastic Oligodendroglioma

Anaplastic oligodendrogliomas make up between 20% and 50% of all oligodendroglial tumors and approximately 5% of anaplastic tumors. The peak incidence is between ages 40 and 50 years. The clinical presentation of these tumors is similar to that of other anaplastic tumors, with focal neurologic signs, seizures, or symptoms of increased intracranial pressure. These lesions, which are usually contrast enhancing, can show calcification on CT scans as well as cystic structures, necrosis, and hemorrhage.

The initial standard therapy for patients with anaplastic oligodendroglioma is surgery, with the goal of gross total resection. In RTOG 94-02, random assignment of 291 eligible patients with anaplastic oligodendroglioma (an important caveat is to note that the historical entity of "mixed oligoastrocytoma" was also included, and therefore some tumors were actually molecular astrocytomas) was made for the patients to receive PCV plus RT versus RT alone. There was no difference in median survival by treatment between the 148 patients randomized to PCV plus RT and the 143 patients randomized to RT.[74] However, the significance of codeletion of 1p/19q was supported by the results of EORTC 26951 with increased survival of both anaplastic oligodendroglioma and anaplastic oligoastrocytoma with 1p/19q codeletion noted regardless of the treatment given: radiation alone versus radiation with chemotherapy.[75] The prognostic significance of 1p/19q was validated in the long-term results of RTOG 9402. Patients with co-deleted tumors treated with both PCV and RT had a median survival period of 15 years, double that of patients who received radiation alone (median OS, 7.5 years). Neither timing (before, during, or after radiation treatment) nor dose intensity of PCV was found to be significant. No difference in median survival by treatment arm was appreciated in patients with non–co-deleted tumors.[74]

Although PCV is the most studied regimen in oligodendroglioma, in clinical practice, temozolomide is sometimes used instead because of its more tolerable toxicity profile. A discussion of the evidence for temozolomide use in anaplastic 1p19q-intact glioma follows in the next section. Despite initially high response rates, these tumors usually recur. The median survival period for anaplastic oligodendroglioma treated with surgery, irradiation, and chemotherapy ranges from

TABLE 48–5 Management of High-Grade Gliomas

Consider clinical trials at all stages: up front, adjuvant, and at relapse (especially at first or second recurrence).
Multidisciplinary approach is necessary for optimal outcome:
Neurosurgery
Neuro-oncology
Radiation therapy
Psychiatry
Neuropsychology
Rehabilitation
Social work
Maximal, safe resection
Concurrent chemoradiotherapy with temozolomide for glioblastoma.
Adjuvant chemotherapy for glioblastoma (temozolomide)
For 1p/19q co-deleted anaplastic oligodendroglioma, PCV or temozolomide after radiation therapy or vice versa
For 1p/19q intact anaplastic glioma, temozolomide after radiation therapy (radiation with or without concurrent temozolomide)
Avoid use of anticonvulsants that induce cytochrome P-450 3A4 metabolism when possible.
Progressive disease
Consider clinical trials.
Consider surgical resection at relapse (especially to rule out radiation necrosis).
Salvage chemotherapy agents include single-agent and combination regimens incorporating temozolomide, nitrosoureas, irinotecan, and platinum agents.
Consider re-irradiation.

CCNU, and vincristine; PCV, procarbazine.

TABLE 48–6 Chemotherapy Regimens for Gliomas

NEWLY DIAGNOSED GLIOMAS
Temozolomide
Newly diagnosed glioblastoma:
75 mg/m^2/day by mouth days 1–42 during radiotherapy followed by 150–200 mg/m^2/day[a] by mouth days 1–5 of a 28-day cycle
PCV[b]
Newly diagnosed oligodendroglioma and anaplastic oligodendroglioma:
Procarbazine 60–75 mg/m^2/day by mouth days 8–21 of a 42-day cycle
and
Lomustine 110–130 mg/m^2/day by mouth day 1 of a 42-day cycle
and
Vincristine 1.4 mg/m^2/day IV days 8 and 29 (maximum dose, 2 mg) of a 42-day cycle
RECURRENT GLIOMAS
Temozolomide
150–200 mg/m^2/day[a] by mouth days 1–5 of a 28-day cycle
Lomustine monotherapy
90–110 mg/m^2 by mouth day 1 of a 42-day cycle
Carboplatin monotherapy
AUC 4–5 IV day 1 of a 28-day cycle
Bevacizumab monotherapy or in combination with chemotherapy
10 mg/kg/dose IV days 1 and 15 of a 28-day cycle *or* days 1, 15, and 29 of a 42-day cycle
Bevacizumab and lomustine
Bevacizumab 10 mg/kg/dose IV days 1, 15, and 29 of a 42-day cycle
and
Lomustine 90 mg/m^2 by mouth day 1 of a 42-day cycle
Bevacizumab and carboplatin
Bevacizumab 10 mg/kg/dose IV days 1 and 15 of a 28-day cycle
and
Carboplatin AUC 4–5 IV on day 1 of a 28-day cycle

[a]Begin at 150 mg/m^2/day for cycle 1; increase to 200 mg/m^2/day for cycle 2 if no myelosuppression.
[b]Dose adjusted based on timing of radiotherapy.
AUC, area under the curve; IV, intravenous.

3 to 5 years, although some patients survive past 10 years.[5] Patients with recurrent disease are often treated with salvage regimens similar to those used for patients with anaplastic astrocytoma and glioblastoma (Tables 48–5 and 48–6).

Anaplastic Astrocytoma

Anaplastic astrocytomas are diffusely infiltrating with nuclear atypia and anaplasia as well as marked proliferation, features that distinguish them from low-grade astrocytomas. A lack of vascular proliferation or necrosis distinguishes these tumors histologically from glioblastoma. The highest incidence of anaplastic astrocytoma is in the fourth decade of life followed by the third decade, with nearly equal incidence rates in the second, fifth, and sixth decades. These tumors account for 7.5% of all glial tumors.[5] Some patients may have a history of prior low-grade astrocytoma. Brain imaging shows diffuse hypointense tumor on CT scans and T1-weighted MRI. There is usually more mass effect and edema compared with low-grade astrocytomas, and contrast enhancement is typical. Because these tumors can occasionally be nonenhancing, neuroimaging alone is not sufficient to distinguish these lesions from low-grade astrocytomas. The median survival for patients with anaplastic astrocytoma ranges from 5 to 7 years.

Optimal initial management begins with surgery with the goal of maximal, safe resection, both to provide adequate tissue for accurate analysis of pathology

and to improve survival. After surgery, limited-field radiation therapy to a target dose of 60 Gy is commonly recommended. The target radiation field typically includes the contrast-enhancing region of the tumor as well as the surrounding edema or nonenhancing tumor plus a 2-cm margin. The size of this field is often reduced after a 46-Gy dose has been applied to the contrast-enhancing lesion alone plus a 2-cm margin. Clinical trials using alternate radiation schemes of hyperfractionation or accelerated fractionation have not demonstrated an increased survival benefit over conventional fractionated conformal radiation therapy.[76] Adjuvant chemotherapy following radiation therapy increases time to progression and survival. A phase III study (CATNON) with a factorial design was done to evaluate the efficacy of concurrent and adjuvant temozolomide in patients with anaplastic 1p19q-intact glioma.[77] Recent results revealed that adjuvant temozolomide increased OS in IDH-mutant but not IDH wild-type tumors. Concurrent temozolomide during radiation did not demonstrably increase OS, but there was a trend to benefit in IDH-mutant tumors. Therefore, in anaplastic astrocytoma temozolomide is favored, though combination therapy composed of PCV has been used in the past as well (see Table 48–6) temozolomide.[78]

Patients with recurrent anaplastic astrocytoma should be considered for clinical trials. Surgical resection should also be considered to provide a palliative benefit, relieve mass effect, allow dose reduction of steroids, and confirm histology. The recurrent tumor may actually have progressed to glioblastoma from anaplastic astrocytoma, and such patients are often eligible for a wider array of clinical trials than are available for recurrent anaplastic astrocytoma. Trials have used temozolomide in combination with agents such as interferon-α (IFN-α), *cis*-retinoic acid, metalloproteinase inhibitors, carmustine, irinotecan, and thalidomide.[79–81] Other agents that have been used for recurrent anaplastic astrocytoma include tamoxifen, carboplatin, etoposide, irinotecan, and combination chemotherapy. To date, no single trial has proven to be superior. Reirradiation can be considered for patients who are more than 2 years beyond their original radiation treatment and for patients whose site of recurrent disease lies outside the initial radiation treatment field.

Glioblastoma

Glioblastoma is the most common and most malignant glial tumor of the brain. It comprises 50% of all glial tumors, with an incidence of approximately two to three per 100,000 per year.[5] Glioblastomas are characterized by poorly differentiated astrocytes with cellular polymorphism, nuclear atypia, microvascular proliferation, and necrosis. The peak incidence is in the fifth decade of life followed by the sixth and fourth decades. Glioblastoma is rare in children and young adults.[5] Clinically, these tumors often present with signs of increased intracranial pressure, such as headache. They can also present with seizures or focal neurologic symptoms such as hemiparesis and aphasia, often with a short history of symptoms.

Imaging with CT or MRI usually reveals a contrast-enhancing lesion with irregular borders, frequently with a necrotic center. Vasogenic edema and nonenhancing tumor often surround the area of contrast enhancement and are best seen on T2-weighted or FLAIR imaging on MRI. Glioblastomas commonly spread through white matter tracts across the corpus callosum, internal capsule, and optic radiations. Multifocal lesions are seen. If these multiple lesions truly arise independently as opposed to spreading diffusely through tracts that are not visualized by imaging or pathology, they may have a polyclonal origin.

Glioblastomas are highly lethal. Despite extensive clinical research, survival has not changed greatly during the last 20 years. Prognostic factors include age and Karnofsky performance status (KPS). Surgical resection has shown some benefit, especially gross total resection, described when 90% or more of the enhancing tumor is removed.[82]

The addition of chemotherapy to radiation emerged as the standard of care for glioblastoma based on the seminal large prospective, randomized, phase III trial from the EORTC. This trial randomized 573 patients to receive either standard RT (60 Gy in 30 daily fractions) or concurrent temozolomide (75 mg/m^2/day) with RT followed by adjuvant temozolomide for 6 months (150 to 200 mg/m^2/day for 5 days every 28 days). The group receiving concurrent and adjuvant temozolomide had a significant improvement in PFS (median, 7.2 months vs 5.0 months), survival (median, 14.6 months vs 12 months), and 2-year survival rate (median, 26% vs 8%). Both groups had similar age, KPS, and surgical resection rates.

Our center strongly recommends patient participation in clinical trials, which enroll patients in either the newly diagnosed or recurrent setting. Patients are eligible for entry into a clinical trial for recurrent disease if it has been more than 12 weeks since completion of concurrent chemoradiation to avoid enrolling patients with pseudoprogression (radiographic change that can mimic tumor progression but is actually caused by radiation-induced changes) or if the patient has clear evidence of progression outside the prior radiation treatment field. For patients new to our institution after surgery at an outside hospital, we always consider if a patient is a candidate for a more optimized up-front resection. It is not unusual for our patients to have repeat resection of tumor after biopsy or subtotal

resection at an outside institution. After resection, we treat patients with concurrent temozolomide (75 mg/m^2/day throughout radiation therapy) and standard conformal radiation therapy (59.4 Gy in 1.8-Gy fractions). After radiation therapy, we use adjuvant temozolomide, which is the only Food and Drug Administration (FDA)–approved treatment specifically for patients with newly diagnosed glioblastoma. Although the EORTC study only used adjuvant temozolomide for 6 months, we typically continue treatment for at least 1 year, given the lethal natural history of this disease.

Dose-dense scheduling of temozolomide was evaluated in a large randomized, phase III trial based on the premise that prolonged exposure to temozolomide would result in prolonged depletion of MGMT, possibly translating into an improved survival in patients with newly diagnosed glioblastoma. Standard adjuvant temozolomide (days 1–5 every 28 days) was compared with a dose-dense schedule (days 1–21 every 28 days). No statistically significant difference in either median OS or median PFS was observed between the two treatment arms. Treatment toxicity was higher with the dose-dense schedule.[3] Toxicity can include nausea, vomiting, fatigue, and myelosuppression.

The only other treatment modality specifically approved for newly diagnosed glioblastoma is tumor-treating fields (TTFs). This approval was based on a study in which patients were randomized after concurrent radiation to either adjuvant temozolomide alone or adjuvant temozolomide with TTFs.[83] The patients who were treated with TTFs in addition to temozolomide had survival time of 20.9 months versus 16.0 months for patients treated with temozolomide alone. The survival of the control group was notably worse than for historical cohorts. Also, there was no placebo arm with a sham device, and there is therefore some possibility that patients did better due to other factors such as an increase in supportive care. Theoretically, TTFs exert an electrical field on the charged DNA and mitotic spindles of dividing tumor cells.

Patients with glioblastoma and progressive disease are offered salvage therapy if their KPS is adequate. We consider options including resection of tumor, laser interstitial thermal therapy (LITT), chemotherapy, and repeat radiation therapy. Some novel neurosurgical clinical trials have offered local therapy with gene therapy using *p53*, although this was limited by lack of dispersion of the therapy into surrounding tissues.[84] An interleukin-13–conjugated *Pseudomonas* exotoxin has been studied using convection-enhanced delivery to lead to higher tissue concentration with larger volumes of distribution in phase I.[85,86] Another ongoing trial uses a conditionally replication-competent adenovirus (Delta-24-RGD) injected into the resection cavity for recurrent malignant gliomas.

Laser interstitial therapy is another emerging modality in the treatment of patients with primary brain tumors.[87] A laser catheter is inserted into the tumor and heated to kill tumor cells. It is used at our institution as a salvage therapy in recurrent unresectable glioblastoma and is under investigation in the treatment of patients with brain metastases and radiation necrosis as well. Re-resection of progressive disease can be considered with or without concomitant LITT.

One advantage of re-resection of progressive disease is to confirm pathology and specifically to determine whether the progressive enhancement on MRI represents tumor or radiation necrosis. MRI dynamic contrast and MR spectroscopy imaging, FDG-PET scanning, and brain SPECT thallium imaging sometimes help to distinguish between these two possibilities. However, all of these modalities have limited sensitivity and specificity, and sometimes the pathology reveals both treatment-related necrosis and foci of active tumor. Patients with pathology-confirmed radiation necrosis are often treated with steroids. More recently, bevacizumab, a monoclonal antibody targeted against VEGF, has been used to treat radiation necrosis.[88]

Chemotherapy for recurrent disease typically produces response rates less than 10% and a 6-month PFS of 15%.[4] Response rates that include stable disease and complete or PRs are 40% at best, but as the 6-month PFS value indicates, these responses are not durable. It is hypothesized that the multiple mutations and alterations in glioblastoma and the heterogeneity of the tumor cell population may partially explain the striking resistance of these tumors to therapy. Younger patients respond best to chemotherapy, although responses to alkylating agents can be seen in patients older than 60 years of age. Long-term survivors of glioblastoma (>5 years) have typically had gross total resection, radiation therapy to a dose of 60 Gy, and chemotherapy, generally with temozolomide or a nitrosourea or other alkylating agent.

Salvage agents used for malignant glioma are identical to those used for recurrent anaplastic astrocytoma (see Table 48–6). Rechallenging with continuous dose-intense temozolomide 50 mg/m^2/day is a valuable therapeutic option as evidenced by the RESCUE study. The overall 6-month PFS for recurrent progressive glioblastoma was 23.9%[89] in contrast to 15% based on a pooled analysis of eight consecutive phase II trials of cytostatic and cytotoxic agents. In this study, the greatest therapeutic benefit was observed in patients with progressive disease during the first six cycles of conventional adjuvant temozolomide therapy (150–200 mg/m^2 × 5 days every 28 days) or after a treatment-free interval.[4]

Bevacizumab has been approved by the FDA for progressive disease after prior therapy based on two trials.

One study showed a 6-month PFS of 42% and OS of 8.7 months in patients receiving bevacizumab alone.[90] Another study showed a response rate of 19.6% with a median duration of 3.9 months. The 6-month PFS was 29%, and the 6-month survival rate was 57%. In addition, 50% of patients experienced decreased cerebral edema, 58% were able to decrease corticosteroid dependency, and 52% had improvement in neurologic symptoms.[91]

Bevacizumab was subsequently evaluated in phase III clinical trials for newly diagnosed glioblastoma. Unfortunately, no effect was seen on overall patient survival. Two recent large randomized, phase III trials, AVAglio and RTOG 0825, demonstrated that the addition of bevacizumab to up-front treatment with radiation and temozolomide conferred no benefit in terms of OS. PFS was prolonged in both studies by approximately 3 to 4 months, reaching statistical significance in the AVAglio study but not in the RTOG 0825 study based on predefined criteria.[92,93]

Other active agents include CCNU (lomustine), irinotecan, and carboplatin, which have been investigated both as single agents in the salvage setting and in combination with bevacizumab in patients with bevacizumab-naïve recurrent glioblastoma.[94] Lomustine, also referred to as CCNU, is a nitrosourea BBB-penetrant alkylating agent increasingly used in recurrent glioblastoma. Clinical trials have increasingly used lomustine as a control arm in comparison with other novel therapies providing relevant clinical efficacy data in a phase 3 setting. Although its utility is largely extrapolated from the significant role it plays in PCV combination chemotherapy, as well as several older studies of the related compound BCNU in glioblastoma, it is nevertheless a standard of care chemotherapy regimen in recurrent GBM. Potential toxicities include thrombocytopenia, liver failure, and a cumulative risk of pulmonary fibrosis. Pulmonary function tests are recommended intermittently for patients on CCNU chemotherapy.

The optimal schedule and combination of bevacizumab with alternative drugs has not been identified. Agents targeting angiogenesis have also been studied, although the use of IFN, thalidomide, EGF-RTK antagonists, and integrin receptor antagonists is not standard. Many of these targeted therapies demonstrated only limited activity as single agents, and efforts are underway to combine them with cytotoxic therapy.[95] Other cellular pathways being investigated with small-molecule inhibitors include the *ras* pathway with farnesyl-transferase inhibitors and the PI3Kinase pathway with *mTOR* inhibitors. Other novel approaches to malignant brain tumor therapy include use of oncolytic adenovirus, vaccine and dendritic cell immunotherapy, and histone deacetylase inhibitors. An important reaction has been discovered from the interaction between anticonvulsants that induce the hepatic cytochrome P450 3A4 enzyme and other chemotherapy agents also metabolized by this same enzyme. Pharmacokinetic studies of patients with malignant glioma on single-agent irinotecan and sirolimus found significantly lower levels of active drug in patients on enzyme-inducing anticonvulsant drugs.[96] We recommend that patients on chemotherapy avoid the use of anticonvulsants that induce the expression of the P450 3A4 enzyme whenever possible.

Given the success of immunotherapy in other malignancies there has been much interest in using similar strategies in primary brain tumors, specifically glioblastoma. There may be utility in using checkpoint-blockade immunotherapy in patients with hypermutated glioblastoma secondary to disorders such as constitutional mismatch repair deficiency.[97] In other situations, the "cold" immune microenvironment of brain tumors may limit the efficacy of checkpoint-blockade and chimeric antigen-receptor T-cells, although further studies are needed.

Meningioma

Meningiomas comprise 38% of primary brain tumors, with a rate of 5.35 per 100,000 person-years. The incidence of meningioma increases with age; the median age at diagnosis is 64 years.[5] The tumor is often discovered incidentally without any symptoms. The main treatment is surgical resection, with the goal of complete resection when possible, accounting for relative risks and benefits depending on the patient's age and condition.[98] Options for residual tumor include observation and radiation therapy, which can incorporate stereotactic delivery to minimize effects to local tissue.[99]

Chemotherapy for meningioma has been used for patients who have progressive disease after resection and RT; it is sometimes used in an adjuvant setting after RT when pathology indicates malignant meningioma. Response rates have been disappointing in small case series. Agents that have been used include hydroxyurea,[100] IFN-α,[101] and liposomal doxorubicin.[102] Results using temozolomide have been discouraging, with no responders.[103] Because there are no established treatments after surgery and radiation have been exhausted and response to chemotherapy has been disappointing, the use of molecularly targeted therapy is being explored in aggressive meningioma. Frequently, EGF, PDGF, and VEGF receptors are overexpressed in meningiomas. Clinical trials using small-molecule signal transduction inhibitors such as erlotinib, gefitinib, and imatinib are being explored.[104,105] In a recent phase II trial, sunitinib, a small-molecule tyrosine kinase inhibitor that targets VEGF and PDGF receptors, was found to have activity in patients with recurrent atypical or

malignant meningiomas and warrants investigation in a randomized trial.[106]

Primary Central Nervous System Lymphoma

In contrast to most other brain tumors, chemotherapy is the initial treatment of choice for patients with CNS lymphoma given it is often deep and multifocal. The traditional view has been that gross total resection conferred no survival benefit over biopsy, but this view has been challenged recently. In a phase III trial of 526 patients, PFS was found to be significantly shorter in patients who were biopsied compared with patients who had undergone subtotal or gross total resections, with no difference in outcome attributable to KPS or age, suggesting that surgical resection could be considered for otherwise healthy patients with single lesions for which resection is deemed safe.[107]

Methotrexate-based, multiagent chemotherapy has been viewed as the treatment of choice in PCNSL. The incorporation of high-dose methotrexate (>1 g/m^2) has resulted in a significantly greater response and improved survival compared with previous regimens using a CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) regimen before whole-brain radiation therapy (WBRT). A report by DeAngelis et al,[108] incorporating methotrexate (1 g/m^2), followed by WBRT and two cycles of high-dose cytarabine (ara-C) (3 g/m^2), demonstrated a median survival of 42.5 months. This strategy is the basis for current CNS lymphoma protocols that have increased the dose of methotrexate and incorporated agents that more easily cross the BBB, such as procarbazine. A follow-up clinical trial incorporating methotrexate at 3.5 g/m^2 with procarbazine and vincristine, followed by WBRT and cytarabine demonstrated a median survival of 60 months.[109] The improvement in patient survival has also brought to attention significant rates of cognitive decline and radiation-induced dementia, especially in patients older than 60 years.[110]

Current approaches to therapy of CNS lymphoma are investigating whether radiation therapy can be avoided or delayed to reduce cognitive decline and dementia without adversely affecting survival. Preliminary results from a trial using single-agent methotrexate at 8 g/m^2 every 2 weeks demonstrated a PFS of 12.8 months. Median survival had not been reached at more than 22.8 months.[111] Many clinicians at our center are cautiously delaying radiation therapy until relapse and continuing to use high-dose–based methotrexate regimens such as R-MVP (rituximab, methotrexate, vincristine, procarbazine).

Patients with recurrent disease may respond again to methotrexate. Other regimens used include PCV,[112] high-dose cytarabine,[113] temozolomide,[114] rituximab,[115] and the combination of temozolomide and rituximab.[116]

After induction chemotherapy, if patients achieve CR, either WBRT or high-dose chemotherapy with autologous stem cell transplant may be effective as consolidation.[117]

Brain Metastasis

The treatment of brain metastasis involves optimal interactions between oncology, neurosurgery, and radiation therapy. Depending on the setting of relapse, patient survival may depend more on local tumor control in the brain or on systemic control for progressive metastasis. Advances in local brain tumor control with surgery and radiosurgery will not improve patient survival if the patient ultimately succumbs to progressive systemic disease or continues to develop new brain metastases. The median survival of patients with brain metastases is 3 to 6 months.[118]

The options for therapy include surgical resection, WBRT, stereotactic radiosurgery (SRS), and systemic chemotherapy. Surgical resection is the treatment option considered primarily in patients with single large tumors. Resection of brain metastases has emerged as a standard treatment option for patients with surgically accessible single lesions, good performance status, and controlled or absent extracranial disease. SRS uses multiple convergent beams to deliver a single high dose of radiation to a discrete target volume and is usually reserved for lesions whose maximum diameter is 3 cm or less. The ability to treat locations that were otherwise considered surgically inaccessible is a distinct advantage of SRS. WBRT via 30 to 40 Gy (in daily fractions of 2 to 3 Gy) is the standard therapy for brain metastasis, with an established body of literature supporting its use for multiple metastases. This therapy has the ability to eradicate micrometastatic disease to delay recurrence[118,119] and is often used in conjunction with surgical resection or radiosurgery. It is well tolerated and can be effective for radiosensitive tumors such as metastases from small cell lung cancer or germ cell tumors. The greatest concern about WBRT has been the risk of neurocognitive effects, which can range from mild impairment to dementia.

We frequently treat patients at our institution with surgery if the lesions are greater than 3 cm and the patients are symptomatic. If the patient's medical condition makes a surgical procedure risky, the patient may receive WBRT. Patients who have lesions smaller than 3 cm can receive radiosurgery if they are asymptomatic or if the lesion is in a deep region not amenable to resection.

Classically, chemosensitive types of brain metastases include breast cancer, small cell lung cancer, and germ cell tumors. The primary consideration in

choosing a given regimen chemotherapy regimen is to use agents with known activity in a given tumor type.

Many clinical trials of investigational agents for solid tumors explicitly exclude patients with brain metastases. Compounding this omission is their common inclusion in studies of a heterogeneous group of patients with mixed tumor types and differing prior exposures to chemotherapy. Patients might also be expected to be more resistant to treatment with chemotherapeutic agents if they had failed RT. If chemotherapy is given during and after RT, it may be difficult to separate the efficacy due to RT versus chemotherapy. These factors make it difficult to compare treatment regimens and interpret studies.[120]

Newer drugs have been developed targeting specific intracellular transduction mechanisms or extracellular receptors. Owing to their specificity, they often lack the side effects commonly associated with standard cytotoxic chemotherapy. If the therapeutic target is crucial for the cancer cell's continued viability, the drug can be especially effective. The identification of *BRAF* mutations in 50% to 60% of advanced melanomas resulted in the development of potent and selective inhibitors. Vemurafenib and dabrafenib are FDA approved for the treatment of advanced melanoma and have transformed melanoma therapy, with high response rates seen in patients even with advanced, symptomatic, metastatic disease.[121]

Recently, a number of small-molecule BBB-penetrant chemotherapies have been found to control both systemic and CNS disease. Several are pertinent to make mention of, based on recent data. Osimertinib is a third-generation EGFR inhibitor used to treat non–small cell lung cancer (NSCLC) that has also been shown to have activity against brain metastases, in one case report inducing complete remission.[122] The BLOOM study further demonstrated that osimertinib at a dose of 160 mg/day was efficacious in treating leptomeningeal disease, with a median OS of 11.0 months representing a significant improvement from the historically dismal prognosis of this manifestation of cancer.[123] Alectinib, as noted earlier in this chapter, is an ALK inhibitor that has been found to have significant CNS activity relative to previous generation ALK inhibitors such as crizotinib and now is commonly used as a first-line agent in patients who have brain metastases from NSCLC at diagnosis.[124] Last, tucatinib is an agent that selectively targets HER2 in breast cancer and has been shown to improve survival in patients with brain metastases when added to trastuzumab and capecitabine.[125] Other similar agents are under development and may further revolutionize the treatment of patients with brain metastases.

The use of chemotherapy for patients with brain metastases is faced with great challenges. The most important imperative is to discover new agents that can overcome tumor resistance to standard chemotherapy, whether through selection by prior pretreatment or inherent chemoresistance of tumor cell clones that metastasize from a primary site. Improvement in patient survival result in a multimodality approach to the treatment of the patient with brain metastases.

Seizure Control

The management of seizures in patients with brain tumors is important to improve patient functioning and quality of life. Typically, antiepileptics are not given until the patient has had a seizure, though many neurosurgeons may temporarily prophylax patients perioperatively. A decline in seizure control may indicate tumor progression or worsening edema. It may also indicate a systemic infection or a drug interaction leading to decreased anticonvulsant drug effectiveness. In the case of tumor progression, a reduction in the amount of brain edema with high-potency corticosteroids (dexamethasone) may be sufficient to prevent further seizures. A second anticonvulsant is often necessary. Dexamethasone is a hepatic cytochrome P450 3A4–inducing agent and often causes a reduction in serum levels of antiepileptic medications such as phenytoin and carbamazepine (also enzyme inducers) when the dose is increased. Similarly, patients can become symptomatic with toxic levels of anticonvulsants in the midst of a dexamethasone taper. It is important to follow serum anticonvulsant levels when using agents metabolized by the cytochrome P450 system. Anticonvulsants that are highly protein bound can demonstrate significant changes in levels of circulating free drug without significantly changing the total serum level. It is useful to check serum-free phenytoin or valproic acid levels when patients taking these agents have seizures or show signs of toxicity.

Despite the numerous choices of anticonvulsants, it can be difficult to control seizures. Of the newer generation of anticonvulsants, we have had success using levetiracetam and lacosamide, which are easily titrated without significant drug interactions. Phenobarbital and clonazepam can be useful in resistant cases of seizures. Short-term use of lorazepam can help bridge changes in anticonvulsant regimens.

Quality-of-Life Considerations

It is critical to provide effective supportive care to patients with brain tumors to improve their functional status and quality of life for themselves and their caregivers. This care is typically labor intensive and often beyond the means of patients and their families to provide. We involve social work and case management early in the

treatment of patients. They can provide interventions that may prevent a later breakdown in care.

The incidence of depression is high among this population and should be treated early. The causes of depression are typically multifactorial and may include direct effects of the tumor, side effects of chemotherapy and radiation therapy, and side effects of steroids in addition to issues associated with a loss of independence and a diagnosis of cancer. We suggest referral to psychiatry to optimally address these issues. A related concern is the impact of fatigue and somnolence, common side effects of brain radiation. We advocate the use of psychostimulants such as methylphenidate to treat both fatigue and cognitive side effects.[58] Although there are theoretical concerns that the use of stimulants may exacerbate seizures, we have not observed this in practice.

Patients often require high doses of steroids to manage edema and experience both acute and chronic toxicities from their administration. Acutely, the steroids may induce hyperglycemia requiring an insulin sliding scale. Patients often become agitated and irritable, have extreme mood swings, and even become psychotic when taking steroids. Low-dose neuroleptics can be effective in treating these side effects. Clinicians should aim to taper steroid use to the lowest doses necessary. Patients typically tolerate initial steroid weaning but often experience fatigue or worsening of neurologic function as dexamethasone doses are reduced to below 4 mg/day. This can be ameliorated with an extremely slow steroid taper and only lowering doses every 1 to 2 weeks by decrements of 1 mg or even 0.5 mg. Psychostimulants can help treat the inevitable fatigue experienced with the steroid taper. There is no effective treatment for steroid myopathy other than tapering off steroids and initiating physical therapy and rehabilitation as early as possible.

MD ANDERSON PRACTICE TIPS

- All patients with brain tumors are best treated with a collaborative multidisciplinary approach involving medical and neuro-oncologists, radiation oncologists, and neurosurgeons. The neuropathological and molecular differences between different brain tumors can be subtle and have significant ramifications for treatment planning. Therefore, review by an experienced neuropathologist to render an accurate diagnosis is critical.
- There is some equipoise regarding the optimal treatment of low-grade glioma, given their overall favorable natural history. At our institution, maximal safe surgical resection is followed by sequential radiation and chemotherapy in high-risk patients. In patients who are thought to be low risk, a period of close surveillance may be reasonable. For astrocytomas, temozolomide is typically selected as adjuvant therapy. For oligodendrogliomas, the strongest evidence supports use of PCV, though temozolomide is considered reasonable.
- In glioblastoma, IDH mutation and MGMT methylation status should be checked due to their prognostic significance. Standard of care for glioblastoma includes maximal safe surgical resection followed by concurrent radiation (59.4 Gy in 1.8-Gy fractions) with temozolomide (75 mg/m^2/day throughout radiation therapy). Although studies have used adjuvant temozolomide for 6 months after completion of radiation, we typically continue treatment for 1 year, or 12 cycles, given the lethal natural history of glioblastoma. However, the patient should be closely monitored because of the increased risk of myelosuppression with cumulative exposure to alkylating agents.
- The options for treating brain metastases include surgical resection, WBRT, SRS, and systemic chemotherapy. Surgical resection is considered primarily in patients with few, surgically accessible single lesions; good performance status; and controlled or absent extracranial disease.
- Leptomeningeal disease commonly presents insidiously with cranial nerve deficits, symptoms of raised intracranial pressure, radiculopathy, saddle anesthesia, and bowel or bladder habit changes. Diagnostic evaluation includes an MRI of the entire neuroaxis (brain and spine) with and without gadolinium contrast followed by up to three lumbar punctures for examination of CSF parameters, including protein, glucose, cell count, and cytology. Treatment typically includes radiation to symptomatic areas and, if possible, optimizing systemic chemotherapy to CNS penetrant agents. Intrathecal chemotherapy via Ommaya reservoir can be considered in selected patients with good performance status.

REFERENCES

1. Schouten LJ, Rutten J, Huveneers HA, Twijnstra A. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. *Cancer*. 2002;94:2698-2705.
2. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352:987-996.
3. Gilbert MR, Wang M, Aldape KD, et al. Dose-dense temozolomide for newly diagnosed glioblastoma: a randomized phase III clinical trial. *J Clin Oncol*. 2013;31:4085-4091.
4. Wong ET, Hess KR, Gleason MJ, et al. Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. *J Clin Oncol*. 1999;17:2572-2578.
5. Ostrom QT, Cioffi G, Gittleman H, et al. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2012-2016. *Neuro Oncol*. 2019;21(suppl 5):v1-100.
6. Fan YS, Lui PC, Tam FK, et al. A 33-year-old Chinese woman with a left frontal tumor. *Brain Pathol*. 2009;19:337-340.
7. Sawaya R, Bindal, RK, Lang FF. Metastatic brain tumors. *Brain Tumors*. 2001;999-1026.
8. Skibber JM, Soong SJ, Austin L, et al. Cranial irradiation after surgical excision of brain metastases in melanoma patients. *Ann Surg Oncol*. 1996;3:118-123.
9. Kadan-Lottick NS, Skluzacek MC, Gurney JG. Decreasing incidence rates of primary central nervous system lymphoma. *Cancer*. 2002;95:193-202.
10. Neglia JP, Robison LL, Stovall M, et al. New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *J Natl Cancer Inst*. 2006;98:1528-1537.
11. Sadetzki S, Flint-Richter P, Ben-Tal T, Nass D. Radiation-induced meningioma: a descriptive study of 253 cases. *J Neurosurg*. 2002;97:1078-1082.
12. Sodickson A, Baeyens PF, Andriole KP, et al. Recurrent CT, cumulative radiation exposure, and associated radiation-induced cancer risks from CT of adults. *Radiology*. 2009;251:175-184.
13. Wrensch M, Minn Y, Chew T, et al. Epidemiology of primary brain tumors: current concepts and review of the literature. *Neuro Oncol*. 2002;4:278-299.
14. Ostrom QT, Adel Fahmideh M, Cote DJ, et al. Risk factors for childhood and adult primary brain tumors. *Neuro Oncol*. 2019;21(11):1357-1375.
15. Huncharek M, Kupelnick B, Wheeler L. Dietary cured meat and the risk of adult glioma: a meta-analysis of nine observational studies. *J Environ Pathol Toxicol Oncol*. 2003;22:129-137.
16. Hurley SF, McNeil JJ, Donnan GA, et al. Tobacco smoking and alcohol consumption as risk factors for glioma: a case-control study in Melbourne, Australia. *J Epidemiol Community Health*. 1996;50:442-446.
17. Dziurzynski K, Chang SM, Heimberger AB, et al. Consensus on the role of human cytomegalovirus in glioblastoma. *Neuro Oncol*. 2012;14:246-255.
18. Linos E, Raine T, Alonso A, Michaud D. Atopy and risk of brain tumors: a meta-analysis. *J Natl Cancer Inst*. 2007;99:1544-1550.
19. Scheurer ME, El-Zein R, Thompson PA, et al. Long-term anti-inflammatory and antihistamine medication use and adult glioma risk. *Cancer Epidemiol Biomarkers Prev*. 2008;17:1277-1281.
20. Amirian E, Scheurer ME, Bondy ML. The association between birth order, sibship size, and glioma development in adulthood. *Int J Cancer*. 2009;126(11):2752-2756.
21. Preston-Martin S. Epidemiology of primary CNS neoplasms. *Neurol Clin*. 1996;14:273-290.
22. Segal L, Darvish-Zargar M, Dilenge ME, et al. Optic pathway gliomas in patients with neurofibromatosis type 1: follow-up of 44 patients. *J AAPOS*. 2010;14(2):155-158
23. Campian J, Gutmann DH. CNS tumors in neurofibromatosis. *J Clin Oncol*. 2017;35:2378-2385.
24. Brennan CW, Verhaak RG, McKenna A, et al. The somatic genomic landscape of glioblastoma. *Cell*. 2013;155:462-477.
25. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med*. 2011;364:2507-2516.
26. Singh D, Chan JM, Zoppoli P, et al. Transforming fusions of FGFR and TACC genes in human glioblastoma. *Science*. 2012;337:1231-1235.
27. Wong AJ, Ruppert JM, Bigner SH, et al. Structural alterations of the epidermal growth factor receptor gene in human gliomas. *Proc Natl Acad Sci U S A*. 1992;89:2965-2969.
28. Chakravarti A, Zhai G, Suzuki Y, et al. The prognostic significance of phosphatidylinositol 3-kinase pathway activation in human gliomas. *J Clin Oncol*. 2004;22:1926-1933.
29. Guha A, Feldkamp MM, Lau N, et al. Proliferation of human malignant astrocytomas is dependent on Ras activation. *Oncogene*. 1997;15:2755-2765.
30. Maher EA, Furnari FB, Bachoo RM, et al. Malignant glioma: genetics and biology of a grave matter. *Genes Dev*. 2001;15:1311-1333.
31. Ohgaki H, Kleihues P. The definition of primary and secondary glioblastoma. *Clin Cancer Res*. 2013;19:764-772.
32. Cairncross JG, Ueki K, Zlatescu MC, et al. Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. *J Natl Cancer Inst*. 1998;90:1473-1479.
33. Ino Y, Betensky RA, Zlatescu MC, et al. Molecular subtypes of anaplastic oligodendroglioma: implications for patient management at diagnosis. *Clin Cancer Res*. 2001;7:839-845.
34. Hoang-Xuan K, Capelle L, Kujas M, et al. Temozolomide as initial treatment for adults with low-grade oligodendrogliomas or oligoastrocytomas and correlation with chromosome 1p deletions. *J Clin Oncol*. 2004;22:3133-3138.
35. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med*. 2005;352:997-1003.
36. Parsons DW, Jones S, Zhang X, et al. An integrated genomic analysis of human glioblastoma multiforme. *Science*. 2008;321:1807-1812.
37. Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. *N Engl J Med*. 2009;360:765-773.
38. Hartmann C, Hentschel B, Wick W, et al. Patients with IDH1 wild type anaplastic astrocytomas exhibit worse prognosis than IDH1-mutated glioblastomas, and IDH1 mutation status accounts for the unfavorable prognostic effect of higher age: implications for classification of gliomas. *Acta Neuropathol*. 2010;120:707-718.
39. Appay R, Dehais C, Maurage CA, et al. CDKN2A homozygous deletion is a strong adverse prognosis factor in diffuse malignant IDH-mutant gliomas, *Neuro-Oncology,* 2019;21(12):1519-1528.
40. Brat DJ, Aldape K, Colman H, et al. cIMPACT-NOWupdate3: recommended diagnostic criteria for "diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV". *Acta Neuropathologica2018*;136(5):805–810.
41. Choy W, Kim W, Nagasawa D, et al. The molecular genetics and tumor pathogenesis of meningiomas and the future directions of meningioma treatments. *Neurosurg Focus*. 2011;30:E6.
42. Louis D, Stemmer-Rachamimov AO, Wiestler OD. Neurofibromatosis type 2. In: Kleihues P, Cavenee K, eds. *Pathology and Genetics of Tumors of the Nervous System*. IARC Press; 2000:219-222.
43. Xiao GH, Chernoff J, Testa JR. NF2: the wizardry of merlin. *Genes Chromosomes Cancer*. 2003;38:389-399.
44. Brastianos PK, Horowitz PM, Santagata S, et al. Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations. *Nat Genet*. 2013;45:285-289.

45. Ruat M, Hoch L, Faure H, Rognan D. Targeting of Smoothened for therapeutic gain. *Trends Pharmacol Sci*. 2014;35:237-246.
46. Puduvalli VK. Brain metastases: biology and the role of the brain microenvironment. *Curr Oncol Rep*. 2001;3:467-475.
47. Marchetti D, Nicolson GL. Human heparanase: a molecular determinant of brain metastasis. *Adv Enzyme Regul*. 2001;41:343-359.
48. Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases. *Nature*. 2000;407:249-257.
49. Gottesman MM, Fojo T, Bates SE. Multidrug resistance in cancer: role of ATP-dependent transporters. *Nat Rev Cancer*. 2002;2:48-58.
50. Fidler IJ, Yano S, Zhang RD, et al. The seed and soil hypothesis: vascularisation and brain metastases. *Lancet Oncol*. 2002;3:53-57.
51. Muldoon LL, Soussain C, Jahnke K, et al. Chemotherapy delivery issues in central nervous system malignancy: a reality check. *J Clin Oncol*. 2007;25:2295-2305.
52. Deguchi, S., Oishi, T., Mitsuya, K. *et al.* Clinicopathological analysis of T2-FLAIR mismatch sign in lower-grade gliomas. *Sci Rep* 10, 10113 (2020)
53. Miller AM, Shah RH, Pentsova EI, Pourmaleki M, et al. Tracking tumour evolution in glioma through liquid biopsies of cerebrospinal fluid. *Nature*. 2019;565(7741):654-658.
54. Bruner JM, Inouye L, Fuller GN, Langford LA. Diagnostic discrepancies and their clinical impact in a neuropathology referral practice. *Cancer*. 1997;79(4):796-803.
55. Theeler BJ, Yung WK, Fuller GN, De Groot JF. Moving toward molecular classification of diffuse gliomas in adults. *Neurology*. 2012;79:1917-1926.
56. World Health Organization. *WHO Classification of Tumours of the Central Nervous System*. International Agency for Research on Cancer; 2007.
57. Shaw E. Management of low-grade gliomas in adults. *Brain Cancer*. 2002;279-302.
58. Bauman G, Lote K, Larson D, et al. Pretreatment factors predict overall survival for patients with low-grade glioma: a recursive partitioning analysis. *Int J Radiat Oncol Biol Phys*. 1999;45:923-929.
59. Berger MS, Deliganis AV, Dobbins J, Keles GE. The effect of extent of resection on recurrence in patients with low grade cerebral hemisphere gliomas. *Cancer*. 1994;74:1784-1791.
60. Shaw EG, Daumas-Duport C, Scheithauer BW, et al. Radiation therapy in the management of low-grade supratentorial astrocytomas. *J Neurosurg*. 1989;70:853-861.
61. Taphoorn MJ. Neurocognitive sequelae in the treatment of low-grade gliomas. *Semin Oncol*. 2003;30:45-48.
62. Meyers CA, Weitzner MA, Valentine AD, Levin VA. Methylphenidate therapy improves cognition, mood, and function of brain tumor patients. *J Clin Oncol*. 1998;16:2522-2527.
63. Karim AB, Maat B, Hatlevoll R, et al. A randomized trial on dose-response in radiation therapy of low-grade cerebral glioma: European Organization for Research and Treatment of Cancer (EORTC) Study 22844. *Int J Radiat Oncol Biol Phys*. 1996;36:549-556.
64. Shaw E, Arusell R, Scheithauer B, et al. Prospective randomized trial of low- versus high-dose radiation therapy in adults with supratentorial low-grade glioma: initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study. *J Clin Oncol*. 2002;20:2267-2276.
65. National Comprehensive Cancer Network. CCN Guidelines. Central Nervous System Cancers (Version 1.2019). https://www.nccn.org/.
66. Eyre HJ, Crowley JJ, Townsend JJ, et al. A randomized trial of radiotherapy versus radiotherapy plus CCNU for incompletely resected low-grade gliomas: a Southwest Oncology Group study. *J Neurosurg*. 1993;78:909-914.
67. Buckner JC, Stephanie L. Pugh, Edward G. Shaw, et al. Phase III study of radiation therapy (RT) with or without procarbazine, CCNU, and vincristine (PCV) in low-grade glioma: RTOG 9802 with Alliance, ECOG, and SWOG. *ASCO Annual Meeting Proceedings*. 2014;32((15 suppl):5S
68. Buckner JC, Shaw EG, Pugh SL, et al. Radiation plus Procarbazine, CCNU, and Vincristine in Low-Grade Glioma. *N Engl J Med*. 2016;374(14):1344-1355.
69. Bell EH, Zhang P, Shaw EG, et al. Comprehensive genomic analysis in NRG Oncology/RTOG 9802: a phase III Trial of radiation versus radiation plus procarbazine, lomustine (CCNU), and vincristine in high-risk low-grade glioma. *J Clin Oncol*. 2020;38(29):3407-3417.
70. van den Bent M. Can chemotherapy replace radiotherapy in low-grade gliomas? Time for randomized studies. *Semin Oncol*. 2003;30:39-44.
71. Buckner JC, Gesme D Jr, O'Fallon JR, et al. Phase II trial of procarbazine, lomustine, and vincristine as initial therapy for patients with low-grade oligodendroglioma or oligoastrocytoma: efficacy and associations with chromosomal abnormalities. *J Clin Oncol*. 2003;21:251-255.
72. Sanson M, Cartalat-Carel S, Taillibert S, et al. Initial chemotherapy in gliomatosis cerebri. *Neurology*. 2004;63:270-275.
73. Tabrizi S, Yeap BY, Sherman JC, et al. Long-term outcomes and late adverse effects of a prospective study on proton radiotherapy for patients with low-grade glioma. *Radiother Oncol*. 2019;137:95-101.
74. Cairncross G, Wang M, Shaw E, et al. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. *J Clin Oncol*. 2013;31:337-343.
75. van den Bent MJ, Carpentier AF, Brandes AA, et al. Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organisation for Research and Treatment of Cancer phase III trial. *J Clin Oncol*. 2006;24:2715-2722.
76. Levin VA, Yung WK, Bruner J, et al. Phase II study of accelerated fractionation radiation therapy with carboplatin followed by PCV chemotherapy for the treatment of anaplastic gliomas. *Int J Radiat Oncol Biol Phys*. 2002;53:58-66.
77. van den Bent MJ, Erridge S, Vogelbaum MA, et al. PL3.3 second interim and first molecular analysis of the EORTC randomized phase III intergroup CATNON trial on concurrent and adjuvant temozolomide in anaplastic glioma without 1p/19q codeletion. *Neuro Oncol*. 2019;21(suppl 3):iii3.
78. Yung WK, Albright RE, Olson J, et al. A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. *Br J Cancer*. 2000;83:588-593.
79. Jaeckle KA, Hess KR, Yung WK, et al. Phase II evaluation of temozolomide and 13-cis-retinoic acid for the treatment of recurrent and progressive malignant glioma: a North American Brain Tumor Consortium study. *J Clin Oncol*. 2003;21:2305-2311.
80. Groves MD, Puduvalli VK, Hess KR, et al. Phase II trial of temozolomide plus the matrix metalloproteinase inhibitor, marimastat, in recurrent and progressive glioblastoma multiforme. *J Clin Oncol*. 2002;20:1383-1388.
81. Gilbert M. Phase I/II study of combination temozolomide (TMZ) and irinotecan (CPT-11) for recurrent malignant gliomas: a North American Brain Tumor Consortium (NABTC) study [Abstract 410]. *Proc Am Soc Clin Oncol*. 2003;22.
82. Lacroix M, Abi-Said D, Fourney DR, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J Neurosurg*. 2001;95:190-198.
83. Stupp R, Taillibert S, Kanner A, et al. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. *JAMA*. 2017;318(23):2306-2316.

84. Lang FF, Bruner JM, Fuller GN, et al. Phase I trial of adenovirus-mediated p53 gene therapy for recurrent glioma: biological and clinical results. *J Clin Oncol*. 2003;21:2508-2518.
85. Kunwar S. Convection enhanced delivery of IL13-PE38QQR for treatment of recurrent malignant glioma: presentation of interim findings from ongoing phase 1 studies. *Acta Neurochir Suppl*. 2003;88:105-111.
86. Kunwar S, Prados MD, Chang SM, et al. Direct intracerebral delivery of cintredekin besudotox (IL13-PE38QQR) in recurrent malignant glioma: a report by the Cintredekin Besudotox Intraparenchymal Study Group. *J Clin Oncol*. 2007;25:837-844.
87. Thomas JG, Rao G, Kew Y, Prabhu SS. Laser interstitial thermal therapy for newly diagnosed and recurrent glioblastoma. *Neurosurg Focus*. 2016;41(4):E12.
88. Torcuator R, Zuniga R, Mohan YS, et al. Initial experience with bevacizumab treatment for biopsy confirmed cerebral radiation necrosis. *J Neurooncol*. 2009;94:63-68.
89. Perry JR, Belanger K, Mason WP, et al. Phase II trial of continuous dose-intense temozolomide in recurrent malignant glioma: RESCUE study. *J Clin Oncol*. 2010;28:2051-2057.
90. Vredenburgh JJ, Desjardins A, Herndon JE 2nd, et al. Phase II trial of bevacizumab and irinotecan in recurrent malignant glioma. *Clin Cancer Res*. 2007;13:1253-1259.
91. Kreisl TN, Kim L, Moore K, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. *J Clin Oncol*. 2009;27:740-745.
92. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl J Med*. 2014;370:699-708.
93. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N Engl J Med*. 2014;370:709-722.
94. Reardon DA, Desjardins A, Peters KB, et al. Phase II study of carboplatin, irinotecan, and bevacizumab for bevacizumab naive, recurrent glioblastoma. *J Neurooncol*. 2012;107:155-164.
95. Reardon DA. A phase I/II trial of PTK787/ZK 222584 (PTK/ZK): a novel oral angiogenesis inhibitor in combination with either temozolomide or lomustine for patients with recurrent glioblastoma multiforme (GBM). ASCO Annual Meeting Proceedings. *J Clin Oncol*. 2004;22(suppl 14S):1513.
96. Prados MD, Yung WK, Jaeckle KA, et al. Phase 1 trial of irinotecan (CPT-11) in patients with recurrent malignant glioma: a North American Brain Tumor Consortium study. *Neuro Oncol*. 2004;6:44-54.
97. Johanns TM, Miller CA, Dorward IG, et al. Immunogenomics of hypermutated glioblastoma: a patient with germline POLE deficiency treated with checkpoint blockade immunotherapy. *Cancer Discov*. 2016;6(11):1230-1236.
98. Mcdermott M, Quinones-Hinosa A, Bollen AW. Meningiomas. *Brain Cancer*. 2002;333-364.
99. Ojemann SG, Sneed PK, Larson DA, et al. Radiosurgery for malignant meningioma: results in 22 patients. *J Neurosurg*. 2000;93(suppl 3):62-67.
100. Mason WP, Gentili F, Macdonald DR, et al. Stabilization of disease progression by hydroxyurea in patients with recurrent or unresectable meningioma. *J Neurosurg*. 2002;97:341-346.
101. Kaba SE, DeMonte F, Bruner JM, et al. The treatment of recurrent unresectable and malignant meningiomas with interferon alpha-2B. *Neurosurgery*. 1997;40:271-275.
102. Travitzky M, Libson E, Nemirovsky I, et al. Doxil-induced regression of pleuro-pulmonary metastases in a patient with malignant meningioma. *Anticancer Drugs*. 2003;14:247-250.
103. Chamberlain MC, Tsao-Wei DD, Groshen S. Temozolomide for treatment-resistant recurrent meningioma. *Neurology*. 2004;62:1210-1212.
104. Gupta V, Samuleson CG, Su S, Chen TC. Nelfinavir potentiation of imatinib cytotoxicity in meningioma cells via survivin inhibition. *Neurosurg Focus*. 2007;23:E9.
105. Norden AD, Raizer JJ, Abrey LE, et al. Phase II trials of erlotinib or gefitinib in patients with recurrent meningioma. *J Neurooncol*. 2010;96:211-217.
106. Kaley TJ, Wen P, Schiff D, et al. Phase II trial of sunitinib for recurrent and progressive atypical and anaplastic meningioma. *Neuro Oncol*. 2015;17:116-121.
107. Weller M, Martus P, Roth P, et al. Surgery for primary CNS lymphoma? Challenging a paradigm. *Neuro Oncol*. 2012;14:1481-1484.
108. DeAngelis LM, Yahalom J, Thaler HT, Kher U. Combined modality therapy for primary CNS lymphoma. *J Clin Oncol*. 1992;10:635-643.
109. Abrey LE, Yahalom J, DeAngelis LM. Treatment for primary CNS lymphoma: the next step. *J Clin Oncol*. 2000;18:3144-3150.
110. Harder H, Holtel H, Bromberg JE, et al. Cognitive status and quality of life after treatment for primary CNS lymphoma. *Neurology*. 2004;62:544-547.
111. Batchelor T, Carson K, O'Neill A, et al. Treatment of primary CNS lymphoma with methotrexate and deferred radiotherapy: a report of NABTT 96-07. *J Clin Oncol*. 2003;21:1044-1049.
112. Herrlinger U, Brugger W, Bamberg M, et al. PCV salvage chemotherapy for recurrent primary CNS lymphoma. *Neurology*. 2000;54:1707-1708.
113. Abrey LE, DeAngelis LM, Yahalom J. Long-term survival in primary CNS lymphoma. *J Clin Oncol*. 1998;16:859-863.
114. Lerro KA, Lacy J. Case report: a patient with primary CNS lymphoma treated with temozolomide to complete response. *J Neurooncol*. 2002;59:165-168.
115. Pels H, Schulz H, Schlegel U, Engert A. Treatment of CNS lymphoma with the anti-CD20 antibody rituximab: experience with two cases and review of the literature. *Onkologie*. 2003;26:351-354.
116. Enting RH, Demopoulos A, DeAngelis LM, Abrey LE. Salvage therapy for primary CNS lymphoma with a combination of rituximab and temozolomide. *Neurology*. 2004;63:901-903.
117. Soussain C, Suzan F, Hoang-Xuan K, et al. Results of intensive chemotherapy followed by hematopoietic stem-cell rescue in 22 patients with refractory or recurrent primary CNS lymphoma or intraocular lymphoma. *J Clin Oncol*. 2001;19:742-749.
118. Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys*. 1997;37:745-751.
119. Gaspar LE, Scott C, Murray K, Curran W. Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. *Int J Radiat Oncol Biol Phys*. 2000;47:1001-1006.
120. Gilbert M. Brain metastases: still an "orphan" disease? *Curr Oncol Rep*. 2001;3:463-466.
121. Ribas A, Flaherty KT. BRAF targeted therapy changes the treatment paradigm in melanoma. *Nat Rev Clin Oncol*. 2011;8:426-433.
122. Ameku K, Higa M. Complete remission of multiple brain metastases in a patient with EGFR-mutated non-small-cell lung cancer treated with first-line osimertinib without radiotherapy. *Case Rep Oncol Med*. 2020;2020:9076168.
123. Yang JCH, Kim SW, Kim DW, et al. Osimertinib in patients with epidermal growth factor receptor mutation-positive non-small-cell lung cancer and leptomeningeal metastases: the BLOOM study. *J Clin Oncol. 2020*;38(6):538-547.
124. Kim DW, Mehra R, Tan DS, et al. Activity and safety of ceritinib in patients with ALK-rearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial. *Lancet Oncol*. 2016;17(4):452.

SECTION XI Malignant Melanoma

Section Editor: Michael A. Davies

49 Melanoma

This page intentionally left blank

49 Melanoma

Houssein Safa
Jane Mattei
Andrew J. Bishop
Emily Z. Keung
Sirisha Yadugiri
Michael A. Davies
Isabella C. Glitza Oliva

KEY CONCEPTS

- Mutations in the RAS-RAF-MAPK signaling pathway are detected in most cutaneous melanomas, most commonly affecting *BRAF, NRAS,* and *Nf1*. The prevalence and pattern of mutations differs between cutaneous melanomas and noncutaneous (ie, mucosal, uveal) melanomas.
- Surgery is the mainstay of initial treatment for patients with primary cutaneous melanoma without clinical evidence of regional nodal or distant metastatic disease. Sentinel lymph node biopsy should be considered in patients with a significant risk of regional metastasis. For patients with sentinel lymph node involvement, it is no longer standard practice to perform completion lymph node dissection based on recent prospective trials that showed no significant impact on melanoma-specific survival (MSS). Surgery is an important component in the multidisciplinary management of patients with clinically detected regional nodal disease and in select patients with distant metastases.
- Adjuvant radiation therapy (RT) reduces the risk of locoregional recurrence in patients with regionally metastatic disease but without significant impact on overall survival (OS). Radiation may provide palliative benefit in patients with distant metastases. Treatment decisions regarding radiation should be tailored based on potential risks, benefits, and multidisciplinary input.
- Several adjuvant systemic therapies reduce the risk of recurrence in patients with regionally metastatic disease. While adjuvant immune checkpoint inhibitor immunotherapy was first approved for the anti–CTLA-4 (cytotoxic T lymphocyte-associated antigen 4) antibody ipilimumab, adjuvant therapy with anti–PD-1 (programmed cell death protein 1) antibodies (nivolumab, pembrolizumab) was shown to be safer and more effective. Adjuvant targeted therapy with the combination of dabrafenib, a BRAF inhibitor, and trametinib, a MEK inhibitor, is approved for stage III melanomas with a BRAF V600 mutation. No prospective trials to date have compared adjuvant immunotherapy versus adjuvant targeted therapy. Both immunotherapy and targeted therapy are being investigated in the neoadjuvant setting.
- After decades without progress, in the past decade, multiple systemic therapies have been approved for the treatment for patients with stage IV or unresectable stage III disease. Ipilimumab was the first immunotherapy to be approved in this setting. Subsequent trials demonstrated improved safety and efficacy with single-agent nivolumab and with single-agent pembrolizumab versus ipilimumab, leading to their approval. Combination immunotherapy with ipilimumab and nivolumab is also more effective than ipilimumab and has been approved, but the combination has increased toxicity versus either agent alone. For patients with a BRAF V600 mutation, three different targeted therapy combinations of a BRAF and a MEK inhibitor (dabrafenib + trametinib; vemurafenib + cobimetinib; encorafenib + binimetinib) have been approved after demonstrating superiority compared to single-agent BRAF inhibitor therapy. The BRAF + MEK inhibitor combinations have not been compared in prospective clinical trials versus each other or versus immunotherapy. Intratumoral injection of talimogene laherparepvec is approved for patients with unresectable injectable metastatic disease.
- Although much progress has been made for patients with cutaneous melanoma, the efficacy of immune checkpoint inhibitors is much lower in patients with mucosal and with uveal melanoma. These tumor types also have a much lower prevalence of targetable mutations.

Melanoma is the most aggressive form of skin cancer. Although its incidence pales compared with basal cell carcinoma and squamous cell carcinoma (SCC), melanoma is the cause of approximately 75% of all skin cancer–related deaths. Most patients diagnosed with early-stage melanoma have very good outcomes

with appropriate surgical management. Patients with regional and distant metastases have historically had poor outcomes because of the ineffectiveness of traditional systemic therapies, particularly chemotherapy. However, the management and outcomes of patients with metastatic melanoma have improved dramatically because of the translation of improved understanding of molecular drivers and key regulators of the antitumor immune response in this disease.

EPIDEMIOLOGY AND RISK FACTORS

Melanoma is the fifth most common cancer in men and the sixth most common cancer in women in the United States. In 2019, there were an estimated 96,480 new cases of and more than 7000 deaths from melanoma.[1] The age-adjusted incidence for cutaneous melanoma in the United States from 2013 to 2017 was 22.7 per 100,000.[2] In contrast to the reduced incidence observed with almost all other major cancers, the annual incidence of melanoma continues to rise by approximately 2% to 3% per year and has increased more than 500-fold since the 1950s.[3]

Several factors correlate with an increased risk of being diagnosed with melanoma (Table 49–1). Based on epidemiological studies, many of these factors reflect a strong association between melanoma and ultraviolet radiation (UVR) exposure.[4] Consistent with this clinical association, whole-exome sequencing studies have shown that cutaneous melanomas overall have a higher somatic mutation rate than almost all other solid tumors and that the majority of these mutations bear the molecular signature of UVR-related DNA damage.[5] Several risk assessment aids have been developed to identify high-risk individuals, including the Melanoma Risk Assessment Tool, which is available online (http://www.cancer.gov/melanomarisktool).

Patients with dysplastic (atypical) nevi with irregular borders, multiple colors, and larger than 5 mm diameter have a 3- to 20-fold higher risk of developing melanomas than the general population.[6] Although most melanomas are sporadic, the familial atypical multiple mole and melanoma (FAMMM) syndrome is an autosomal dominant disorder characterized by the occurrence of melanoma in one or more first- or second-degree relatives and the presence of a high number of acquired nevi or atypical nevi. This syndrome is associated with germline mutations of the *CDKN2A* gene and an increased risk of other cancers, especially pancreatic cancer.[7] Congenital nevi can also be a precursor of melanoma, and individuals with large congenital nevi (>20 cm) have an increased risk of developing melanoma.[8]

CLASSIFICATION

Cutaneous melanomas are the most common manifestation of this disease, arising from melanocytes in the skin. The four major types of cutaneous melanoma are superficial spreading, nodular, lentigo maligna, and acral lentiginous melanoma. Desmoplastic melanomas represent a distinct subtype that arise from melanocytes in the skin regions with chronic sun exposure, which are characterized by highly invasive local growth that often tracks along the nerves. Melanomas can also arise from melanocytes in other areas, including the uveal tract of the eye (uveal melanomas) and mucosal surfaces throughout the body (mucosal melanoma). Very rare subtypes include primary central nervous system melanomas, which arise from melanocytes in the leptomeninges, and melanomas of soft parts (also known as clear cell sarcoma), which arise in soft tissues and dermis. Although the melanoma subtypes are not independent prognostic factors, they can be associated with distinct clinical (Table 49–2) and molecular (Table 49–3) features.[9]

TABLE 49–1 Factors Associated with Increased Risk of Melanoma

Risk Factor	Features
Personal history of melanoma	9× increased risk of developing a second melanoma (vs the general population)
Family history of melanoma	First-degree relatives have a higher risk, and 10% of all melanomas are familial (FAMMM syndrome and dysplastic nevus syndrome)
Total number of nevi	Relative risk of 5 to 17 with presence of >50 nevi
Congenital nevi	6% lifetime risk with large (>20 cm) congenital nevi
Dysplastic nevi	3- to 20-fold higher risk of developing melanoma than the general population
Immunosuppression	Chronic immune suppressant use, HIV infection, and organ transplantation
MC1R variants	Associated with fair skin, red hair, and freckles
Exposure to ultraviolet light	Tanning bed use, sunburn

FAMMM, familial atypical multiple mole and melanoma.

TABLE 49–2 Melanoma Subtypes

Type	Frequency (%)	Sites	Features
Cutaneous			
Superficial spreading	70	Any site (more common on the upper back in both sexes and the lower extremities in women)	Most common subtype of cutaneous melanomas
Nodular	15–30	Any site (common on the trunk or legs)	Presents with vertical growth phase without radial growth phase
Lentigo maligna	4–15	Sun-exposed area (the head, neck, and arms)	
Acral lentiginous	2–8	The palms, soles, and beneath the nail plates	More common in African Americans and Asians
Uveal	Rare	Uveal tract of the eye (iris, ciliary body, and the choroid)	Frequent, and often exclusive, metastatic involvement of the liver
Mucosal	Rare	Mucosal surfaces (head and neck, respiratory, gastrointestinal, and genitourinary tracts)	Poor prognosis, potentially because of delayed diagnosis and the rich lymphovascular supply of the mucosa
Desmoplastic	Rare	Areas with chronic sun exposure, especially the head and neck	High risk for local recurrence and growth along nerves
Primary CNS	Rare	Leptomeninges	
Melanoma of soft parts (clear cell sarcoma)	Rare	Soft tissues, dermis	Associated with fusions involving the *EWSR1* gene

CNS, central nervous system.

TABLE 49–3 Classification of Melanoma by Oncogenic Mutations

Melanoma Subtype	Mutations			
	BRAF (%)	*NRAS* (%)	*KIT* (%)	*GNAQ/GNA11* (%)
Cutaneous without CSD	50	15–20	1–2	—
Cutaneous with CSD	5–30	10–15	2–17	—
Acral lentiginous	10–15	10–15	15–20	—
Mucosal	5	5–10	15–0	—
Uveal	—	—	—	85

CSD, chronic sun damage.

MOLECULAR BIOLOGY

Cutaneous melanomas are characterized by an extremely high rate of somatic mutations. The first cutaneous melanoma analyzed by whole-genome sequencing identified more than 33,000 somatic changes in the tumor.[10] Most of the somatic changes detected in cutaneous melanomas are representative of DNA damage induced by UVR. Despite the challenges presented by this overall high background mutation rate, confirmed driver mutations are detectable in majority of the cutaneous melanomas. Recent research has extensively focused on identifying mutational changes of the signaling pathway components and a brief description of the most common mutational changes is provided below.

RAS-RAF-MEK-ERK Pathway

The RAS-RAF-MEK-ERK pathway promotes cellular proliferation and survival, and activation of this pathway has been implicated in multiple tumor types. Genetic events that activate this pathway are detected in almost all cutaneous melanomas.[11] The most common alterations detected are point mutations in the *BRAF* gene. The *BRAF* encodes a serine-threonine kinase

in the RAS-RAF-MEK-ERK cascade. Point mutations in *BRAF* are detected in approximately 45% of cutaneous melanomas, and approximately 95% of these mutations result in substitutions for valine at position 600 in the BRAF protein.[12] The most common mutations result in the substitution of a glutamic acid (*BRAF*,^{V600E} 70%) or lysine (*BRAF*,^{V600K} 20%) residue. These and other substitutions at codon 600 increase the kinase activity of the BRAF protein 200-fold or more and result in constitutive activation of downstream components of the RAS-RAF-MEK-ERK pathway. The *BRAF*^{V600E} mutation is also frequently detected in benign nevi, supporting that this molecular event occurs very early in melanoma development.[13] Consistent with this theory, *BRAF* mutation status is highly concordant between primary melanomas and their metastases. Mutations at other sites in *BRAF* (*BRAF*$^{Non–V600}$) are detected in approximately 5% of cutaneous melanomas. These mutations have variable effects on BRAF's catalytic activity, but preclinical data support that they still activate the RAS-RAF-MEK-ERK pathway.[14] Rarely, translocations involving the *BRAF* locus also occur in melanoma,[15] which generate fusion proteins that appear to activate the RAS-RAF-MEK-ERK pathway.

Mutations in *NRAS* are detected in 20% of cutaneous melanomas.[11] These mutations overwhelmingly occur in hotspot regions that result in substitutions at amino acid residues Q61 (~80%) or G12/G13 (~20%). Like *BRAF*,^{V600E} the mutant NRAS proteins potently activate the RAS-RAF-MEK-ERK pathway and are commonly detected in benign nevi. Notably, hotspot mutations in *NRAS* are mutually exclusive (<1% co-occurrence) with *BRAF*^{V600E} mutations but co-occur relatively frequently with *BRAF*$^{Non–V600}$ mutations.[16] Also, rare mutations are detected in other members of the RAS GTPase family, *KRAS* and *HRAS* (<2%). Loss-of-function mutations of *NF1*, a negative regulator of RAS, are detected in approximately 15% of cutaneous melanomas, predominantly in melanomas without *NRAS* or *BRAF*^{V600} mutations.[11]

Additional Pathways Implicated in Cutaneous Melanomas

The PI3K (phosphoinositide 3-kinase)-AKT pathway is a key regulator of many cellular processes, including proliferation, survival, motility, and metabolism.[17] The identification of *NRAS* mutations was the first evidence for PI3K-AKT activation in melanoma because oncogenic *RAS* mutations activate the PI3-AKT pathway in addition to RAS-RAF-MEK-ERK to transform cells. The PI3K-AKT pathway is also activated by loss of function of *PTEN*, which is a lipid phosphatase that normally inhibits the activation of the PI3K-AKT pathway. Loss-of-function mutations and deletions involving *PTEN* are detected in up to 30% of cutaneous melanomas.[18,19] Loss of *PTEN* appears to be mutually exclusive in melanomas with *NRAS* mutations, but it occurs frequently in tumors with concurrent *BRAF*^{V600} mutations. Experiments in preclinical models have shown that loss of *PTEN* cooperates with *BRAF*^{V600} mutations to promote transformation, invasiveness, and metastasis of melanocytes, providing functional support for this clinical association.[20] Rare (<2% each) activating mutations in *AKT1*, *AKT3*, and *PIK3CA* have also been detected in cutaneous melanomas, again generally in tumors with *BRAF*^{V600} mutations.[17]

Alterations in key cell cycle regulators are also pervasive in cutaneous melanomas.[11,21] Germline loss-of-function mutations in the *CDKN2A* gene are the most common events detected in familial melanoma. The *CDKN2A* gene encodes two different proteins, P14^{ARF} and P16.^{INK4A} P16^{INK4A} regulates cell cycle progression by binding to cyclin-dependent kinase 4 (CDK4). Point mutations in the gene encoding CDK4 are the most common germline events detected in familial melanoma cases without *CDKN2A* mutations. The mutations alter the site in CDK4 that binds to P16,^{INK4A} thereby promoting cell cycle progression.[22] Somatic mutations and copy number changes in both *CDKN2A* and *CDK4* are commonly detected in cutaneous melanomas. Cyclin D1, which forms a protein complex with CDK4 or CDK6 to promote cell cycle progression, can also be amplified in this disease.[23] Loss of function of P14^{ARF} inhibits the function of *TP53* via increased MDM2 activity. In addition, mutations in *TP53* are present in approximately 20% of cutaneous melanomas.[19]

Molecular Features of Noncutaneous Melanomas

Activating mutations in *BRAF* are relatively rare events in acral lentiginous (~15%) and mucosal (~5%) melanomas, and they are not detected at all in uveal melanomas.[9] However, several other prevalent oncogenic events have been identified in these melanoma subtypes.

KIT is a type III transmembrane receptor tyrosine kinase that activates several pro-survival signaling pathways following binding of its ligand, stem cell factor. *KIT* amplifications and mutations are more frequently (20%–30%) detected in acral, mucosal, and cutaneous melanoma with chronic sun-induced damage compared with cutaneous melanomas without chronic sun-induced damage (<5%).[24] The two most common *KIT* mutations in melanoma are *L576P* (34%) and *K642E* (15%) in exons 11 and 13, respectively, and overall, 70% of *KIT* mutations occur in exon 11, which encodes the juxtamembrane domain.[25] *KIT* mutations in exon 11 prevent the juxtamembrane domain's inhibitory function and induce the constitutive activation of KIT and its associated pathways.

GNAQ and *GNA11* encode regulatory subunits of G protein–coupled receptors that are frequently mutated in uveal melanomas. Hotspot mutations affecting residues Q209 (exon 5) and R183 (exon 4) in these genes are mutually exclusive events. Combined, mutations in either *GNAQ* or *GNA11* are present in 85% of uveal melanomas.[26] The mutant GNAQ/11 proteins hyperactivate several cellular signaling pathways, including RAS-RAF-MEK-ERK and PI3K-AKT. *GNAQ* and *GNA11* mutations appear to be extremely rare (≤1%) in cutaneous melanomas, but they have been detected in both blue nevi and primary CNS melanoma.

STAGING

After a patient is diagnosed with melanoma, staging of melanoma is important for prognosis and treatment. The eighth edition of the American Joint Committee on Cancer (AJCC) staging system for cutaneous melanoma was implemented in 2018 (Tables 49–4 and 49–5). In the updated staging system, primary tumor Breslow thickness and ulceration were predictive of melanoma-specific survival (MSS) in patients both with clinically localized disease and with regional metastases.[27] In contrast to the seventh edition, the primary tumor mitotic rate is no longer incorporated in the T staging system of the AJCC eighth edition. However, increasing mitotic rate is associated with decreased MSS in patients with node-negative and node-positive melanoma and remains associated with outcomes in tumors of all thickness categories.[27] For regional metastasis staging, the number of involved lymph nodes is the strongest predictor of outcome, but tumor burden (microscopic vs macroscopic), pattern of involvement (regional lymph node [RLN], satellite, microsatellite, and in-transit metastases), and primary tumor features (T stage) are also prognostic.[28] In patients with distant metastases, staging is organized into four subgroups (M1a, M1b, M1c, and M1d), reflecting the site(s) of metastasis. Serum lactate dehydrogenase (LDH) level remains a clinically significant factor associated with response, progression-free survival (PFS), MSS, and overall survival (OS),[29–32] and thus each M subcategory is modified based on whether LDH is elevated (designated as "(0)" for "not elevated" and "(1)" for "elevated".)

TABLE 49–4 Staging System for Melanoma

T Classification	Primary Tumor (Breslow) Thickness (mm)	Ulceration Status
Tis	NA	Melanoma in situ
T1	<0.8 <0.8 0.8–1.0	a: without ulceration b: with ulceration b: without ulceration
T2	>1.0–2.0	a: without ulceration b: with ulceration
T3	>2.0–4.0	a: without ulceration b: with ulceration
T4	>4.0	a: without ulceration b: with ulceration
N Classification	**Tumor-Involved Regional Lymph Nodes (*n*)**	**Present of In-Transit, Satellite, and/or Microsatellite Metastases**
N0	No regional metastases detected	N/A
N1 N1a N1b N1c	 1 clinically occult (ie, detected by SLNB) 1 clinically detected No regional lymph node disease	 No No Yes
N2 N2a N2b N2c	 2–3 clinically occult (ie, detected by SLNB) 2–3, at least 1 of which was clinically detected 1 clinically occult or clinically detected	 No No Yes
N3 N3a N3b N3c	 ≥4 clinically occult (ie, detected by SLNB) ≥4, at least 1 of which was clinically detected ≥2 clinically occult or clinically detected or presence of any number of matted nodes	 No No Yes

(*Continued*)

TABLE 49–4 Staging System for Melanoma (*Cont.*)

M Classification	Distant Metastatic Site(s)	Serum LDH Level
M0	No evidence of distant metastasis	N/A
M1a M1a^0 M1a^1	Distant skin, soft tissue including muscle, and/or non-regional lymph node(s)	 Not elevated Elevated
M1b M1b^0 M1b^1	Distant metastasis to lung with or without M1a sites of disease	 Not elevated Elevated
M1c M1c^0 M1c^1	Distant metastasis to non-CNS visceral sites with or without M1a-b sites of disease	 Not elevated Elevated
M1d M1d^0 M1d^1	Distant metastasis to CNS with or without M1a-c sites of disease	 Not elevated Elevated

CNS, central nervous system; LDH, lactate dehydrogenase; mets, metastases; N/A, not applicable; SLNB, sentinel lymph node biopsy.
Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the *AJCC Cancer Staging System* (2020).

TABLE 49–5a Stage Groupings for Cutaneous Melanoma

Clinical Staging				Pathologic Staging			
	T	N	M		T	N	M
0	Tis	N0	M0	0	Tis	N0	M0
IA	T1a	N0	M0	IA	T1a	N0	M0
IB	T1b	N0	M0		T1b	N0	M0
	T2a	N0	M0	IB	T2a	N0	M0
IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
IIC	T4b	N0	M0	IIC	T4b	N0	M0
III	Any T, Tis	≥N1	M0	IIIA	T1a/b-T2a	N1a or N2a	M0
				IIIB	T0	N1b or N1c	M0
					T1a/b-T2a	N1b/c or N2b	M0
					T2b/T3a	N1a-N2b	M0
				IIIC	T0	N2b, N2c, N3b or N3c	M0
					T1a-T3a	N2c or N3a/b/c	M0
					T3b/T4a	Any N ≥N1	M0
					T4b	N1a-N2c	M0
				IIID	T4b	N3a/b/c	M0
IV	Any T	Any N	M1	IV	Any T, Tis	Any N	M1

Data from Edge SB, Byrd DR, Byrd DR, et al: *AJCC Cancer Staging Manual*, 8th ed. New York, NY: Springer; 2017.

SURGICAL MANAGEMENT

For patients with primary cutaneous melanoma and clinically negative RLNs, surgery represents the mainstay of initial clinical management. It is useful to consider this approach in the context of two themes: (1) wide excision of the primary tumor site and (2) approach to the regional nodal basin. Before definitive surgery, it is important to identify other lesions suspicious for a synchronous cutaneous malignancy, evidence of regional metastasis, and signs

TABLE 49–5b Pathological Prognostic Groups for Stage III Cutaneous Melanoma

N Category	Tumor-Involved Regional Lymph Nodes (*n*)	Presence of In-transit, Satellite, and/or Microsatellite Metastases	T Category								
			T0 No Evidence of Primary Tumor	T1a <0.8 mm without Ulceration	T1b <0.8 mm with Ulceration or 0.8–1.0mm with or without Ulceration	T2a >1.0–2.0 mm without Ulceration	T2b >1.0–2.0 mm with Ulceration	T3a >2.0–4.0 Mm without ulceration	T3b >2.0-4.0 mm with Ulceration	T4a >4.0 mm without Ulceration	T4b >4.0 mm with Ulceration
N0	No regional metastases detected	No	—	IA	IA	IB	IIA	IIA	IIB	IIB	IIC
N1a	1 clinically occult (ie, detected by SLN biopsy)	No	—	IIIA	IIIA	IIIA	IIIB	IIIB	IIIC	IIIC	IIIC
N1b	1 clinically detected	No	IIIB	IIIB	IIIB	IIIB	IIIB	IIIB	IIIC	IIIC	IIIC
N1c	No regional lymph node disease	Yes	IIIB	IIIB	IIIB	IIIB	IIIB	IIIB	IIIC	IIIC	IIIC
N2a	2 or 3 clinically occult (ie, detected by SLN biopsy)	No	—	IIIA	IIIA	IIIA	IIIB	IIIB	IIIC	IIIC	IIIC
N2b	2 or 3, at least 1 of which was clinically detected	No	IIIC	IIIB	IIIB	IIIB	IIIB	IIIB	IIIC	IIIC	IIIC
N2c	1 clinically occult or clinically detected	Yes	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC
N3a	≥4 clinically occult (ie, detected by SLN biopsy)	No	—	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIID
N3b	≥4, at least 1 of which was clinically detected, or the presence of any number of matted nodes	No	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIID
N3c	≥2 clinically occult or clinically detected and/or presence of any number of matted nodes	Yes	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIID

T0, no evidence of primary tumor (eg, unknown primary or completely regressed melanoma); Tis, melanoma in situ. Exception: Pathological N category is not required for T1 melanomas; use cN.
Data from Edge SB, Byrd DR, Byrd DR, et al: *AJCC Cancer Staging Manual*, 8th ed. New York, NY: Springer; 2017.

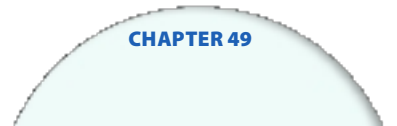


TABLE 49–6 Recommended Wide Local Excision Surgical Margins

Primary Tumor Thickness (mm)	Excision Margin[a] (cm)
In situ	0.5–1
≤1.0	1.0
>1.0–2.0	1.0–2.0
>2.0	2.0

[a]Margins may be modified to accommodate individual or functional considerations.

and symptoms that may raise suspicion for distant metastatic disease. Such findings may alter treatment plans.

Recommended wide excision margins are based on primary tumor thickness (Breslow thickness), and they are measured from the melanoma biopsy site edges or residual intact disease.[33] Wide excision includes subcutaneous tissue down to the level of, but generally not including, underlying muscular fascia. Recommended margins of excision are summarized in Table 49–6.

The surgical approach to the RLN basin staging is guided by Breslow thickness, other tumor factors, and host factors, including the presence of ulceration or high mitotic rate. The technique of lymphatic mapping and sentinel lymph node biopsy (SLNB) is based on the observation that finite regions of skin drain via afferent lymphatics to RLNs and that the most common site of melanoma metastasis is the RLN basin. Additionally, because most RLN metastases are clinically occult, the technique of SLNB was developed to identify and selectively excise the RLNs most likely to contain occult metastatic disease (termed sentinel lymph nodes [SLNs]) if any are involved.[34] Overall, for patients with clinically negative regional nodes, the risk of RLN metastasis ranges from less than 1% for patients with very thin primary tumors to approximately 50% for patients with thick, ulcerated primary tumors. The American Society of Clinical Oncology and Society of Surgical Oncology clinical practice guidelines recommend that SLNB be considered for patients with T1b melanoma, after a thorough discussion with the patient of the potential benefits and risks associated with the procedure.[35] Routine SLNB is not recommended for patients with T1a melanoma because of the overall low risk of microscopic regional metastasis (<5%).[36,37] Preoperative or intraoperative lymphoscintigraphy is recommended to identify RLN basins at risk and to localize the sentinel nodes; a dual-modality approach (ie, in the United States, isosulfan blue dye and technetium-99 sulfur colloid) along with a handheld gamma probe is used intraoperatively.[34,38] After surgery, enhanced histologic analysis is performed, generally as a combination of step sectioning and immunohistochemical analysis. In contrast to many other solid tumors, intraoperative frozen section assessment is rarely employed.

SLN pathologic status is an important independent prognostic factor for disease-free survival (DFS) and MSS.[39,40] The Multicenter Selective Lymphadenectomy Trial-I (MSLT-I) prospective, randomized, clinical trial compared wide excision and SLNB (with completion lymph node dissection [CLND] for patients with positive a SLNB) versus wide excision and nodal observation (followed by therapeutic lymphadenectomy for patients who developed nodal recurrence). This trial confirmed the strong prognostic significance of SLNB in patients with early-stage melanoma but did not demonstrate an OS benefit for the procedure. However, subset analysis among all node-positive patients did show a survival advantage to SLNB-positive patients who had CLND compared with the patients who had nodal observation and subsequently recurred in regional nodes.[40] Thus, until recently, CLND (also known as completion lymphadenectomy or early therapeutic lymph node dissection) had been a standard of care for patients with a positive SLNB. However, CLND carries significant risks, including wound infections, wound dehiscence, and lymphedema. Furthermore, because only 10% to 20% of SLN-positive patients have tumor-involved non-SLNs at CLND,[41,42] SLNB alone may be sufficient to confer the survival benefit seen in a subset of MSLT-I patients. Thus, two multicenter randomized controlled trials German Dermatologic Cooperative Oncology Group - Selective Lymphadenectomy Trial (DeCOG-SLT), Multicenter Selective Lymphadenectomy Trial-II - (MSLT-II) compared immediate CLND with nodal observation in patients with positive SLNB.[41,43] Although CLND provided prognostic information and was associated with improved regional control, both studies showed that CLND did not improve MSS compared with nodal observation. Furthermore, CLND was associated with increased lymphedema. These results have been practice changing, with significantly fewer SLN-positive patients undergoing CLND. It is important to recognize, however, that nodal observation in MSLT-II mandated close follow-up, with physical examination and nodal basin ultrasound every 4 months for the first 2 years, then every 6 months for the next 3 years, and thereafter annually. Current National Comprehensive Cancer Network guidelines recommend either surveillance with physical exam and nodal basin ultrasound or consideration of CLND for patients with SLN-positive melanoma.[44]

For patients with suspected regional nodal metastasis on physical examination or imaging, core needle biopsy or fine-needle aspiration is recommended.[44] For patients with resectable regional nodal metastasis in the absence of distant metastasis, treatment remains wide local excision (with recommended margins summarized in Table 49–6) and therapeutic lymph

node dissection. For patients with clinical evidence of resectable satellite or in-transit lesions in the absence of distant metastasis, treatment options include resection with clear margins (with or without SLNB), intralesional Talimogene laherparepvec (TVEC) (see section on TVEC), or systemic therapy. Adjuvant therapy (see sections on adjuvant systemic therapy and adjuvant radiation therapy [RT]) may be considered and should be discussed in a multidisciplinary setting. For patients with bulky regional nodal metastasis, consideration should be given to clinical trials of neoadjuvant therapy (see section of neoadjuvant systemic therapy), which may facilitate resection if tumor shrinkage occurs and may improve local disease control and MSS. Additionally, the efficacy of neoadjuvant treatment can be evaluated preoperatively by monitoring tumor response and postoperatively by pathologic evaluation of resected tumor tissue to allow for tailoring of adjuvant therapy.[45]

Surgery for isolated distant metastases may be rarely considered in carefully selected patients upon multidisciplinary review, such as for palliation of symptoms (bleeding or obstructing small bowel metastasis), resection of residual lesion after a good overall response to systemic therapy, or as part of a clinical protocol.

ADJUVANT RADIATION THERAPY

Considerations for the Primary Site

Recurrences at the primary tumor site after surgery are rare and occur in fewer than 5% of cutaneous melanomas.[46] However, certain histopathologic features portend a higher risk of local recurrence, in which case RT may be used to mitigate the risk. In particular, desmoplastic melanomas have a rate of local recurrence of 20% to 50% after surgery alone.[46–50] Retrospective reports have demonstrated a significant decrease (17%–19%) in local recurrence with postoperative RT.[51,52] Therefore, adjuvant RT should be considered for patients with desmoplastic melanomas. Other features that correlate with increased risk of local recurrence include Breslow tumor thickness 4 mm or greater,[53–56] satellitosis,[57,58] and ulceration.[46,59,60] Primary tumor location in the head and neck region is also associated with increased risk, perhaps because wide excision is limited by critical normal anatomy in many cases.[53,60–62] For patients that have a higher risk of local recurrence, particularly if a salvage procedure for local recurrence would be unacceptably morbid, adjuvant RT should be considered.

Considerations for Nodal Basins

Similar to local relapse risk in primary site, some pathologic features confer a high risk of regional recurrence in the dissected nodal basin. One of the most important prognostic factors is the presence of extracapsular extension (ECE). Retrospective studies have reported a regional recurrence rate ranging from 24% to 63% in patients with ECE compared with as low as 9% in patients without ECE.[63–66] Other pathologic features associated with an increased risk of regional recurrence include higher number of involved lymph nodes (≥4 lymph nodes vs fewer, 46%–53% v. 14%–25%, respectively) and increased lymph node size (≥3 cm vs <3 cm, 42% vs 24%, respectively).[64,65] Additionally, similar to the data related to risk of a local primary recurrence, there is a higher risk of regional relapse with nodal involvement in the head and neck region compared with other sites (33%–43% cervical vs 9%–28% axilla vs 13%–23% inguinal).[64]

These retrospective and single-arm studies prompted the Australian and New Zealand Melanoma Trials Group (ANZMTG) and Trans-Tasman Radiation Oncology Group (TROG) to conduct a randomized study evaluating the role of adjuvant RT for 250 high-risk patients.[67] The trial included patients with palpable lymph node involvement and a high risk of further lymph node field relapse based on the number of involved nodes (≥1 parotid nodes, ≥2 cervical or axillary nodes, or ≥3 inguinal nodes), large nodal size (≥3 cm for cervical, or ≥4 cm for axillary or inguinal), or ECE. With a median follow-up period of 40 months, adjuvant RT significantly reduced the risk of regional recurrence (19% vs 31% for no adjuvant RT; hazard ratio [HR], 0.56; ; 95% confidence interval [CI] 0.32–0.98; P = .04). A subsequent update by Henderson and colleagues[68] confirmed this observation. Although these data demonstrate the benefit of adjuvant RT on local or regional relapse, there was no significant impact on the risk of distant metastasis or OS. The role of adjuvant RT is also less clear with the development of effective adjuvant systemic therapies, which were not available at the time of this study. Thus, the use of adjuvant RT for patients with regional metastases requires a multidisciplinary discussion regarding relative risks and benefits.

ADJUVANT SYSTEMIC THERAPY

Adjuvant Interferon

Early reports of activity of interferon (IFN) α-2b in metastatic melanoma led to an investigation of the efficacy of this agent in the adjuvant setting after definitive surgery. The Eastern Cooperative Oncology Group (ECOG) 1684 showed a statistically significant improvement in relapse-free survival (RFS) for high-dose interferon (HDI) compared with observation (1.72 years vs 0.98 years; P = .0023). Although HDI was

approved by the Food and Drug Administration (FDA) in 1995, the initial impact on OS was not significant with longer follow-up.[69,70] Pegylation of IFN provided a way to increase the half-life of the drug in the body, reduced dosing frequency compared with the standard HDI, and mitigated some of the associated toxicities. The European Organization for Research and Treatment of Cancer (EORTC)C 18991 phase III trial randomized patients to pegylated IFN (PEG-IFN) for 5 years versus observation.[71] PEG-IFN treatment resulted in improved recurrence-free survival (RFS; 34.8 months vs 25.6 months; $P = .01$) and was eventually approved by the FDA in 2011. However, PEG-IFN did not significantly impact time to distant relapse or OS.[72] Because of the lack of OS benefit and significant toxicity, neither HDI nor PEG-IFN was used widely, nor were they used on comparator arms for the registration trials of adjuvant checkpoint inhibitors and targeted therapies. The use of HDI and PEG-IFN as adjuvant therapy for patients with melanoma has ceased.

Adjuvant Ipilimumab

Cytotoxic T lymphocyte-associated antigen 4 (CTLA4) is an inhibitory immune checkpoint molecule that is expressed on the surface of activated and regulatory T-cells.[73] Ipilimumab is a fully human immunoglobulin (Ig) G1 anti-CTLA4 monoclonal Ab that binds to the T-cells and enhances antitumor immunity.[74] After being approved in 2011 for the treatment of patients with stage IV melanoma, ipilimumab received regulatory approval as an adjuvant treatment for patients with high-risk resected stage III melanoma in 2015 (Table 49–7). This approval was based on the results of the double-blind, phase III EORTC 18071 trial for patients with melanoma with AJCC seventh edition stage III melanoma who had undergone CLND and had not received adjuvant RT. A total of 951 patients were randomized one to one to treatment with ipilimumab (10 mg/kg) ($n = 475$) or placebo ($n = 476$) every 3 weeks for four infusions and then every 3 months for up to 3 years. Notably, the dose of ipilimumab used in this trial was threefold higher than the dose approved for patients with stage IV melanoma.[75] The trial showed that adjuvant ipilimumab significantly improved RFS, distant metastasis-free survival (DMFS), and OS vs placebo. However, adjuvant ipilimumab was resulted in grade 3 or 4 adverse events (AEs) in 54% of patients, including five treatment-related deaths. Different doses of ipilimumab (high dose at 10 mg/kg and low dose at 3 mg/kg) versus HDI were compared in the **E1609 trial, which was** a multicenter phase 3 study.[76] Interestingly, low-dose ipilimumab (3 mg/kg) significantly improved OS (HR, 0.78; 95.6% repeated CI, 0.61–0.99; $P = .044$) and RFS (HR, 0.85; 99.4% CI, 0.66–1.09; $P = .065$) versus HDI, but high-dose ipilimumab (10 mg/kg) did not. Furthermore, nearly 60% of patients experienced toxicities when treated with ipilimumab 10 mg/kg. Thus, even though ipilimumab 10 mg/kg was approved as adjuvant therapy for patients with stage III melanoma, concerns about its toxicity and cost generally limited its use, particularly with the emergence of safer alternatives.

Adjuvant Nivolumab

Programmed death 1 protein (PD-1) has emerged as another important immune checkpoint receptor expressed on the surface of activated T-cells. PD-1 has two known ligands, programmed cell death ligand 1 (PD-L1; B7-H1) and PD-L2 (B7-DC). The PD-1–PD-L1 interaction inhibits T-cell proliferation and activation and induces apoptosis of antigen-specific T-cells to prevent collateral tissue damage and autoimmune disease. The PD-1–PD-L1 pathway is hijacked by tumor cells to suppress antitumor immunity.[77] Therefore, blocking the interaction of PD-1 and PD-L1 has been studied as a therapeutic approach for cancers.

Nivolumab (anti–PD-1), which was approved for patients with stage IV melanoma in 2014, received regulatory approval as adjuvant therapy for patients with stage III melanoma in 2017 based on the results of the CheckMate 238 trial[78] (see Table 49–7). In this double-blind, phase III, randomized controlled trial patients with melanoma with surgically resected AJCC seventh edition stage IIIB, IIIC, or stage IV melanoma were treated with nivolumab ($n = 453$) 3 mg/kg every 2 weeks or ipilimumab ($n = 453$) 10 mg/kg (dosed every 3 weeks for four doses and then every 12 weeks), each for a maximum of 1 year. Treatment with nivolumab significantly improved RFS versus ipilimumab (HR for disease recurrence or death, 0.65; 97.56% CI, 0.51–0.83; $P < .001$). This difference was seen in patients both with high and low PD-L1 expression. Importantly, adjuvant nivolumab was much safer than ipilimumab, with lower rates of grade 3 or 4 AEs (14.4% vs 45.9%) and treatment discontinuation for toxicity (9.7 vs 42.6%) and was associated with no deaths because of toxicity (2 with ipilimumab).[78]

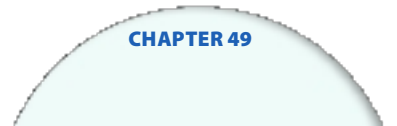
Adjuvant Pembrolizumab

Pembrolizumab (anti–PD-1) (approved for stage IV melanoma in 2014) was approved as adjuvant therapy for stage III melanoma patients in 2019 based on the EORTC 1325/KEYNOTE-054 phase III trial[79] (see Table 49–7). Patients ($n = 1019$) with stage IIIA, IIIB, or IIIC melanoma (AJCC seventh edition) who had undergone CLND were randomized one to one to treatment with pembrolizumab 200 mg intravenously ($n = 514$) or placebo ($n = 505$) every 3 weeks for up to 1 year. Pembrolizumab significantly improved RFS vs placebo (HR, 0.57; 98.4% CI, 0.43–0.74; $P = .001$) regardless of PD-L1 status. The grade 3 or higher AE rate

TABLE 49–7 Approved Adjuvant Therapies for Patients with Melanoma

Agent (FDA Approval)	Study; Total Patients Enrolled (*n*); Stage	Design	Regimen and Follow-up	OS	RFS	DMFS
Ipilimumab (2015)	EORTC 18071[75]; *n* = 951; stage IIIA, IIIB, or IIIC	Phase III double-blind, randomized	Arm A: ipilimumab 10 mg/kg Arm B: placebo q 3 weeks for 4 infusions; then q 3 months for up to 3 years Follow-up: 6.9 years	65.4% .vs 54.4% (ipilimumab .vs placebo); *P* = .001; HR, 0.73; 95% CI, 0.60–0.89; *P* = .002	40.8% .vs 30.3% (ipilimumab .vs placebo); *P* <.001; HR, 0.75; 95% CI, 0.63–0.88; *P* <.001	48.3% .vs 38.9% (ipilimumab .vs placebo); *P* = .002; HR, 95% CI, 0.76, 0.64–0.90; *P* = .002
Nivolumab (2017)	CheckMate 238[78] (updated); *n* = 906; stage IIIB, IIIC, or IV	Phase III double-blind, randomized	Arm A: nivolumab 3 mg/kg; q 2 weeks Arm B: ipilimumab 10 mg/kg q 3 weeks for four doses and then q 12 weeks ≤1 year of treatment Follow-up: 3 years	None reported yet	45% .vs 58% (nivolumab .vs ipilimumab); HR, 0.68; 95% CI, 0.56–0.82; *P* <.0001 **PD-L1 <5%:** HR, 0.73; 95% CI, 0.58–0.92 **PD-L1 <5%**: HR, 0.57; 95% CI, 0.39–0.83 **BRAF mutated:** HR, 0.84; 95% CI, 0.58–1.20 **BRAF wild type:** HR, 0.75; 95% CI, 0.53–1.07	Nivolumab .vs ipilimumab; HR, 0.78; 95% CI, 0.62–0.99
Pembrolizumab (2019)	KEYNOTE-054[79]; *n* = 1019; stage IIIA, IIIB, or IIIC	Phase III double-blind, randomized	Arm A: pembrolizumab 200 mg q 2 weeks Arm B: placebo for ≤1 year of treatment Follow-up: 18 months	None reported yet	Longer RFS with pembrolizumab: HR, 0.57; 98.4% CI, 0.43–0.74; *P* = .001 71.4% (95% CI 66.8–75.4) .vs 53.2% (95% CI 47.9–58.2) (pembrolizumab .vs placebo) **PD-L1 +:** HR, 0.54; 95% CI, 0.42–0.69; *P* <.001 **PD-L1 -:** HR, 0.47; 95% CI, 0.26–0.85; *P* = .01	
Dabrafenib and trametinib (2018)	COMBI-AD[80]; *n* = 870; stage IIIA, IIIB, or IIIC	Phase III double-blind, randomized	Arm A: dabrafenib 150 mg twice a day + trametinib 2 mg once a day (TT) Arm B: placebo for ≤1 year of treatment Follow-up: 48 months (15–48 months)	3-year OS: 86% .vs 77% (TT .vs placebo) HR, 0.57; 95% CI, 0.42–0.79; *P* = .000019	3-year RFS: 58% .vs 39% (TT .vs placebo); HR, 0.47; 95% CI, 0.39–0.58; *P* <.001 4-year RFS: 54% .vs 38% (TT .vs placebo)	

CI, confidence interval; DMFS, distant metastasis-free survival; EORTC, European Organization for Research and Treatment of Cancer; FDA, Food and Drug Administration; HR, hazard ratio; OS, overall survival; PD-L1, programmed cell death ligand 1; q, every; RFS, relapse-free survival.



for pembrolizumab was 14.7%, very similar to that observed with adjuvant nivolumab. Immune-related adverse events (irAEs) of any grade occurred in 37.3% patients, which were mostly endocrine disorders, including hypothyroidism (14.3%), hyperthyroidism (10.2%), and thyroiditis (3.1%). One treatment-related death was reported in the pembrolizumab arm due to myositis. Notably, because the CheckMate 238 and the KEYNOTE-054 studies differed in both their patient populations and their control groups, meaningful cross-trial comparisons of adjuvant nivolumab and pembrolizumab are challenging, if not impossible.

Adjuvant Dabrafenib and Trametinib

As noted previously, *BRAF*^{V600} mutations are detected in about 50% of cutaneous melanomas. As will be discussed later, multiple targeted therapy regimens combining BRAF and MEK inhibitors have been approved for the treatment of BRAF-mutant patients with stage IV melanoma. Among these regimens, only combination treatment with dabrafenib and trametinib has also been approved by the FDA as adjuvant therapy for BRAF-mutant patients with stage III disease (see Table 49–7). This approval in 2018 was based on the results of the COMBI-AD trial, which was a double-blind, phase III trial that randomized 870 patients with *BRAF*$^{V600E/K}$ mutant stage IIIA, IIIB, r IIIC melanoma (AJCC seventh edition) who had undergone CLND to receive either dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) or placebo for up to 1 year.[80] Treatment with dabrafenib and trametinib improved the RFS (HR, 0.47; P <.001) and DMFS (HR, 0.51; P <.001) versus placebo.[81] Recent analysis at a median follow-up period of 60 months showed that the median RFS for dabrafenib and trametinib had not been reached (not reached, NR; 95% CI, 47.9 months–NR) versus 16.6 months in the placebo arm (95% CI, 12.7–22.1 months).[82] The 4- and 5-year RFS rates were 55% (95% CI, 50%–60%) and 52% (95% CI, 48%–58%) with dabrafenib and trametinib versus 38% (95% CI, 34%–43%) and 36% (95% CI, 32%–41%) with placebo.

Dabrafenib and trametinib did have a higher rate of grade 3 or 4 toxicities (41% vs 14%) and toxicity-related treatment discontinuation (26% vs 3%) versus placebo. Although the toxicity rates with targeted therapy appear higher than with the PD-1 antibodies, the toxicities almost always resolve with treatment discontinuation, but toxicities with immunotherapy are sometimes long-lasting.

Adjuvant Chemotherapy

Although adjuvant chemotherapy is not approved for patients with cutaneous melanoma, there is evidence to support benefit in patients with mucosal melanoma. A randomized three-arm phase II trial assigned 189 patients with surgically resected mucosal melanoma (clinically localized or regionally metastatic) to observation, HDI (for 1 year), or chemotherapy (cisplatin 25 mg/m^2 on days 1–3 and temozolomide 200 mg/m^2 on days 1–5 every 3 weeks for six cycles).[83] Adjuvant cisplatin and temozolomide significantly improved RFS and OS compared with both HDI and observation. HDI also improved RFS and OS versus observation. Whereas fever and fatigue were more common toxicities in the HDI arm, anorexia and nausea and vomiting were more common with chemotherapy.

NEOADJUVANT THERAPY

The current standard of care for patients with clinical stage III melanoma to date is surgery followed by consideration of adjuvant systemic therapy (anti-PD-1 or targeted therapy) and/or potentially adjuvant radiation. However, several recent studies have demonstrated the feasibility and potential benefit of upfront neoadjuvant treatment with systemic therapy followed by surgery. Neoadjuvant approaches have the potential benefit of reducing surgical morbidity because of tumor shrinkage, personalizing adjuvant therapy based on pathologic response assessment, and facilitating insights into treatment resistance through the collection and analysis of biospecimens.[19] Neoadjuvant therapy is currently investigational for melanoma, but this strategy has become a pathway to drug approval in other diseases.

Neoadjuvant Immunotherapy

The effects of a single dose of neoadjuvant pembrolizumab before definitive surgery was evaluated in 27 patients with resectable stage IIIB/C or stage IV melanoma. All patients underwent surgery and then received adjuvant pembrolizumab for up to 1 year. A complete pathologic response (pCR) or near-complete pathologic response (near pCR) was observed in 8 of 27 patients (30%), all of whom remained recurrence free at a median follow-up period of 25 months after surgery. The DFS and OS rates at 2 years were 63% and 93%, respectively. The treatment was well tolerated, with no reported increase in postoperative complications.[84]

Combination neoadjuvant immunotherapy with nivolumab (anti–PD-1) and ipilimumab (anti–CTL-4) was studied in the phase II OpACIN-neo trial, which evaluated three different dosing schedules.[85,86] Patients with resectable stage III melanoma (n = 86) were randomized to two cycles of ipilimumab 3 mg/kg with nivolumab 1 mg/kg once every 3 weeks (group A), two cycles of ipilimumab 1 mg/kg with

nivolumab 3 mg/kg once every 3 weeks (group B), or two cycles of ipilimumab 3 mg/kg once every 3 weeks followed by two cycles of nivolumab 3 mg/kg every 2 weeks (group C). The pCR rates were 80%, 77%, and 65% in groups A, B, and C, respectively, and no pCR patients had recurred after a median follow-up period of more than 8 months. At a median follow-up period of 24.6 months, the median RFS and EFS were not reached in any of the three arms. Estimated 24-months RFSs were 84% (95% CI, 76%–92%) for the total population, 97% (95% CI, 93%–100%) for patients with a pathological response, and 36% (95% CI, 17%-74%) for patients without a pathological response. Group B regimen, which consisted of two cycles of neoadjuvant treatment with ipilimumab 1 mg/kg and nivolumab 3mg/kg, was well tolerated with only 20% grade 3 or 4 irAEs and a pathologic response rate of 77%.

Another trial evaluated neoadjuvant nivolumab as a single agent and in combination with ipilimumab followed by adjuvant nivolumab.[72] Patients (n = 23) with resectable stage III or oligometastatic stage IV melanoma were randomized to receive either neoadjuvant nivolumab (3 mg/kg) for four doses or neoadjuvant nivolumab (1 mg/kg) and ipilimumab (3 mg/kg) for three doses before definitive surgery. Neoadjuvant combination therapy achieved higher response rates (overall response rate [ORR], 73%; pCR, 45%) compared with single-agent neoadjuvant nivolumab (ORR, 25%; pCR, 25%) but also incurred much higher grade 3 to 4 toxicity (8% for monotherapy, 73% for combination). The trial was stopped early because of concerns regarding the efficacy of nivolumab monotherapy and the toxicity of nivolumab with ipilimumab.

Neoadjuvant Targeted Therapy

The safety and efficacy of neoadjuvant dabrafenib and trametinib have been evaluated in two phase II trials in patients with resectable *BRAF*$^{V600E/K}$ mutant clinical stage III or oligometastatic stage IV disease. In the NeoDT study, patients were randomized to standard-of-care surgery and adjuvant therapy (which at that time did not include adjuvant PD-1 or adjuvant dabrafenib and trametinib) or to neoadjuvant (8 weeks) and adjuvant (44 week) treatment with dabrafenib and trametinib.[87] Although initially planned for enrollment of 84 patients, the trial was halted early because the patients receiving neoadjuvant and adjuvant dabrafenib and trametinib (n = 14) had a markedly reduced risk of relapse compared with the control (n = 7) arm (HR, 0·016; 95% CI, 0.00012–0.14; P <.0001).[88] The radiographic response rate with neoadjuvant treatment was 85%, and the pCR rate was 58%. None of the patients with a pCR had developed evidence of distant metastasis in the initial report of the study (median follow-up, 7.1 months).[87]

In the single-arm NeoCombi study,[89] 35 patients with stage IIIB–C *BRAF*^{V600} mutant melanoma were treated with neoadjuvant (12 weeks) and adjuvant (40 weeks) dabrafenib and trametinib. At the median follow-up period of 27 months (interquartile range, 21–36), 35 patients had no evidence of clinical or radiologic progression during resection of the pretherapy tumor bed. All 35 patients achieved a pathological response after resection and pathological evaluation, with 17 (49%) patients achieving pCR and 18 (51%) achieving noncomplete pCR.

MANAGEMENT OF METASTATIC DISEASE

After decades of minimal progress, multiple immune and targeted therapies have received FDA approval for the treatment of patients with unresectable stage III or stage IV disease since 2011. These advances have improved the management and outcomes for patients dramatically.

Immunotherapy

Interleukin-2

Interleukin-2 (IL-2) is a growth factor normally secreted by CD4 T-helper cells that can activate effector CD8 T-cells and natural killer cells. Importantly, IL-2 provided the proof of principle that immunotherapy can achieve long-term cures in patients with stage IV melanoma, albeit only in about 5% (Table 49–8).[90] In addition to this low cure rate, IL-2 causes many toxicities, requiring hospitalization to administer and incurring a 1% to 2% treatment-related mortality rate. Thus, IL-2 is rarely used outside clinical trials, particularly in combination with adoptive T-cell therapy.[91]

Ipilimumab (Anti–Cytotoxic T Lymphocyte-Associated Antigen 4 Ab)

Ipilimumab was the first agent to significantly improve the OS of patients with stage IV or unresectable stage III metastatic melanoma. In the first positive phase III study in patients with melanoma, previously treated patients with advanced melanoma were randomized to receive gp100 vaccine, ipilimumab (3 mg/kg every 3 weeks for four doses), or ipilimumab with gp100 vaccine.[92] The response rates were 10.9% for ipilimumab and only 5.7% for ipilimumab with gp100. Both ipilimumab containing regimen improved OS (ipilimumab and gp100: median, 10 months; HR, 0.68; P <.001; ipilimumab single agent: median, 10.1 months; HR, 0.66;

TABLE 49–8 Approved Systemic Therapies for Melanoma

Agent (FDA Approval)	Phase; Total Patients Enrolled (*n*)	Comparator Arm(s)	ORR (Experimental Arm .vs Comparator Arm)	Median PFS (Experimental Arm .vs Comparator arm)	OS (Experimental Arm .vs Comparator Arm)
Dacarbazine (1975)[129]	N/A; *n* = N/A	N/A	N/A	N/A	N/A
Interleukin-2 (1998)[90]	N/A[a]; *n* = 270	N/A	0.16	13.1 months	N/A
Ipilimumab (2011)[92]	III; *n* = 676	Ipilimumab + gp100 .vs gp100 alone;	10.9% (ipilimumab) .vs 5.7% (ipilimumab + gp100) .vs 1.5% (gp100)	2.86 months (ipilimumab) .vs 2.76 months (ipilimumab + gp100) .vs 2.76 months (gp100)	Median OS (ipilimumab), 10.1 .vs 10 months (ipilimumab + gp100) .vs 6.4 months (gp100); Median months: 18-month OS, 33.2% (ipilimumab) .vs 30.0% (ipilimumab + gp100) .vs 16.3% (gp100)
Vemurafenib (2011)[107]	III; *n* = 675	Dacarbazine	48% .vs 5%	5.3 months .vs 1.6 months	6-month OS, 84% .vs 64%
Dabrafenib (2013)[109]	III; *n* = 250	Dacarbazine	50% .vs 6%	5.1 months .vs 2.7 months (*P* <.0001)	N/A
Trametinib; (2013)[111]	III; *n* = 322	Chemotherapy (dacarbazine or paclitaxel)	22% .vs 8% (*P* = .01)	4.8 months .vs 1.5 months (*P* <.001)	6-month OS, 81% .vs 67%
Dabrafenib + trametinib (2014)[112]	II; *n* = 247	Dabrafenib	76% .vs 54%[b]	9.4 months .vs 5.8[b] months (*P* <.001)	1-year OS, 79% .vs 70%[a]
Pembrolizumab (2014)[96]	I; *n* = 173	Pembrolizumab 2 mg/kg .vs 10 mg/kg	26% for both arms	22 weeks .vs 14 weeks	1-year OS, 58% .vs 63%
Nivolumab (2014)[98]	III; *n* = 405	Investigator's choice of chemotherapy	31.7% .vs 10.6%	4.7 months .vs 4.2 months	N/A
Vemurafenib + cobimetinib (coBRIM trial); (2015)[119]	III; *n* = 495	Vemurafenib	70% .vs 50%	12.3 .vs 7.2 month (*P* <.0001)	Median OS, 22.3 months .vs 17.4 months (*P* = .005); 2-year OS, 48.3% vs 38.0%
Nivolumab + ipilimumab , (CheckMate-067) (2016)[102,104]	III; *n* =945	Nivolumab (arm B); ipilimumab (arm C)	Arm A (nivolumab + ipilimumab) :58% Arm B (nivolumab): 45% Arm C (ipilimumab): 19%	Arm A: 11.5 months Arm B: 6.9 months Arm C: 2.9 months	5-year OS: Arm A:52% Arm B: 44% Arm C: 26%
Encorafenib + binimetinib (COLUMBUS trial) (2018)[121]	III; *n* = 577	Encorafenib monotherapy and vemurafenib monotherapy	63% (encorafenib + binimetinib) .vs 51% (encorafenib) .vs 40% (vemurafenib)	14.9 (encorafenib + binimetinib) .vs 9.6 (encorafenib) .vs 7.3 months (vemurafenib)	Median OS, 33.6 (encorafenib+ binimetinib) .vs 23.5 (encorafenib) .vs 16.9 months (vemurafenib) 2-year OS, 57.6% (encorafenib+ binimetinib) .vs 49.1% (encorafenib) .vs 43.2% (vemurafenib)

[a]Pooled results from eight clinical trials.
[b]Results reported here are from part C of the clinical trial.
FDA, Food and Drug Administration; N/A, not applicable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

P = .003) compared with gp100 (median, 6.4 months). No difference in OS was detected between the ipilimumab groups (HR with ipilimumab plus gp100 ,1.04; P = .76).

Although the improvement in OS was important, gp100 was not a standard agent for the treatment of patients with this disease. Thus, 502 treatment-naïve patients with metastatic melanoma were randomized to treatment with dacarbazine alone or in combination with ipilimumab in another phase III study.[93] Ipilimumab was dosed at 10 mg/kg for four doses followed by maintenance therapy every 12 weeks. Both OS (median, 11.2 vs 9.1 months; HR, 0.72; P <.001) and PFS (HR, 0.76; P <.006) were significantly improved in the patients receiving ipilimumab. The ORRs were 15.2% with ipilimumab plus dacarbazine and 10.3% with dacarbazine alone. Although the response rate with ipilimumab was relatively low in both phase III studies, long-term follow-up has shown that the majority of these responses last more than 5 years and may even represent cures.[94] Ipilimumab (3 mg/kg every 3 weeks for four doses) was approved in 2011 for the treatment of patients with metastatic melanoma (see Table 49–8). Ipilimumab is associated with significant grade 3 and 4 toxicities,[95] with the most common irAEs being dermatitis (pruritus, rash), enterocolitis, endocrinopathies (hypophysitis, thyroiditis), and liver abnormalities (elevated serum liver test results, hepatitis) in approximately 20% of patients.

Anti–Programmed Death-1 Protein Antibodies

Pembrolizumab

Pembrolizumab was approved by the FDA in 2014 for patients with metastatic melanoma with disease progression after ipilimumab (and BRAF inhibitor therapy if $BRAF^{V600}$ mutation positive)[96] (see Table 49–8). The initial approval was based on a phase I trial comparing the efficacy of two different doses of pembrolizumab (2 mg/kg vs 10 mg/kg every 3 weeks) in patients with ipilimumab-refractory advanced melanoma. Both treatments achieved a 26% clinical response rate.[96,97] Notably, most clinical responses to pembrolizumab were ongoing at the time of those reports, and the median OS had yet to be reached. Subsequently, a phase III trial randomized 834 patients to treatment with pembrolizumab (2 mg/kg every 2 weeks or every 3 weeks for up to 2 years) versus ipilimumab (3 mg/kg every 3 weeks for four cycles). Pembrolizumab achieved significant improvements in response rate (33% for both dosing regimens vs 12%; P <.001), PFS (HR, 0.58; P <.001 for both dosing regimens) and OS (HR, 0.63; P <.0005 for every-2-week dosing; HR, 0.69; P <.0036 for every 3-week dosing).[97] In addition to being more active than ipilimumab, pembrolizumab was also safer because fewer than 5% of patients treated with pembrolizumab experienced grade 3 or 4 irAEs, and only approximately 10% experienced grade 3 or 4 toxicity of any kind.

Nivolumab

Nivolumab was also approved in 2014 for the treatment of patients with metastatic melanoma previously treated with ipilimumab (and a BRAF inhibitor for patients with a $BRAF^{V600}$ mutation)[98] (see Table 49–8). In a phase I study, 296 previously treated patients with advanced solid cancers received nivolumab at a dose of 0.1 to 10 mg/kg every 2 weeks for up to 2 years.[99] Objective responses were observed in 28% of 96 evaluable patients with melanoma, and the responses were durable, lasting at least 1 year in 13 of 18 patients treated for 1 year or more.

Nivolumab has also been shown to be more effective than chemotherapy in treatment-naïve patients. In a randomized phase III study of 418 previously untreated patients with metastatic melanoma, the 1-year OS rates were 72.9% with nivolumab and 42.1% with dacarbazine (HR, 0.42; P <.001)[100] The response rates with nivolumab and dacarbazine were 40% and 14%, respectively, and the median PFS times were 5.1 and 2.2 months, respectively (HR, 0.43; P <.001). Grade 3 or 4 treatment-related AEs were also less common with nivolumab (11.7%) than with dacarbazine (17.6%). At minimum follow-up periods of 38.4 months, 3-year OS rates remained higher for nivolumab compared with dacarbazine (51.2% vs 21.6%, respectively).[101]

Combination Immunotherapy: Anti–PD-1 with Anti–CTLA-4

Combination immunotherapy with nivolumab and ipilimumab received FDA approval in 2016 based on CheckMake-067 study.[102] In this randomized, three-arm, double-blind, phase III study, 945 previously untreated patients with stage IV or unresectable stage III metastatic melanoma received nivolumab -ipilimumab (n = 314), nivolumab monotherapy (n = 316) or ipilimumab monotherapy (n = 315) until progression or unacceptable toxic effects were observed, with PFS and OS as primary endpoints. Patients were randomly assigned one to one to one to receive intravenous nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four doses followed by nivolumab 3 mg/kg every 2 weeks, nivolumab 3 mg/kg every 2 weeks plus placebo, or ipilimumab 3 mg/kg every 3 weeks for four doses plus placebo. The trial was powered to compare single-agent nivolumab and nivolumab plus ipilimumab treatments versus the ipilimumab monotherapy

arm. Randomization was stratified based on BRAF mutation status, metastasis stage, and PD-L1 status. A longer PFS was observed for nivolumab -ipilimumab (median, 11.5 months; 95% CI, 8.7–16.7) and for nivolumab immunotherapy (median, 6.9 months; 95% CI, 4.3–9.5) compared with ipilimumab monotherapy (median, 2.9 months; 95% CI, 2.8–3.4). Response rates were 58% for the combination, 45% for nivolumab, and 19% for ipilimumab. Treatment with nivolumab plus ipilimumab, however, also resulted in a higher rate (55%) of grade 3 or 4 AEs than nivolumab (16.3%) or ipilimumab (27.3%). Importantly, encouraging results were also seen in follow-up reports for the trial at both 3 years[103] and 5 years.[104] At 5-year minimum follow-up, the OSs were 52% in the nivolumab plus ipilimumab group, 44% in the nivolumab group, and 26% in the ipilimumab group.[104] The median OSs were more than 60 months (median not reached) in the nivolumab plus ipilimumab group and 36.9 months in the nivolumab group compared with 19.9 months in the ipilimumab group (HR for death with nivolumab plus ipilimumab vs ipilimumab, 0.52; HR for death with nivolumab vs ipilimumab, 0.63). No new toxicity concerns were noted, but grade 3 or 4 AEs were seen in 59% of patients in the nivolumab plus ipilimumab group, in contrast to 23% and 28% for single-agent nivolumab or ipilimumab, respectively. Of note, this study compared ipilimumab treatment with nivolumab -plus ipilimumab and nivolumab monotherapy, but it was not powered to directly compare the combination therapy with nivolumab monotherapy. An earlier randomized double-blind study in advanced untreated patients with melanoma compared nivolumab plus ipilimumab combination with single-agent ipilimumab and showed a similar significantly higher response rates and longer PFS rates for combination group than ipilimumab alone.[105]

In an effort to lower toxicity associated with the combination strategy, the CheckMate 511 study investigated whether nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg (NIVO3 + IPI1) versus the inversed doses of the same drugs (ipilimumab 1 mg/kg, nivolumab 3 mg/kg: NIVO1 + IPI3) was associated with an improved safety profile.[106] Patients were randomly assigned to receive the investigated dose (NIVO1 + IPI3; $n = 180$) or the inversed dose (NIVO3 + IPI1; $n = 178$) once every 3 weeks for four doses. After 6 weeks, all patients received NIVO 480 mg once every 4 weeks until disease progression or unacceptable toxicity. The primary endpoint was incidence comparison the rate of grade 3 to 5 AEs between the treatment groups and results showed a much better safety profile for the NIVO3 + IPI1 group compared with its counterpart. The incidence of grade 3 to 5 AEs was 34% for the investigated doses compared with 48% with the NIVO1 + IPI3 arm ($P = .006$). Interestingly, OS, ORR, and median PFS were similar between the two arms. Although the efficacy endpoints were descriptive and secondary, this study suggests that low doses of ipilimumab can decrease toxicity without risking the established clinical benefit of combination therapy.

Pembrolizumab (2 mg/kg) was also tested in combination with low-dose ipilimumab (1 mg/kg) in the KEYNOTE-029, a phase 1b trial.[107] Most of the 153 patients enrolled (87%) were treatment naïve; however, some received prior targeted therapy or chemotherapy. ORR reached 61%, which is similar to that observed with nivolumab and ipilimumab combination therapy.[108] The estimated 1-year PFS and OS were 69% and 89%, respectively. Treatment-related grade 3 and 4 AEs occurred in 45% of patients.

Taken together, in patients without brain metastases, there is still uncertainty about which patients will benefit sufficiently from single-agent anti–PD-1 and in which patients the addition of ipilimumab is preferred or needed. However, in patients with brain metastases, the combination of ipilimumab and nivolumab is the preferred option despite the toxicity associated with this regimen. Trials with single-agent anti–PD-1 in patients with melanoma with asymptomatic brain metastases have reported overall intracranial response rates of about 20%.[109–111] Although the responses were durable, this response rate is about 50% lower than was reported in patients without brain metastases. In contrast, clinical trials evaluating the combination of ipilimumab (3 mg/kg) and nivolumab (1 mg/kg) in patients with melanoma reported durable intracranial responses in 50% to 55%, which is similar to results in previous studies in patients without brain metastases.[111,112] Although the combination regimen had a toxicity rate similar to previous trials, no new or unexpected toxicities were observed in patients with brain metastases. These results have led to ipilimumab plus nivolumab being considered as the standard systemic therapy option for patients with asymptomatic brain metastases.

Targeted Therapy

Targeted therapies are agents that inhibit the proteins or pathways (or both) that are activated in tumors by oncogenic events. Targeted therapies demonstrated efficacy in several cancers in which critical oncogenes have been identified, including melanoma, chronic myelogenous leukemia (*BCR-ABL*), breast cancer (*HER2/neu*), and gastrointestinal stromal tumors (GISTs; *KIT*), among others.

BRAF Inhibitors

As noted previously, point mutations that cause substitutions at the V600 residue of the BRAF protein ($BRAF^{V600}$) are the most common oncogenic events in

cutaneous melanoma. Vemurafenib was the first BRAF inhibitor to be approved for patients with this mutation, based on the results of the BRIM-3 phase III trial. In this study, 675 patients with metastatic melanoma with a *BRAF*^{V600E} mutation were randomized to treatment with vemurafenib or dacarbazine.[113] This trial was terminated at its first interim analysis because vemurafenib treatment significantly improved PFS (median, 5.3 months vs 1.6 months; HR, 0.26; P <.001) and OS (HR, 0.37; P <.001). The extended follow-up showed the ORRs were 57% for vemurafenib and 9% for dacarbazine treatments.[114] Vemurafenib also improved OS and thus was approved for the treatment of metastatic melanoma patients with a *BRAF*^{V600} mutation in 2011 (see Table 49–8).

Dabrafenib, another BRAF inhibitor, was evaluated in the BREAK-3 phase III trial in which 250 patients with *BRAF*^{V600E} mutant metastatic melanoma were randomized to treatment with dabrafenib or dacarbazine.[115] The ORRs were 50% for dabrafenib and 6% for dacarbazine, and dabrafenib treatment significantly improved PFS (median, 5.1 months vs 2.7 months; HR, 0.30; P <.0001), and OS (HR, 0.61; 95% CI, 0.25–1.48). At 5 years, PFS was 12% in the dabrafenib arm, whereas all dacarbazine-arm patients progressed or were censored.[82] Dabrafenib was approved for the treatment of patients with metastatic melanoma with a *BRAF*^{V600} mutation in 2013 (see Table 49–8).

Although most patients with metastatic melanoma with a *BRAF*^{V600} mutation achieve clinical benefit with single-agent BRAF inhibitor treatment, the median duration of response was only about 6 months, and about 90% of patients develop resistance by 1 year.[113,115] Multiple studies showed that the most common feature of the tumors at the time of resistance is reactivation of the MAPK (mitogen-activated protein kinase) signaling pathway, which is caused by a variety of mechanisms. Importantly, preclinical studies showed that inhibition of MEK, which is an effector of BRAF, could inhibit the growth of melanomas with acquired resistance to single-agent BRAF inhibitor treatment. This finding supported the rationale to determine if combining BRAF and MEK inhibitors was more effective than single-agent BRAF inhibitor treatment.[116] Interestingly, preclinical studies also suggested that MEK inhibitors could decrease the skin toxicity that was a unique side effect of the BRAF inhibitors[116] because up to 20% of patients developed proliferative skin lesions, including SCCs or keratoacanthomas.

Combination Therapy with BRAF and MEK Inhibitors

The first combination targeted therapy regimen to be tested in patients with metastatic melanoma with a *BRAF*^{V600} mutation was dabrafenib and trametinib. As noted earlier, single-agent dabrafenib was approved in the setting, with an approved dosage of 150 mg twice a day. Trametinib, a potent inhibitor of MEK1/2, was also approved for the treatment of patients with metastatic melanoma with a *BRAF*^{V600} mutation based on a randomized trial versus chemotherapy, at a dosage of 2 mg/day.[117] Although trametinib was more effective than chemotherapy, it had a lower response rate than single-agent BRAF inhibitors and more toxicity, and thus was generally not used as a single agent. In a phase I/II study, it was shown that combined treatment with dabrafenib and trametinib was well tolerated at the full dose of each drug.[118] Consistent with preclinical studies, the incidence of cutaneous SCC was 5% with dabrafenib combined with trametinib (D/T) and 17% with dabrafenib alone. Although toxicity was decreased, the most common side effect with D/T was pyrexia, which occurred more frequently with the combination (71%) than with dabrafenib alone (26%). Importantly, treatment with D/T was more effective than dabrafenib. Treatment with D/T resulted in significant improvements in response rate (76% vs 54%), with all patients achieving disease control, and PFS (median, 9.4 vs 5.8 months; HR, 0.39; P <.001).[118] These results formed the basis for comparison of D/T with single-agent dabrafenib and with single-agent vemurafenib in two separate phase III trials (COMBI-D and COMBI-V, respectively).[119,120] Combination treatment with D/T resulted in significant improvements in both PFS and OS compared with vemurafenib (HR, 0.56 for PFS; HR, 0.69 for OS) and dabrafenib (HR, 0.75 for PFS; HR, 0.63 for OS). Based on these results, D/T was approved for metastatic melanoma patients with a *BRAF*^{V600} mutation in 2014 (see Table 49–8). A recent pooled analysis of patients (n = 563) treated with D/T in the phase III studies with at least 5 years of follow-up showed that the median PFS was 11.1 months (95% CI, 9.5–12.8), and the median OS was 25.9 months (95% CI, 22.6–31.5). The 5-year PFS and OS rates were 19% and 34%, respectively. Thus, although many patients progress, a subset may achieve long-term disease control and survival with D/T.[121] D/T was also evaluated in patients with a *BRAF*^{V600} mutation with brain metastases in the COMBI-MB study.[122] In patients with a previously untreated brain metastases and a *BRAF*^{V600E} mutation, treatment with D/T achieved an intracranial response rate of 58% and an intracranial disease control rate of 78%, with no new or unexpected toxicities. Although these results were similar to those seen in previous studies, the median duration of response was 6.5 months, which was much shorter than that reported in patients without brain metastases in previous trials, and in contrast to the duration of intracranial responses reported for immunotherapies. The cause of the shorter duration of responses in brain metastases with D/T is currently unknown.

Combination therapy with vemurafenib and cobimetinib (V/C), another MEK1/2 inhibitor, was also superior to single-agent vemurafenib treatment in a phase III trial (see Table 49–8).[123] Both median PFS (9.9 vs 6.2 months; HR, 0.51; P <.001) and response rates (68% vs 45%; P <.001) were higher in the V/C group. Importantly, although slightly more grade 3 and 4 AEs were observed with V/C, there was no significant difference in the rate of study-drug discontinuation, and the number of secondary cutaneous cancers decreased with the combination therapy. V/C has less pyrexia than D/T but more photosensitivity.

The third approved BRAF–MEK combination, encorafenib and binimetinib (E/B), was approved by the FDA in 2018.[124] In the COLUMBUS phase III trial, patients with $BRAF^{V600E}$ and/or $BRAF^{V600K}$ mutated melanoma were randomly assigned to receive encorafenib 450 mg orally once daily with binimetinib 45 mg orally twice daily (n = 192), encorafenib 300 mg orally once daily (n = 194), or vemurafenib 960 mg orally twice daily (n = 191).[124,125] In the first head-to-head comparison of BRAF inhibitors, treatment with encorafenib achieved improved OS compared with vemurafenib (median, 23.5 months vs 16.9 months; HR, 0.76; P = .03). Although the maximum tolerated dose of single-agent encorafenib was 300 mg/day, a higher dose (450 mg/day) was feasible when it was given in combination with binimetinib. Consistent with other combinations, treatment with E/B achieved improved ORR (64% vs 41%), PFS (median, 14.9 months vs 7.3 months; HR, 0.51; 95% CI 0.39–0.67; P <.0001), and OS (median, 33.6 vs 16.9 months; HR, 0.54; 95% CI 0.41–0.71; P <.0001) compared with single-agent BRAF inhibitor (vemurafenib). Despite the use of the higher dose of encorafenib, E/B treatment had a slightly lower rate of grade 3 and 4 AE toxicities (58%) than either single-agent vemurafenib (63%) or encorafenib (66%).

KIT Inhibitors

Phase II studies of imatinib in metastatic melanoma patients with *KIT* mutations or amplifications have demonstrated much more promising results than observed in unselected patients.[126–128] The response rates reported in these trials range from 15% to 30%, with subgroup analyses demonstrating response rates of up to 50% in patients with the most common recurrent mutations detected in melanomas. Although these results are a marked improvement compared with those observed in unselected patients, the response rates are not as high as those in patients with GISTs with *KIT* mutations treated with the same inhibitors. Studies are ongoing to identify the KIT-mutant melanoma patients who are most likely to benefit from KIT inhibitors and combinatorial strategies that are more effective.

Other Therapies

Talimogene Laherparepvec

TVEC is an attenuated and genetically coded herpes simplex virus type 1 (HSV-1) engineered to express human granulocyte-macrophage colony-stimulating factor (GM-CSF) and designed to selectively replicate in tumor cells to facilitate antigen release, presentation, and systemic antitumor immune response.[129,130] Local GM-CSF expression promotes the migration and maturation of dendritic cells, aiding in antigen presentation specific to CD4 T-helper and CD8 C cytotoxic T-cells, initiating an immune response by activating both adaptive and innate immune cells.[130,131] TVEC was approved in 2015 for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with recurrent melanoma after initial surgery based on the results of the OPTiM trial. In this multicenter international phase III trial, 436 patients with unresectable stage IIIB to IV melanoma were randomly assigned to receive either TVEC (n = 295) or GM-CSF (n = 141).[132] TVEC was injected directly into the tumors, and subsequent doses were administered 3 weeks after the first dose and then once every 2 weeks. GM-CSF was administered subcutaneously every day for 14 days in 28-day cycles. The ORR in the TVEC group was 26.4% compared with 5.7% in the GM-CSF group. Furthermore, responses were more durable in the TVEC arm (16.3% vs 2.1%; P <.001) with 10.8% of complete responses. The OS was 23.3 months compared with 18.9 months with GM-CSF (P = .051). No unexpected or new toxicities were reported and included fatigue, chills, low-grade fevers, nausea, flulike symptoms, and pain at the injection site.

Although TVEC achieved a high rate of local responses, it had very low activity against distant metastases and in patients with advanced stage IV disease. Thus, clinical trials have tested if combining TVEC with systemic immunotherapy would prove more effective. In one study, 198 patients were randomized to treatment with ipilimumab alone or with TVEC.[133] Although the combination arm achieved a higher response rate (39% vs 18%; odds ratio, 2.9; P = .002), there was no significant improvement in PFS (median, 8.2 months vs 6.4 months; HR, 0.83; P = .35). Trials evaluating TVEC in combination with anti–PD-1 antibodies are ongoing after promising results in initial small studies.[134]

Chemotherapy

Dacarbazine is the only chemotherapy agent approved by the FDA for the treatment of metastatic melanoma[135] (see Table 49–8). Approved in 1975, dacarbazine achieves clinical responses in 5% to 10% of patients. The overwhelming majority of these responses are

short-lived, and dacarbazine has never been proven to be superior to another agent in a phase III trial. Temozolomide is an orally available prodrug that is metabolized to the same active intermediate as dacarbazine. Temozolomide was shown to be noninferior to dacarbazine in a phase III trial.[136] Temozolomide has the ability to cross the intact blood–brain barrier, but a large phase II trial failed to show significant efficacy.

In addition to these single agents, a variety of combination chemotherapy regimens have been evaluated in patients with melanoma.[137] Although these regimens achieve clinical responses in up to 20% to 25% of patients, none has been shown to significantly improve OS versus single-agent chemotherapy, and all are associated with increased toxicity.

SPECIAL CLINICAL SCENARIOS

Mucosal Melanoma

Unlike cutaneous melanoma, mucosal melanomas are rare and only represent only about 1 % of all melanomas.[138] Mucosal melanomas can originate in almost any part of mucosal membranes, but they most often arise from the mucosa of the nasal cavity and accessory sinuses, oral cavity, anorectum, vulva, and vagina. Surgical resection is the primary treatment modality if complete resection is feasible.

Overall, patients with metastatic mucosal melanoma have a significantly worse prognosis than patients with cutaneous melanomas.[139] Retrospective studies have reported median OS of only 6 to 18 months after treatment with checkpoint inhibitors and a decreased response rate compared with cutaneous melanomas.[140–143] Although *BRAF* mutations are common in patients with cutaneous melanomas, they are quite rate in mucosal melanomas.[144] *KIT* mutations are more frequent in this disease, and they represent a possible therapeutic target.[24,145,146] As described earlier in this chapter, KIT inhibitors have shown some efficacy in mucosal melanoma with certain *KIT* mutations.[127,147] Finally, different chemotherapy regimen have been used in patients with mucosal melanoma; however, no systemic therapy has been shown to significantly improve outcomes.[148]

Uveal Melanoma

Uveal melanomas, which include melanomas arising in the choroid, ciliary body, and iris of the eye, represent the most common primary intraocular malignancy in adults.[149] Approximately 1500 new cases are diagnosed in the United States each year.[150] BRAF mutations are not detected in these tumors, but more than 80% have an activating mutation in either the GNAQ or *GNA11 gene*.[26,151] For uveal melanoma restricted to the eye, treatment options include brachytherapy, external-beam radiotherapy, photon-based radiation, or surgical approaches (ie, local resection and enucleation of the affected eye). However, about 50% of patients eventually develop metastatic disease.[152] Interestingly, uveal melanoma has a high propensity to metastasize to the liver, with more that 90% of patients with metastatic uveal melanoma found to have hepatic involvement.[153] Treatment options for metastatic patients remain unsatisfactory because even the checkpoint inhibitor combination with ipilimumab and nivolumab have showed poor ORRs in this subtype.[154–156]

MD ANDERSON PRACTICE TIPS

- A standardized and contemporary melanoma staging system allows accurate risk stratification and prognostication to guide and personalize patient management. The eighth edition of the AJCC melanoma staging system, which was formally implemented in January 2018, included several changes from the seventh edition staging system. Revisions were based on analysis of a large international melanoma database and reflect our contemporary understanding of the natural history of metastatic melanoma and the clinical management of patients with cutaneous melanoma.
- The publication of prospective clinical trials showing that CLND did not improve MSS and resulted in increased toxicities (ie, lymphedema) rapidly led to the general discontinuation of this practice in patients with a positive SLNB. However, CLND provides prognostic information (ie, number of involved lymph nodes), and such surgery was required for participation in many adjuvant therapy registration studies. This change in practice needs to be considered when discussing prognosis and treatment outcomes.
- Although neoadjuvant therapy has not achieved regulatory approval in melanoma, this approach is used in many diseases to personalize adjuvant therapy, and early results in patients with melanoma are very promising. Patients with high-risk stage III disease should be managed using a multidisciplinary approach, with strong consideration for clinical trial participation when feasible.
- For patients with a BRAF V600 mutation, both immunotherapy and targeted therapy treatments yield significant benefit as adjuvant therapy for resectable stage III disease and as definitive therapy for stage IV or unresectable stage III disease. The treatments differ in many ways, including route of administration; rates, kinetics, and duration of clinical responses; and the types, duration, and management of toxicities. Both immunotherapy and targeted therapy have shown efficacy in the second-line setting after failure of the other modality. Treatment selection for patients with a BRAF V600 mutation requires an understanding of the relative risks and benefits of each approach, ideally integrating disease features and patient comorbidities, to inform treatment decisions.
- Single-agent anti–PD-1 antibody therapy and combination immunotherapy with ipilimumab and nivolumab were both approved for patients with stage IV or unresectable stage III melanoma based on superior outcomes compared with single-agent anti–CTLA-4 antibody treatment. Definitive data comparing anti–PD-1 versus combination ipilimumab and nivolumab is currently lacking, although the available data do strongly suggest superiority for the combination in patients with asymptomatic brain metastases. Selection of single-agent versus combination immunotherapy should include consideration of efficacy, toxicity, support systems, and sites of disease.
- The trials that led to the approval of the described immunotherapies for metastatic disease were largely conducted in patients with cutaneous melanoma. These agents are approved for patients with mucosal and uveal melanoma but yield significantly lower response rates in such patients.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69(1):7-34.
2. Institute NC. Surveillance, Epidemiology, and End Results Program (SEER). https://seer.cancer.gov/statfacts/html/melan.html
3. Howlader N, Noone AM, Krapcho M, et al, eds. *SEER Cancer Statistics Review*. National Cancer Institute. 2019.
4. Kanavy HE, Gerstenblith MR. Ultraviolet radiation and melanoma. *Semin Cutan Med Surg*. 2011;30(4):222-228.
5. Berger MF, Hodis E, Heffernan TP, et al. Melanoma genome sequencing reveals frequent PREX2 mutations. *Nature*. 2012;485(7399):502-506.
6. Olsen CM, Carroll HJ, Whiteman DC. Estimating the attributable fraction for melanoma: a meta-analysis of pigmentary characteristics and freckling. *Int J Cancer*. 2010;127(10):2430-2445.
7. Lynch HT, Fusaro RM, Lynch JF, Brand R. Pancreatic cancer and the FAMMM syndrome. *Fam Cancer*. 2008;7(1):103-112.
8. Vourc'h-Jourdain M, Martin L, Barbarot S, aRed. Large congenital melanocytic nevi: therapeutic management and melanoma risk: a systematic review. *J Am Acad Dermatol*. 2013;68(3):493-498 e1-14.
9. Curtin JA, Fridlyand J, Kageshita T, et al. Distinct sets of genetic alterations in melanoma. *N Engl J Med*. 2005;353(20):2135-2147.
10. Pleasance ED, Cheetham RK, Stephens PJ, et al. A comprehensive catalogue of somatic mutations from a human cancer genome. *Nature*. 2010;463(7278):191-196.
11. Genomic classification of cutaneous melanoma. *Cell*. 2015;161(7):1681-1696.
12. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. *Nature*. 2002;417(6892):949-954.
13. Pollock PM, Harper UL, Hansen KS, et al. High frequency of BRAF mutations in nevi. *Nat Genet*. 2003;33(1):19-20.
14. Wan PTC, Garnett MJ, Roe SM, et al. Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. *Cell*. 2004;116(6):855-867.
15. Botton T, Yeh I, Nelson T, et al. Recurrent BRAF kinase fusions in melanocytic tumors offer an opportunity for targeted therapy. *Pigment Cell Melanoma Res*. 2013;26(6):845-851.
16. Siroy AE, Boland GM, Milton DR, et al. Beyond BRAFV600: Clinical mutation panel testing by next-generation sequencing in advanced melanoma. *J Invest Dermatol*. 2015;135(2):508-515.
17. Kwong LN, Davies MA. Navigating the therapeutic complexity of PI3K pathway inhibition in melanoma. *Clin Cancer Res*. 2013;19(19):5310-5319.
18. Bucheit AD, Chen G, Siroy A, et al. Complete loss of PTEN protein expression correlates with shorter time to brain metastasis and survival in stage IIIB/C melanoma patients with BRAFV600 mutations. *Clin Cancer Res*. 2014;20(21):5527-5536.
19. Hodis E, Watson IR, Kryukov GV, et al. A landscape of driver mutations in melanoma. *Cell*. 2012;150(2):251-263.
20. Dankort D, Curley DP, Cartlidge RA, et al. Braf(V600E) cooperates with Pten loss to induce metastatic melanoma. *Nat Genet*. 2009;41(5):544-552.
21. Lee B, McArthur GA. CDK4 inhibitors an emerging strategy for the treatment of melanoma. *Melanoma Manag*. 2015;2(3):255-266.
22. Wolfel T, Hauer M, Schneider J, et al. A p16INK4a-insensitive CDK4 mutant targeted by cytolytic T lymphocytes in a human melanoma. *Science*. 1995;269(5228):1281-1284.
23. Sauter ER, Yeo U-C, von Stemm A, et al. Cyclin D1 is a candidate oncogene in cutaneous melanoma. *Cancer Res*. 2002;62(11):3200-3206.
24. Curtin JA, Busam K, Pinkel D, Bastian BC. Somatic activation of KIT in distinct subtypes of melanoma. *J Clin Oncol*. 2006;24(26):4340-4346.
25. Woodman SE, Davies MA. Targeting KIT in melanoma: a paradigm of molecular medicine and targeted therapeutics. *Biochem Pharmacol*. 2010;80(5):568-574.
26. Van Raamsdonk CD, Griewank KG, Crosby MB, et al. Mutations in GNA11 in uveal melanoma. *N Engl J Med*. 2010;363(23):2191-2199.
27. Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017;67(6):472-492.
28. Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma of the skin. In: Amin MB, Edge S, Greene F, et al, eds. *AJCC Cancer Staging Manual* 8th ed. Springer International Publishing; 2017:563-585.
29. Kelderman S, Heemskerk B, van Tinteren H, et al. Lactate dehydrogenase as a selection criterion for ipilimumab treatment in metastatic melanoma. *Cancer Immunol Immunother*. 2014;63(5):449-458.
30. Long GV, Grob JJ, Nathan P, et al. Factors predictive of response, disease progression, and overall survival after dabrafenib and trametinib combination treatment: a pooled analysis of individual patient data from randomised trials. *Lancet Oncol*. 2016;17(12):1743-1754.
31. Long GV, Weber JS, Infante JR, et al. Overall survival and durable responses in patients with BRAF V600–mutant metastatic melanoma receiving dabrafenib combined with trametinib. *J Clin Oncol*. 2016;34(8):871-878.
32. Menzies AM, Wilmott JS, Drummond M, et al. Clinicopathologic features associated with efficacy and long-term survival in metastatic melanoma patients treated with BRAF or combined BRAF and MEK inhibitors. *Cancer*. 2015;121(21):3826-3835.
33. Thomas JM, Newton-Bishop J, A'Hern R, et al. Excision margins in high-risk malignant melanoma. *N Engl J Med*. 2004;350(8):757-766.
34. Gershenwald JE, Ross MI. Sentinel-lymph-node biopsy for cutaneous melanoma. *N Engl J Med*. 2011;364(18):1738-1745.
35. Wong SL, Balch CM, Hurley P, et al. Sentinel lymph node biopsy for melanoma: American Society of Clinical Oncology and Society of Surgical Oncology joint clinical practice guideline. *Ann Surg Oncol*. 2012;19(11):3313-3324.
36. Andtbacka RHI, Gershenwald JE. Role of sentinel lymph node biopsy in patients with thin melanoma. *J Natl Compr Canc Ne*. 2009;7(3):308-317.
37. Gershenwald JE, Coit DG, Sondak VK, Thompson JF. The challenge of defining guidelines for sentinel lymph node biopsy in patients with thin primary cutaneous melanomas. *Ann Surg Oncol*. 2012;19(11):3301-3303.
38. Morton DL, Wen D-R, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg*. 1992;127(4):392-399.
39. Gershenwald JE, Thompson W, Mansfield PF, et al. Multi-institutional melanoma lymphatic mapping experience: the prognostic value of sentinel lymph node status in 612 stage I or II melanoma patients. *J Clin Oncol*. 1999;17(3):976-983.
40. Morton DL, Thompson JF, Cochran AJ, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *N Engl J Med*. 2014;370(7):599-609.
41. Faries MB, Thompson JF, Cochran AJ, et al. Completion dissection or observation for sentinel-node metastasis in melanoma. *N Engl J Med*. 2017;376(23):2211-2222.
42. Gershenwald JE, Andtbacka RHI, Prieto VG, et al. Microscopic tumor burden in sentinel lymph nodes predicts synchronous nonsentinel lymph node involvement in patients with melanoma. *J Clin Oncol*. 2008;26(26):4296-4303.
43. Leiter U, Stadler R, Mauch C, et al. Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT):

a multicentre, randomised, phase 3 trial. *Lancet Oncol*. 2016;17(6):757-767.
44. National Comprehensive Cancer Network. Cutaneous melanoma. NCCN clinical practice guidelines in oncology (NCCN guidelines).https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf
45. Keung EZ, Ukponmwan EU, Cogdill AP, Wargo JA. The rationale and emerging use of neoadjuvant immune checkpoint blockade for solid malignancies. *Ann Surg Oncol*. 2018;25(7):1814-1827.
46. Ballo MT, Ang KK. Radiotherapy for cutaneous malignant melanoma: rationale and indications. *Oncology. (Williston Park)*. 2004;18(1):99-107; discussion 107-110, 113-114.
47. Egbert B, Kempson R, Sagebiel R. Desmoplastic malignant melanoma. A clinicohistopathologic study of 25 cases. *Cancer*. 1988;62(9):2033-2041.
48. Carlson JA, Dickersin GR, Sober AJ, Barnhill RL. Desmoplastic neurotropic melanoma. A clinicopathologic analysis of 28 cases. *Cancer*. 1995;75(2):478-494.
49. Quinn MJ, Crotty KA, Thompson JF, et al. Desmoplastic and desmoplastic neurotropic melanoma: experience with 280 patients. *Cancer*. 1998;83(6):1128-1135.
50. Smithers BM, McLeod GR, Little JH. Desmoplastic melanoma: patterns of recurrence. *World J Surg*. 1992;16(2):186-190.
51. Guadagnolo BA, Prieto V, Weber R, et al. The role of adjuvant radiotherapy in the local management of desmoplastic melanoma. *Cancer*. 2014;120(9):1361-1368.
52. Strom T, Caudell JJ, Han D, et al. Radiotherapy influences local control in patients with desmoplastic melanoma. *Cancer*. 2014;120(9):1369-1378.
53. Cascinelli N, Morabito A, Santinami M, et al. Immediate or delayed dissection of regional nodes in patients with melanoma of the trunk: a randomised trial. WHO Melanoma Programme. *Lancet*. 1998;351(9105):793-796.
54. Ng AK, Jones WO, Shaw JH. Analysis of local recurrence and optimizing excision margins for cutaneous melanoma. *Br J Surg*. 2001;88(1):137-142.
55. Karakousis CP, Balch CM, Urist MM, et al. Local recurrence in malignant melanoma: long-term results of the multiinstitutional randomized surgical trial. *Ann Surg Oncol*. 1996;3(5):446-452.
56. Urist MM, Balch CM, Soong S, et al. The influence of surgical margins and prognostic factors predicting the risk of local recurrence in 3445 patients with primary cutaneous melanoma. *Cancer*. 1985;55(6):1398-1402.
57. Kelly JW, Sagebiel RW, Calderon W, et al. The frequency of local recurrence and microsatellites as a guide to reexcision margins for cutaneous malignant melanoma. *Ann Surg*. 1984;200(6):759-763.
58. Leon P, Daly JM, Synnestvedt M, et al. The prognostic implications of microscopic satellites in patients with clinical stage I melanoma. *Arch Surg*. 1991;126(12):1461-1468.
59. Heaton KM, Sussman JJ, Gershenwald JE, et al. Surgical margins and prognostic factors in patients with thick (>4mm) primary melanoma. *Ann Surg Oncol*. 1998;5(4):322-328.
60. O'Brien CJ, Coates AS, Petersen-Schaefer K, et al. Experience with 998 cutaneous melanomas of the head and neck over 30 years. *Am J Surg*. 1991;162(4):310-314.
61. Byers RM. The role of modified neck dissection in the treatment of cutaneous melanoma of the head and neck. *Arch Surg*. 1986;121(11):1338-1341.
62. Balch CM, Soong SJ, Smith T, et al. Long-term results of a prospective surgical trial comparing 2 cm vs. 4 cm excision margins for 740 patients with 1-4 mm melanomas. *Ann of Surg Oncol*. 2001;8(2):101-108.
63. Calabro A, Singletary SE, Balch CM. Patterns of relapse in 1001 consecutive patients with melanoma nodal metastases. *Arch Surg*. 1989;124(9):1051-1055.
64. Guadagnolo BA, Zagars GK. Adjuvant radiation therapy for high-risk nodal metastases from cutaneous melanoma. *Lancet Oncol*. 2009;10(4):409-416.
65. Lee RJ, Gibbs JF, Proulx GM, et al. Nodal basin recurrence following lymph node dissection for melanoma: implications for adjuvant radiotherapy. *Int J Radiat Oncol Biol Phys*. 2000;46(2):467-474.
66. Shen P, Wanek LA, Morton DL. Is adjuvant radiotherapy necessary after positive lymph node dissection in head and neck melanomas? *Ann Surg Oncol*. 2000;7(8):554-559; discussion 560-561.
67. Burmeister BH, Henderson MA, Ainslie J, et al. Adjuvant radiotherapy versus observation alone for patients at risk of lymph-node field relapse after therapeutic lymphadenectomy for melanoma: a randomised trial. *Lancet Oncol*. 2012;13(6):589-597.
68. Henderson MA, Burmeister BH, Ainslie J, et al. Adjuvant lymph-node field radiotherapy versus observation only in patients with melanoma at high risk of further lymph-node field relapse after lymphadenectomy (ANZMTG 01.02/TROG 02.01): 6-year follow-up of a phase 3, randomised controlled trial. *Lancet Oncol*. 2015;16(9):1049-1060.
69. Kirkwood J, Strawderman M, Ernstoff M, et al. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group Trial EST 1684. *J Clin Oncol*. 1996;14(1):7-17.
70. Kirkwood JM, Manola J, Ibrahim J, et al. A pooled analysis of Eastern Cooperative Oncology Group and intergroup trials of adjuvant high-dose interferon for melanoma. *Clin Cancer Res*. 2004;10(5):1670-1677.
71. Eggermont AM, Suciu S, Santinami M, et al. Adjuvant therapy with pegylated interferon alfa-2b versus observation alone in resected stage III melanoma: final results of EORTC 18991, a randomised phase III trial. *Lancet*. 2008;372(9633):117-126.
72. Eggermont AM, Suciu S, Testori A, et al. Long-term results of the randomized phase III trial EORTC 18991 of adjuvant therapy with pegylated interferon alfa-2b versus observation in resected stage III melanoma. *J Clin Oncol*. 2012;30(31):3810-3818.
73. Wei SC, Duffy CR, Allison JP. Fundamental mechanisms of immune checkpoint blockade therapy. *Cancer Discov*. 2018;8(9):1069-1086.
74. Savoia P, Astrua C, Fava P. Ipilimumab (Anti-CTLA-4 Mab) in the treatment of metastatic melanoma: effectiveness and toxicity management. *Hum Vacc Immunother*. 2016;12(5):1092-1101.
75. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2015;16(5):522-530.
76. Tarhini AA, Lee SJ, Hodi FS, et al. Phase III study of adjuvant ipilimumab (3 or 10 mg/kg) versus high-dose interferon alfa-2b for resected high-risk melanoma: North American Intergroup E1609. *J Clin Oncol*. 2020;38(6):567-575.
77. Taube JM, Klein A, Brahmer JR, et al. Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti–PD-1 therapy. *Clin Cancer Res*. 2014;20(19):5064-5074.
78. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. *N Engl J Med*. 2017;377(19):1824-1835.
79. Eggermont AM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. *N Engl J Med*. 2018;378(19):1789-1801.
80. Long GV, Hauschild A, Santinami M, et al. Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. *N Engl J Med*. 2017;377(19):1813-1823.
81. Hauschild A, Dummer R, Schadendorf D, et al. Longer follow-up confirms relapse-free survival benefit with adjuvant dabrafenib plus trametinib in patients with resected BRAF V600-mutant Stage III melanoma. *J Clin Oncol*. 2018;36(35):3441-3449.
82. Hauschild A, Ascierto PA, Schadendorf D, et al. Long-term outcomes in patients with BRAF V600-mutant metastatic melanoma receiving dabrafenib monotherapy: analysis from phase 2 and 3 clinical trials. *Eur J Cancer*. 2020;125:114-120.
83. Lian B, Si L, Cui C, et al. Phase II randomized trial comparing high-dose IFN-alpha2b with temozolomide plus cisplatin

as systemic adjuvant therapy for resected mucosal melanoma. *Clin Cancer Res*. 2013;19(16):4488-4498.
84. Kingham TP, Panageas KS, Ariyan CE, et al. Outcome of patients with a positive sentinel lymph node who do not undergo completion lymphadenectomy. *Ann Surg Oncol*. 2010;17(2):514-520.
85. Rozeman EA, Menzies AM, van Akkooi ACJ, et al. Identification of the optimal combination dosing schedule of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma (OpACIN-neo): a multicentre, phase 2, randomised, controlled trial. *Lancet Oncol*. 2019;20(7):948-960.
86. Rozeman EA, Reijers ILM, Hoefsmit EP, et al. Twenty-four months RFS and updated toxicity data from OpACIN-neo: a study to identify the optimal dosing schedule of neoadjuvant ipilimumab (IPI) and nivolumab (NIVO) in stage III melanoma. *J Clin Oncol*. 2020;38(15 suppl):10015-10015.
87. Eggermont AM, Suciu S, MacKie R, et al. Post-surgery adjuvant therapy with intermediate doses of interferon alfa 2b versus observation in patients with stage IIb/III melanoma (EORTC 18952): randomised controlled trial. *Lancet*. 2005;366(9492):1189-1196.
88. Amaria RN, Prieto PA, Tetzlaff MT, et al. Neoadjuvant plus adjuvant dabrafenib and trametinib versus standard of care in patients with high-risk, surgically resectable melanoma: a single-centre, open-label, randomised, phase 2 trial. *Lancet Oncol*. 2018;19(2):181-193.
89. Long GV, Saw RPM, Lo S, et al. Neoadjuvant dabrafenib combined with trametinib for resectable, stage IIIB-C, BRAF(V600) mutation-positive melanoma (NeoCombi): a single-arm, open-label, single-centre, phase 2 trial. *Lancet Oncol*. 2019;20(7):961-971.
90. Atkins MB, Kunkel L, Sznol M, Rosenberg SA. High-dose recombinant interleukin-2 therapy in patients with metastatic melanoma: long-term survival update. *Cancer J Sci Am*. 2000;6(suppl 1):S11-S14.
91. Rosenberg SA, Yang JC, Sherry RM, et al. Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy. *Clin Cancer Res*. 2011;17(13):4550-4557.
92. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363(8):711-723.
93. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med*. 2011;364(26):2517-2526.
94. Schadendorf D, Hodi FS, Robert C, et al. Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma. *J Clin Oncol*. 2015;33(17):1889-1894.
95. Fecher LA, Agarwala SS, Hodi FS, Weber JS. Ipilimumab and its toxicities: a multidisciplinary approach. *Oncologist*. 2013;18(6):733-743.
96. Robert C, Ribas A, Wolchok JD, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. *Lancet*. 2014;384(9948):1109-1117.
97. Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. *Lancet Oncol*. 2015;16(8):908-918.
98. Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2015;16(4):375-384.
99. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 2012;366(26):2443-2454.
100. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med*. 2015;372(4):320-330.
101. Ascierto PA, Long GV, Robert C, et al. Survival outcomes in patients with previously untreated BRAF wild-type advanced melanoma treated with nivolumab therapy: three-year follow-up of a randomized phase 3 trial. *JAMA Oncol*. 2019;5(2):187-194.
102. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373(1):23-34.
103. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med*. 2017;377(14):1345-1356.
104. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med*. 2019;381(16):1535-1546.
105. Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma. *N Engl J Med*. 2015;372(21):2006-2017.
106. Flaherty KT, Lee SJ, Zhao F, et al. Phase III trial of carboplatin and paclitaxel with or without sorafenib in metastatic melanoma. *J Clinic Oncol*. 2013;31(3):373-379.
107. Davies MA, Fox PS, Papadopoulos NE, et al. Phase I study of the combination of sorafenib and temsirolimus in patients with metastatic melanoma. *Clin Cancer Res*. 2012;18(4):1120-1128.
108. Avril MF, Aamdal S, Grob JJ, et al. Fotemustine compared with dacarbazine in patients with disseminated malignant melanoma: a phase III study. *J Clinic Oncol*. 2004;22(6):1118-1125.
109. Goldberg SB, Gettinger SN, Mahajan A, et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. *Lancet Oncol*. 2016;17(7):976-983.
110. Goldberg SB, Schalper KA, Gettinger SN, et al. Pembrolizumab for management of patients with NSCLC and brain metastases: long-term results and biomarker analysis from a non-randomised, open-label, phase 2 trial. *Lancet Oncol*. 2020;21(5):655-663.
111. Long GV, Atkinson V, Lo S, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. *Lancet Oncol*. 2018;19(5):672-681.
112. Tawbi HA, Forsyth PA, Algazi A, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. *N Engl J Med*. 2018;379(8):722-730.
113. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med*. 2011;364(26):2507-2516.
114. McArthur GA, Chapman PB, Robert C, et al. Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. *Lancet Oncol*. 2014;15(3):323-332.
115. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet*. 2012;380(9839):358-365.
116. Hu-Lieskovan S, Mok S, Homet Moreno B, et al. Improved antitumor activity of immunotherapy with BRAF and MEK inhibitors in BRAF(V600E) melanoma. *Sci Transl Med*. 2015;7(279):279ra41.
117. Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. *N Engl J Med*. 2012;367(2):107-114.
118. Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med*. 2012;367(18):1694-1703.
119. Long GV, Flaherty KT, Stroyakovskiy D, et al. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study. *Ann Oncol*. 2017;28(7):1631-1639.
120. Grob JJ, Amonkar MM, Karaszewska B, et al. Comparison of dabrafenib and trametinib combination therapy with vemurafenib monotherapy on health-related quality of life in patients

with unresectable or metastatic cutaneous BRAF Val600-mutation-positive melanoma (COMBI-v): results of a phase 3, open-label, randomised trial. *Lancet Oncol*. 2015;16(13):1389-1398.
121. Robert C, Grob JJ, Stroyakovskiy D, et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. *N Engl J Med*. 2019;381(7):626-636.
122. Davies MA, Saiag P, Robert C, et al. Dabrafenib plus trametinib in patients with BRAFV600-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. *Lancet Oncol*. 2017;18(7):863-873.
123. Larkin J, Ascierto PA, Dréno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med*. 2014;371(20):1867-1876.
124. Dummer R, Ascierto PA, Gogas HJ, et al. Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2018;19(10):1315-1327.
125. Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2018;19(5):603-615.
126. Carvajal RD, Antonescu CR, Wolchok JD, et al. KIT as a therapeutic target in metastatic melanoma. *JAMA Netw Open*. 2011;305(22):2327-2334.
127. Hodi FS, Corless CL, Giobbie-Hurder A, et al. Imatinib for melanomas harboring mutationally activated or amplified KIT arising on mucosal, acral, and chronically sun-damaged skin. *J Clin Oncol*. 2013;31(26):3182-3190.
128. Guo J, Si L, Kong Y, et al. Phase II, open-label, single-arm trial of imatinib mesylate in patients with metastatic melanoma harboring c-Kit mutation or amplification. *J Clin Oncol*. 2011;29(21):2904-2909.
129. Bayan C-AY, Lopez AT, Gartrell RD, et al. The role of oncolytic viruses in the treatment of melanoma. *Curr Oncol Rep*. 2018;20(10):80.
130. Conry RM, Westbrook B, McKee S, Norwood TG. Talimogene laherparepvec: first in class oncolytic virotherapy. *Hum Vaccin Immunother*. 2018;14(4):839-846.
131. Perez MC, Miura JT, Naqvi SMH, et al. Talimogene laherparepvec (TVEC) for the treatment of advanced melanoma: a single-institution experience. *Ann Surg Oncol*. 2018;25(13):3960-3965.
132. Andtbacka RHI, Collichio F, Harrington KJ, et al. Final analyses of OPTiM: a randomized phase III trial of talimogene laherparepvec versus granulocyte-macrophage colony-stimulating factor in unresectable stage III–IV melanoma. *J Immunother Cancer*. 2019;7(1):145.
133. Chesney J, Puzanov I, Collichio F, et al. Randomized, open-label phase II study evaluating the efficacy and safety of talimogene laherparepvec in combination with ipilimumab versus ipilimumab alone in patients with advanced, unresectable melanoma. *J Clin Oncol*. 2018;36(17):1658-1667.
134. Ribas A, Dummer R, Puzanov I, et al. Oncolytic virotherapy promotes intratumoral T cell infiltration and improves anti-PD-1 immunotherapy. *Cell*. 2017;170(6):1109-1119. e10.
135. Serrone L, Zeuli M, Sega FM, Cognetti F. Dacarbazine-based chemotherapy for metastatic melanoma: thirty-year experience overview. *J Exp Clin Cancer Res*. 2000;19(1):21-34.
136. Middleton MR, Grob JJ, Aaronson N, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J Clin Oncol*. 2000;18(1):158-166.
137. Garbe C, Eigentler TK, Keilholz U, et al. Systematic review of medical treatment in melanoma: current status and future prospects. *Oncologist*. 2011;16(1):5-24.
138. McLaughlin CC, Wu XC, Jemal A, et al. Incidence of noncutaneous melanomas in the U.S. *Cancer*. 2005;103(5):1000-1007.
139. Kuk D, Shoushtari AN, Barker CA, et al. Prognosis of mucosal, uveal, acral, nonacral cutaneous, and unknown primary melanoma from the time of first metastasis. *Oncologist*. 2016;21(7):848-854.
140. Klemen ND, Wang M, Rubinstein JC, et al. Survival after checkpoint inhibitors for metastatic acral, mucosal and uveal melanoma. *J Immunother Cancer*. 2020;8(1):e000341.
141. Shoushtari AN, Munhoz RR, Kuk D, et al. The efficacy of anti-PD-1 agents in acral and mucosal melanoma. *Cancer*. 2016;122(21):3354-3362.
142. Mignard C, Deschamps AH, Gillibert A, et al. Efficacy of immunotherapy in patients with metastatic mucosal or uveal melanoma. *J Oncol*. 2018;2018:1908065.
143. Postow MA, Luke JJ, Bluth MJ, et al. Ipilimumab for patients with advanced mucosal melanoma. *Oncologist*. 2013;18(6):726-732.
144. Maldonado JL, Fridlyand J, Patel H, et al. Determinants of BRAF mutations in primary melanomas. *J Natl Cancer Inst*. 2003;95(24):1878-1890.
145. Beadling C, Jacobson-Dunlop E, Hodi FS, et al. KIT gene mutations and copy number in melanoma subtypes. *Clin Cancer Res*. 2008;14(21):6821-6828.
146. Zhou R, Shi C, Tao W, et al. Analysis of mucosal melanoma whole-genome landscapes reveals clinically relevant genomic aberrations. *Clin Cancer Res*. 2019;25(12):3548-3560.
147. Kalinsky K, Lee S, Rubin KM, et al. A phase 2 trial of dasatinib in patients with locally advanced or stage IV mucosal, acral, or vulvovaginal melanoma: a trial of the ECOG-ACRIN Cancer Research Group (E2607). *Cancer*. 2017;123(14):2688-2697.
148. Spencer KR, Mehnert JM. Mucosal melanoma: epidemiology, biology and treatment. *Cancer Treat Res*. 2016;167:295-320.
149. Chattopadhyay C, Kim DW, Gombos DS, et al. Uveal melanoma: from diagnosis to treatment and the science in between. *Cancer*. 2016;122(15):2299-2312.
150. Singh AD, Turell ME, Topham AK. Uveal melanoma: trends in incidence, treatment, and survival. *Ophthalmology*. 2011;118(9):1881-1885.
151. Shoushtari AN, Carvajal RD. GNAQ and GNA11 mutations in uveal melanoma. *Melanoma Res*. 2014;24(6):525-534.
152. Wessely A, Steeb T, Erdmann M, et al. The role of immune checkpoint blockade in uveal melanoma. *Int J Mol Sci*. 2020;21(3):879.
153. Assessment of metastatic disease status at death in 435 patients with large choroidal melanoma in the Collaborative Ocular Melanoma Study (COMS): COMS report no. 15. *Arch Ophthalmol*. 2001;119(5):670-676.
154. Algazi AP, Tsai KK, Shoushtari AN, et al. Clinical outcomes in metastatic uveal melanoma treated with PD-1 and PD-L1 antibodies. *Cancer*. 2016;122(21):3344-3353.
155. Shoushtari AN, Navid-Azarbaijani P, Friedman CF, et al. Efficacy of nivolumab and ipilimumab (Nivo plus Ipi) combination in melanoma patients (pts) treated at a single institution on an expanded-access program (EAP). *J Clin Oncol*. 2016;34:15(suppl):9554-9554.
156. Rodriguez JP, Merino LD, Espinosa E, et al. Phase II multicenter, single arm, open label study of nivolumab in combination with ipilimumab in untreated patients with metastatic uveal melanoma (GEM1402.NCT02626962). *Ann Oncol*. 2018;29:viii443. 49–49–49–49–49–49–49–49–49–

Section XII

Sarcomas

Section Editor: Shreyaskumar Patel

50 Soft Tissue and Bone Sarcomas

This page intentionally left blank

50 Soft Tissue and Bone Sarcomas

J. Andrew Livingston
Anthony P. Conley
Ravin Ratan
Vinod Ravi
Shreyaskumar Patel

KEY CONCEPTS

- Sarcomas represent a heterogenous group of more than 70 tumor types, many with unique disease biology, natural history, and chemotherapeutic sensitivity, driving a growing awareness and interest in subtype-specific therapy.
- Tumor histology, size, location, and the presence or absence of metastasis at diagnosis are the most important and well-established prognostic factors for patients with soft tissue sarcoma (STS).
- Although the role of adjuvant chemotherapy remains controversial, adjuvant chemotherapy containing anthracyclines in combination with ifosfamide is associated with improved disease-free and overall survival among patients with high-risk STS.
- The majority of gastrointestinal stromal tumors harbor activating mutations in either *KIT* or *PDGFRA*, conferring sensitivity to imatinib as well as other tyrosine kinase inhibitors. Mutational testing is recommended for both prognosis and to guide treatment selection.
- Patients with osteosarcoma and other high-grade bone sarcomas often present with micrometastatic disease at the time of diagnosis. Contemporary treatment consists of neoadjuvant chemotherapy followed by limb-sparing surgery and additional adjuvant chemotherapy.
- The lung is the most common site of relapse and metastasis for patients with sarcomas after completion of primary treatment. Surgery with or without additional chemotherapy should be pursued in patients with resectable lung metastases and can result in cure in a subset of patients who can be rendered disease free.

INCIDENCE

Sarcomas are a rare and heterogeneous group of tumors that arise from mesenchymal tissues. According to the estimates of the American Cancer Society, approximately 1.8 million people were projected to be diagnosed with cancer in the United States in the year 2020; an estimated 16,730 new sarcoma cases accounts for just less than 1% of new cancer cases and approximately 1% of cancer-related deaths in the United States annually.[1] Approximately 80% (13,130) of new sarcoma cases arise in soft tissue, and the remaining 20% (3600) are of bone origin.

EPIDEMIOLOGY AND PATHOGENESIS

The etiology and pathogenesis of most sarcomas are not well understood. Multiple environmental factors, including radiation and chemical exposures, trauma, and infection, have been associated with the development of soft tissue and bone sarcomas. Both sporadic and inherited molecular and genetic aberrations have been identified in specific subsets of sarcoma and have been implicated in sarcomagenesis.

Several inherited familial cancer syndromes have been associated with a predisposition to development of soft tissue and bone sarcomas. The Li-Fraumeni syndrome resulting from a germline mutation of the *TP53* tumor suppressor gene is associated with increased risk of soft tissue sarcomas (STS) and osteosarcoma among several other cancers in children and young adults.[2] Hereditary retinoblastoma is also associated with the development of sarcomas, both osteosarcoma and STS.[3] Neurofibromatosis type 1 (NF1) is associated with an increased risk of development of sarcoma in a preexisting neurofibroma, resulting in a malignant peripheral nerve sheath tumor.[4] Sarcomas have been associated

with other rare cancer predisposition syndromes, including Werner syndrome, familial adenomatous polyposis, and Gardner syndrome, among others. A more recent genetic study of multiple sarcoma cohorts identified pathogenic germline variants in about half of sarcoma patients, including alterations in *TP53, ATM, ATR,* and *BRCA* as well as other novel cancer genes, revealing the hereditary nature of most cases.[5]

Recurrent cytogenetic abnormalities have been identified in many sarcomas and are thought to contribute to sarcomagenesis. Genetic profiling of bone and STS has expanded the characterization of mesenchymal tumors beyond translocation-positive and translocation-negative categorizations to identify three distinct groups: (1) genetically unstable sarcomas with complex karyotypes; (2) tumors with specific, recurrent genetic alterations such as translocations, deletions, or copy number variations; and (3) tumors with molecular aberrations such as amplifications, mutations, or loss of heterozygosity (Table 50–1). These alterations serve an important role in diagnosis and prognosis and have potential implications for therapy.

TABLE 50–1 Selected Genetic Alterations in Soft Tissue Sarcomas

Tumor	Cytogenetic Abnormality	Gene Product
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14) t(1;13)(p36;q14) t(X;2)(q13;q35)	*PAX3-FOXO1A* *PAX7-FOXO1A* *PAX3-AFX*
Alveolar soft parts sarcoma	t(X;17)(p11.2;q25)	*ASPL-TFE3*
Clear cell sarcoma	t(12;22)(q13;q12) t(2;22)(q32;q12)	*EWSR1-ATF1* *EWSR1-CREB1*
Congenital fibrosarcoma	t(12;15)(p13;q25)	*ETV6-NTRK3*
Dermatofibrosarcoma protuberans	t(17;22)(q22;q13)	*COL1A1-PDGFB*
Desmoplastic small round cell tumor Epithelioid hemangioendothelioma	t(11;22)(p13;q12) t(1;3)(p36;q25)	*EWSR1-WT1* *WWTR1-CAMTA1*
Endometrial stromal sarcoma	t(7;17)(p15;q11)	*JAZF1-SUZ12*
Gastrointestinal stromal tumor	Activating mutations Overexpression Loss of 14q LOH of 22q Loss of 1p	*KIT, PDGFR, BRAF* *ETV1*
Inflammatory myofibroblastic tumor	t(1;2)(q22-23;p23) t(2;19)(p23;p13.1)	*TPM3-ALK* *TPM4-ALK*
Low-grade fibromyxoid sarcoma	t(7;16)(q32–34;p11) t(11;16)(p11;p11)	*FUS-CREB3L2* *FUS-CREB3L1*
Lipoma	t(3;12)(q27-28, q14-15)	*HMGA2-LPP*
Malignant peripheral nerve sheath tumor	Inactivating	Deletion of *NF1*
Myxoid chondrosarcoma	t(9;22)(q22-31;q11-12) t(9;17)(q22;q11) t(9;15)(q22;q21)	*EWSR1-NR4A3* *TAF15-NR4A3* *TCF12-NR4A3*
Myxoid liposarcoma	t(12;16)(q13;p11) t(12;22)(q13;q12)	*FUS-DDIT3* *EWSR1-DDIT3* *PIK3CA* mutation
Solitary fibrous tumor or hemangiopericytoma		*IGF1R dysregulation*
Synovial sarcoma	t(X;18)(p11;q11)	*SS18-SSX1* *SS18-SSX2* *SS18-SSX4*
Tenosynovial giant cell tumor or pigmented villonodular synovitis		*COL6A3-CSF1*
Well-differentiated liposarcoma and dedifferentiated liposarcoma	12q14-15 (supernumerary ring chromosomes; giant marker chromosomes)	Amplification of *MDM2, CDK4, HMGA2, SAS, GLI*, and *JUN*
Uterine leiomyosarcoma	t(12;14)(q7-)	

LOH, loss of heterozygosity.

Molecular testing has become more widely used for diagnosis in STS, identifying specific abnormalities in certain histologic subtypes.[6] For example the t(x;18) translocation is a specific marker for synovial sarcomas. The transcript formed from this translocation (*SYT-SSX*) can be detected using polymerase chain reaction testing. In one study, the *SYT-SSX* transcript was positive in 84.5% of tumors in which the diagnosis of synovial sarcoma was certain based on histology and 24.3% of tumors in which synovial sarcoma was considered but not first in the differential diagnosis.[7] Other examples include the *FUS-DDIT3* translocation in myxoid liposarcoma or presence of *MDM2* amplification in dedifferentiated liposarcoma.

Specific translocations have also been investigated as prognostic biomarkers and potential therapeutic targets. Perhaps the best known is the *EWS-FLI1* transcript in Ewing sarcoma was previously identified as an independent prognostic factor,[8] but more recent studies have not found an association, potentially because of improved therapeutic regimens.[9] Alternatively, in alveolar rhabdomyosarcoma, translocation-negative tumors have better outcomes than translocation-positive tumors despite histologic appearance.[10] More recently, a subset of sarcomas harboring *NTRK* fusions have been identified in which the presence of an oncogenic *NTRK* fusion is a predictive biomarker that confers sensitivity to *NTRK* inhibitors.[11]

SOFT TISSUE SARCOMA

Soft tissues include fibrous, adipose, and vascular structures as well as muscles and tendons and are mesenchymal in origin. STS are a heterogeneous group encompassing approximately 70 different histologic subtypes based on their resemblance to normal tissues rather than the tissue of origin.

Clinical Presentation

STS can occur in any anatomic region. The majority of STS arise from the extremities (60%) followed by the trunk (30%) and the head and neck region (10%). The most common presenting symptom is a soft tissue mass or swelling. Pain is reported by only about one third of patients at presentation. Patients with a soft tissue mass that is increasing in size, a mass larger than5 cm, or a mass that is deep to deep fascia, regardless of pain, should be referred for evaluation of a suspected STS.

Evaluation

Evaluation of a suspected STS begins with a comprehensive history and physical examination. Imaging evaluation is dependent on the site of disease. For soft tissue tumors of the extremities, head and neck, and pelvis, magnetic resonance imaging (MRI) is preferred. STS found in the retroperitoneum and abdomen are generally best evaluated by contrasted computed tomography (CT). Positron emission tomography (PET) imaging can distinguish histologic grade to a degree based on tumor standardized uptake values (SUVs).[12] For both STS and bone sarcomas, PET imaging is also useful for early response assessment where it has been shown to predict survival after initial cycle of therapy among patients receiving neoadjuvant chemotherapy for high-grade STS.[13]

A biopsy is essential to diagnosis, and the method of biopsy chosen should be the least invasive technique available to make a definitive diagnosis. A core-needle biopsy is sufficient; however, multiple cores should be obtained to improve diagnostic yield. If an open biopsy is performed, it should be planned such that the biopsy tract can be removed at the time of definitive surgical resection to reduce the risk of seeding and recurrence. An excisional biopsy may be used for small or superficial lesions; however, careful examination of margins and planning of the orientation of the resection should always be performed. Fine-needle aspiration is not recommended but can be useful in confirming recurrence, assuming that an experienced sarcoma cytopathologist is available.[14]

Pathology

Sarcomas are classified primarily according to their tissue appearance and histologic grade and sometimes the cell of origin. This can be difficult because approximately 70 different histologic types of STS are recognized. Histologic diagnosis is classified by the updated 2020 World Health Organization criteria.[15]

Pathologists often separate sarcomas into three histologic grades using the Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system, which is determined by differentiation, mitotic activity, and necrosis. Natural history and prognosis can be predicted based on histologic grade, and this spectrum varies among the histologic subtypes of sarcoma.[16] Immunohistochemistry, cytogenetics, and molecular pathology can aid in making a diagnosis.

Staging and Prognosis

The American Joint Committee on Cancer (AJCC) staging system may be used for STS and includes tumor, node, metastasis stage as well as histologic grade (G) (https://www.cancer.org/cancer/soft-tissue-sarcoma/detection-diagnosis-staging/staging.html).[17] The updated eighth edition has established separate T stage and prognostic groups for STS arising in the

extremity and trunk or retroperitoneum. In addition, sarcomas of the head and neck or viscera have separate specific T staging. The staging of gastrointestinal stromal tumors (GISTs) is considered separately.

Several clinicopathologic factors are important for treatment planning and prognosis assessment including tumor grade, size of the primary tumor, depth of invasion, and extent of disease. High-risk features for local recurrence or distant metastases are high-grade lesions, primary tumor larger than 5 cm, and deep tumor location. Approximately 50% of patients with intermediate- and high-grade STS will develop metastatic disease requiring systemic therapy.[18] The 5-year overall survival (OS) for STS is around 50%, with local control and distant disease being the key determinants.

Because of limitations with the AJCC staging system, multiple nomograms and prognostic tools have been developed to aid clinicians in risk stratification for both extremity and retroperitoneal sarcomas. The Sarculator is one such publicly available app-based nomogram derived from an international cohort of patients with sarcoma treated in major sarcoma centers that allows for prediction of OS and distant metastasis in patients after surgical resection of STS of the extremity.[19] It also includes a second nomogram for patients with primary retroperitoneal sarcomas to predict histology-specific disease-free survival (DFS) and OS.[20]

Treatment

Treatment of patients with sarcoma requires a multidisciplinary approach with experienced medical, surgical, and radiation oncologists, pathologists, and radiologists. An improved understanding of STS subtypes in regard to natural history, response to chemotherapy, and potential for targeted therapies has led to more subtype-specific treatment according to individual histology.

Treatment of Local Disease

Surgery

For local disease, surgical resection is the mainstay of treatment. Sarcomas tend to expand and compress tissue planes, which produce a pseudo-capsule comprising normal tissue interlaced with tumor tissue. Wide local excision is preferred with the ideal surgical margins being 2 to 3 cm. If positive margins are confirmed by pathology, re-excision to obtain negative margins is important when feasible to improve local control and relapse-free survival. For patients with borderline resectable tumors, consideration should be given to neoadjuvant therapy depending on the tumor histology, patient's performance status, and comorbidities.

Importantly, sarcomas have a less than 4% prevalence of lymph node metastases.[21] For this reason, routine regional lymph node dissection is often not required. However, patients with synovial sarcoma, clear cell sarcoma, rhabdomyosarcoma, angiosarcoma, and epithelioid sarcomas have a higher incidence of lymph node metastases and should be evaluated closely for lymphadenopathy.

Improved surgical techniques and multimodality treatment have resulted in a decrease in radical resection of extremity tumors with a corresponding rise in limb-sparing procedures combining wide local resection with preoperative or postoperative chemotherapy, radiotherapy, or both. The vast majority of patients with localized sarcomas of the extremities can safely undergo limb-sparing procedures to preserve limb function and adequately maintain local control without compromising OS.[22]

Radiation

Although radiation is not effective for the treatment of gross disease, it has been a useful adjunct to surgery in the treatment of microscopic local disease and for palliation of symptoms. Radiation therapy is commonly used in the preoperative or postoperative adjuvant setting. Because there are pros and cons as to the timing of radiation therapy, this topic remains controversial; appropriate discussion between radiation oncologists, medical oncologists, and surgeons is required in planning the treatment of each patient.

Preoperative radiation has several advantages over postoperative radiation, including smaller radiation portals, conversion to a limb-sparing procedure, reduction of the extent of the surgical procedure, and lower radiation doses, which can be used because there are theoretically fewer radio-resistant hypoxic cells within the tumor, and surgical removal can supplement the boost.[23] Preoperative radiation can improve local control, especially with larger tumors that were initially considered unresectable. However, preoperative radiotherapy may lead to difficulty in assessing pathologic responses to preoperative chemotherapy and may also contribute to delayed wound healing. The modality of choice is external-beam radiotherapy (EBRT), and a dose of 50 Gy or more is often required to obtain local control. At these dose levels, the entire circumference of the extremity must not be irradiated to avoid lymphedema. A period of 4 to 6 weeks is needed after preoperative radiation to prevent wound complications. After the surgical resection, close or positive margins could be treated with a radiation boost if feasible. Brachytherapy, EBRT, or intraoperative radiotherapy can be used by experienced clinicians in appropriate situations.

Intensity-modulated proton therapy (IMPT) has become a tool with anatomic specific indications in

patients with sarcoma. Specifically, this modality is frequently used to treat chordomas and chondrosarcomas of the skull base, where a complete resection may not be possible or associated with significant morbidity. In one large study involving 222 patients with chordomas and chondrosarcomas, a mean dose of 72.5 with or without 2.2 Gy relative biologic effectiveness (RBE) was associated with 7-year local control rates of 70.9% and 96.6%, respectively.[24] Pediatric patients with rhabdomyosarcoma may receive IMPT to the parameningeal space or orbital region to effectively target the tumor while reducing morbidity to surrounding structures. In 1 of 83 children with rhabdomyosarcoma (RMS) treated with proton therapy, a median dose of 54 Gy (RBE) was associated with a 5-year local control rate of 78.5% and a 5-year OS of 80.6%.[25]

Postoperative radiation therapy should be considered in patients with high-grade STS of the extremities with positive microscopic margins (<1 mm from the inked margin). In this setting, adjuvant radiation improved the 5-year local control rate compared with the no RT group (74% vs 56%; P =.01).[26] Adjuvant IMRT has been shown to reduce local recurrence as compared with conventional EBRT for primary STS of the extremity (hazard ratio [HR], 0.46; P =.02).[27] The interval of time between surgery and initiation of radiation therapy is a controversial but legitimate concern. The most recent STS guidelines issued by the National Comprehensive Cancer Network (NCCN) suggest the interval should be no greater than 6 weeks.[28]

Radiation therapy is occasionally used as the sole treatment modality for palliation for some patients with STS. These patients are often those who have unresectable disease or who are not appropriate candidates for surgery or chemotherapy. There have been reports of 5-year survival rates ranging from 25% to 40% with radiation therapy alone and of local control rates of approximately 30%, depending on the primary tumor's size and biology.[29] For patients with oligometastatic disease involving the lungs, liver, or musculoskeletal sites, stereotactic body radiation therapy (SBRT) offers a means to exert control with minimal rates of late toxicities. At times it may be used to treat a single chemotherapy-resistant lesion while all other sites of disease may be responding to chemotherapy. Typical doses range from 30 to 60 Gy in 1 to 8 fractions for lesions with a median size of 2 to 12 cm^3.[30] Local control rates at 2 years for selected sites range from 86% to 98%. In addition, an analysis of several multicenter phase I/II trials involving SBRT with long-term follow-up demonstrated grade 3 or greater toxicities at 2 years of 2% and no grade 3 or greater toxicities at 3 years.[31] These toxicities were limited to neurologic adverse events such as radiculopathy.

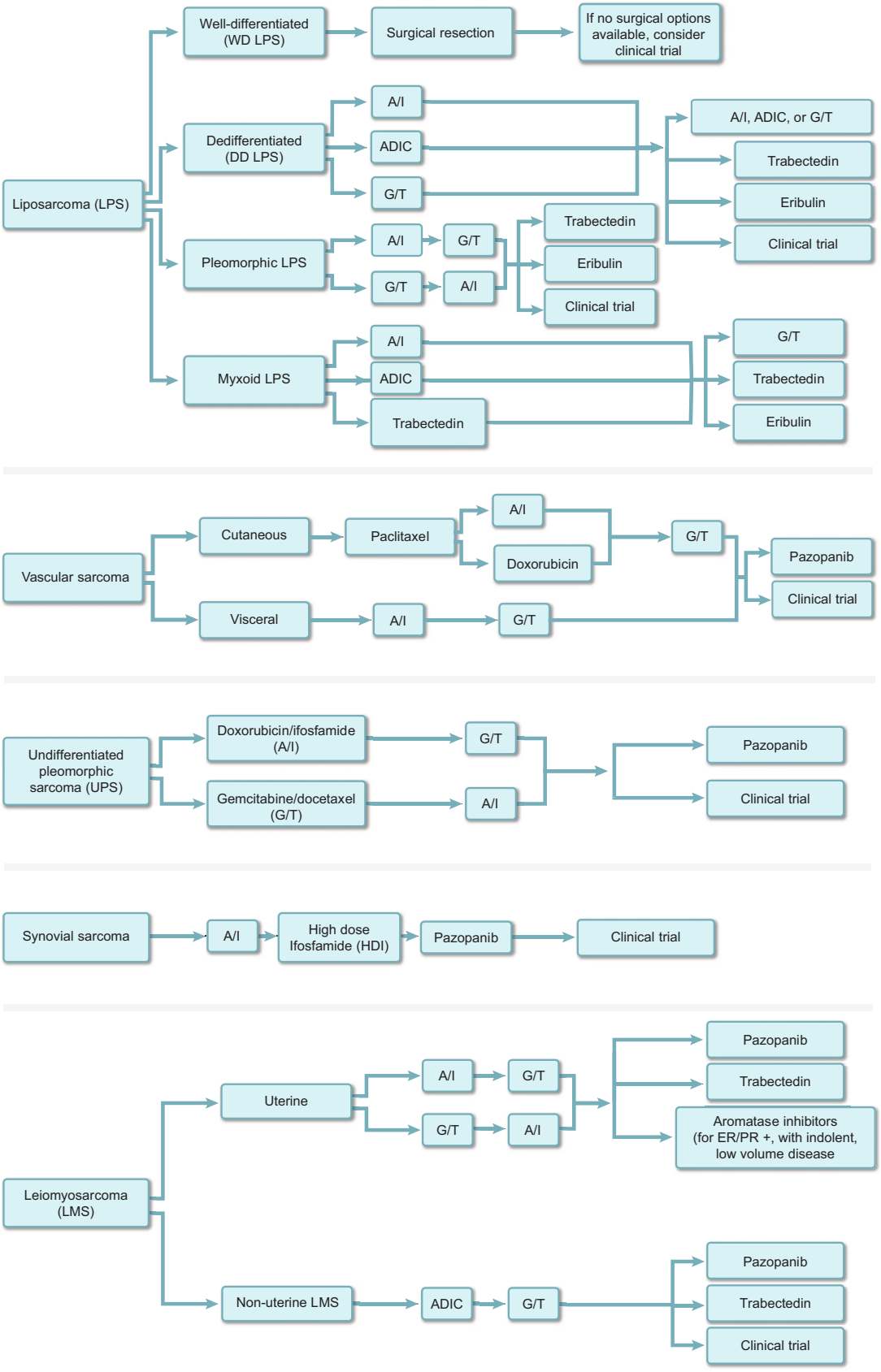
Chemotherapy

Systemic therapy is primarily used in the metastatic or advanced disease setting as well as neoadjuvant or adjuvant therapy for selected patients with high-risk STS. Treatment relies primarily on conventional chemotherapy agents, which are largely unchanged over the past three decades. In general, tumors with a higher grade are more likely to respond to chemotherapy; however, chemosensitivity varies based on histologic subtype (Table 50–2). An understanding of chemosensitivity and molecular aberrations based on sarcoma subtype has led to histology-driven treatment algorithms for specific STS such as leiomyosarcoma (LMS), myxoid liposarcoma, and angiosarcomas (Fig. 50–1). This approach is particularly important in considering targeted therapies for specific subtypes that are considered chemoresistant such as alveolar soft parts sarcoma (ASPS).

The two most active agents in the treatment of STS are doxorubicin and ifosfamide, both of which exhibit a dose-dependent response curve. Doxorubicin is most active at doses of 75 mg/m^2 or greater with single-agent response rates of approximately 20% to 35%.[32] Ifosfamide has been shown to

TABLE 50–2 Relative Chemosensitivity of Soft Tissue Sarcomas

Relative Chemosensitivity	Example
Highly sensitive (chemotherapy standard of care in management)	Ewing sarcoma family of tumors Embryonal and alveolar rhabdomyosarcoma Desmoplastic small round cell tumor (DSRCT)
Sensitive to chemotherapy	Synovial sarcoma Small cell sarcoma Myxoid or round cell liposarcoma Uterine leiomyosarcoma
Moderate sensitivity to chemotherapy	Undifferentiated pleomorphic sarcoma Pleomorphic liposarcoma Myxofibrosarcoma Pleomorphic rhabdomyosarcoma Leiomyosarcoma Malignant peripheral nerve sheath tumor Angiosarcoma
Insensitive to chemotherapy	Dedifferentiated liposarcoma Clear cell sarcoma Endometrial stromal sarcoma Epithelioid sarcoma
Chemoresistant (chemotherapy risk clearly outweighs benefit)	Gastrointestinal stromal tumor Alveolar soft parts sarcoma Extraskeletal myxoid chondrosarcoma Well-differentiated liposarcoma



Visual Art: © 2015 The University of Texas MD Anderson Cancer Center

FIGURE 50–1 Approach to systemic therapies for advanced soft tissue sarcomas. ADIC, doxorubicin and dacarbazine; A/I, doxorubicin and ifosfamide; ER, estrogen receptor; G/T gemcitabine and docetaxel; PR, progesterone receptor.

produce single-agent response rates similar to those of single-agent doxorubicin when used at doses of 10 g/m^2 or higher.[33] The response rate in patients with STS whose disease failed doxorubicin-based therapy and who then received high-dose ifosfamide as a single agent was 29%. Therefore, high-dose ifosfamide as a single agent at doses of 14 g/m^2 is sometimes used as a salvage regimen at the University of Texas MD Anderson Cancer Center (MDACC) for selected histologies.

Combination therapy with dose-intense doxorubicin and ifosfamide has been shown to improve response rates, progression-free survival (PFS), and possibly OS. The combination of doxorubicin (75 or 90 mg/m^2) and ifosfamide (at 10 g/m^2) was evaluated at MDACC in patients with STS and demonstrated a 75% response rate (95% confidence interval [CI], 59%–71%; complete response [CR], 12%) in patients with primary tumors of the extremities and a 68% response rate (95% CI, 56%–80%; CR, 12%) in patients with primary disease at any site.[34] The response rates according to histology were as follows: malignant fibrous histiocytoma, 69%; synovial sarcoma, 88%; unclassified sarcomas, 60%; nongastrointestinal LMS, 50%; liposarcomas, 56%; angiosarcomas, 83%; and neurogenic sarcomas, 40%; other miscellaneous histologies demonstrated objective response rates of 45%. In the large, randomized phase III European Organization for Research and Treatment of Cancer (EORTC) 62012 trial comparing single-agent doxorubicin with doxorubicin in combination with ifosfamide, the combination group had a significantly higher response rate (26% vs 14%) and increased median PFS (7.4 months vs 4.6 months) but also had an increase it grade 3 and 4 toxicities. Although OS at 1 year was increased in the combination group (60% vs 51%; P =.076), this failed to meet statistical significance.[35] These findings have led some sarcoma centers to favor single-agent doxorubicin over combination based on decreased toxicity and lack of statistically significant improvement in OS. At our center, we continue to use combination dose-intense doxorubicin and ifosfamide in appropriately selected patients with metastatic disease and preferentially in the neoadjuvant or adjuvant setting for high-risk (ie, large [≥5 cm], high-grade) resectable STS where regimens that combine anthracycline and ifosfamide remain the standard.

Dacarbazine has activity as a single agent, with response rates of 10% to 15%. The three-drug regimen MAID (mesna, doxorubicin [Adriamycin], ifosfamide, and dacarbazine) has been studied and has shown response rates varying from 25% to 47%.[36] When the MAID regimen was studied at MDACC, significant toxicities related to the addition of dacarbazine were seen.[37] The combination of doxorubicin and dacarbazine (ADIC) is often used in extrauterine LMS or as a second-line regimen in other STS. Response rates for the combination vary up to 30% depending on the histology. In a recent large retrospective study of patients with advanced LMS, ADIC was shown to have favorable activity in comparison with either single-agent doxorubicin or doxorubicin and ifosfamide combination, further supporting its use in this setting.[38]

Gemcitabine alone or in combination with docetaxel is frequently used for the treatment of patients with advanced, recurrent, or metastatic disease after patients fail doxorubicin- and ifosfamide-based therapy or in patients who may not tolerate intensive chemotherapy. An initial phase II study using gemcitabine as a single agent demonstrated a response rate of 18% (95% CI, 7%–29%), including many pretreated patients.[39] The synergistic effect of docetaxel when added to gemcitabine was evaluated in a randomized phase II study, SARC002.[40] By RECIST (Response Evaluation Criteria in Solid Tumours), response rates for the gemcitabine–docetaxel arm and gemcitabine arm were 16% and 8%, respectively. Furthermore, an improvement in median PFS (6.2 months vs 3.0 months) and OS (17.9 months vs 11.5 months) was noted in the gemcitabine–docetaxel arm compared with the gemcitabine arm. The two histologies most responsive to the gemcitabine–docetaxel arm were LMS and high-grade undifferentiated pleomorphic sarcoma (UPS).

Trabectedin, an alkylating agent specifically affecting the minor groove of DNA, has shown activity in the second-line treatment of patients with STS. The mechanism of action of trabectedin is complex but is thought to involve displacement of transcription factors from their promoter.[41] The efficacy and optimal dose schedule of trabectedin in sarcoma were established in a phase II study comparing 1.5 mg/m^2 as a 24-hour infusion every 3 weeks or trabectedin 0.58 mg/m^2 as a weekly 3-hour infusion in which the 24-hour infusion was shown to have greater efficacy among patients with liposarcoma or LMS who had previously received anthracyclines and ifosfamide.[42] A subsequent phase 3 trial of trabectedin versus dacarbazine in this patient population demonstrated an improvement in median PFS (4.2 vs 1.5 months) and a clinical benefit rate of 34%, leading to its U.S. Food and Drug Administration (FDA) approval for the treatment of patients with unresectable or metastatic liposarcoma and leiomyosarcoma (L-type sarcomas) who have received a prior anthracycline-based regimen.[43]

Eribulin is a synthetic analog of halichondrin B that interferes with microtubule assembly.[44] In a randomized, multicenter, phase III clinical trial of 452 patients comparing eribulin with dacarbazine for L-type (liposarcomas and leiomyosarcomas) patients with sarcoma with advanced or metastatic disease refractory to anthracycline-based therapy, eribulin was associated with an OS of 13.5 months, but the dacarbazine arm was associated with an OS of 11.5 months.[45]

Interestingly, there was no statistical difference with regard to PFS. An unplanned subgroup analysis by histology revealed a survival benefit for patients with liposarcomas only.[46] This led to an FDA approval specifically for the treatment of liposarcoma patients with advanced or metastatic disease refractory to anthracycline-based therapies. As such, we typically use eribulin as an option for patients with dedifferentiated liposarcoma or pleomorphic liposarcoma who have become resistant or intolerant to doxorubicin-based frontline chemotherapy.

Adjuvant and Neoadjuvant Chemotherapy

The goals of chemotherapy in the treatment of patients with high-risk local disease are to eradicate micrometastasis, decrease risk of local recurrence, and downsize tumors to facilitate either limb-sparing procedures for extremity tumors or resection for tumors initially deemed unresectable (Fig. 50–2). At MDACC, preoperative chemotherapy is preferred in patients with high-risk (>5 cm and high-grade) tumors and in patients who are considered borderline resectable with chemosensitive STS subtypes.

Postoperative chemotherapy and its benefits continue to be controverted because trials of adjuvant therapy have yielded conflicting results. Data from several small studies were pooled and analyzed in an initial meta-analysis published by the Sarcoma Meta-Analysis Collaboration showing improvements in local recurrence, distant recurrence, and recurrence-free survival with adjuvant chemotherapy.[47] This analysis was updated in 2008 to include trials that evaluated anthracycline- and ifosfamide-containing regimens.[48] In the updated analysis, the risk of local recurrence was significantly decreased for all patients receiving chemotherapy, risk of distant recurrence was also decreased for patients receiving doxorubicin-based chemotherapy, and patients receiving doxorubicin- and ifosfamide-containing chemotherapy demonstrated the greatest survival benefit with an improved hazard ratio of 0.56. The absolute risk reduction for death was 11% in the doxorubicin and

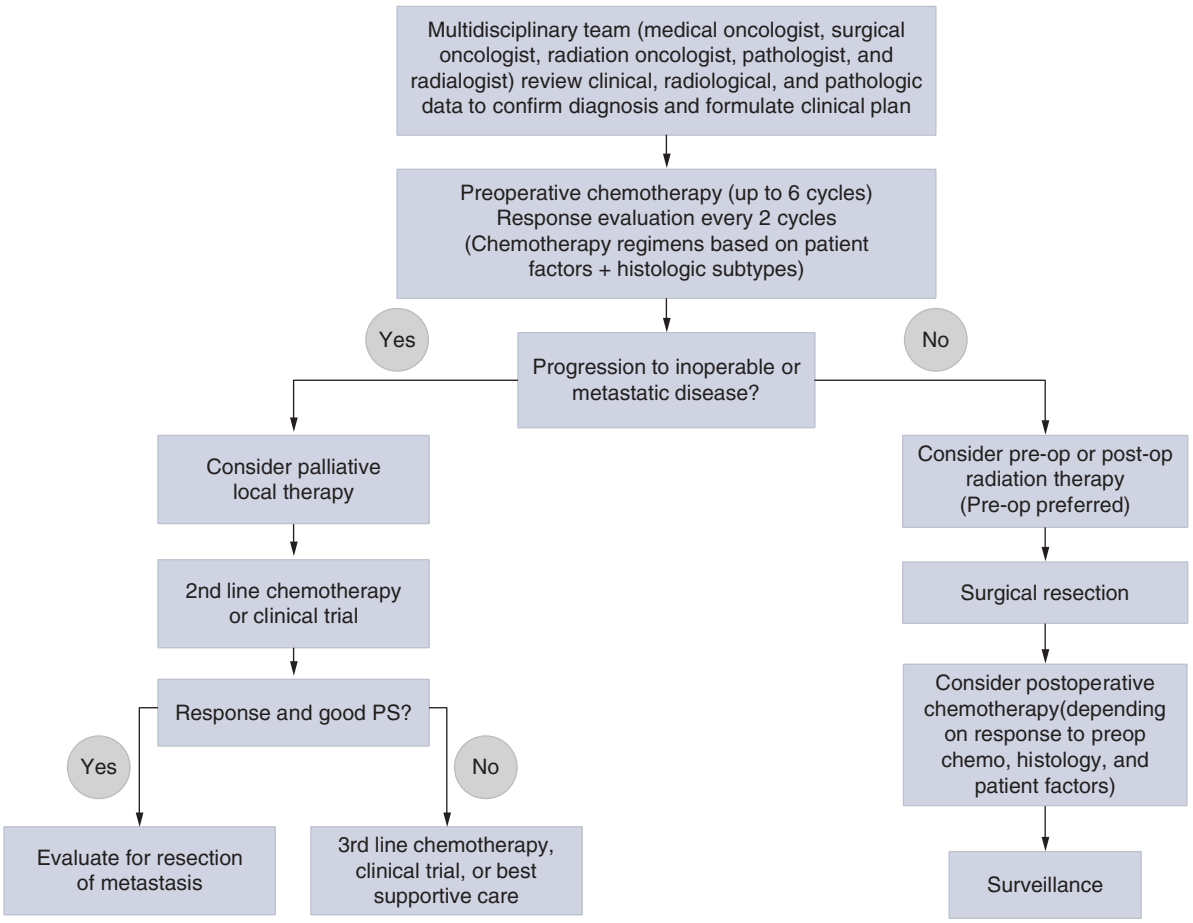


FIGURE 50–2 **Treatment approach for patients with stage III soft tissue sarcomas. © 2015 the University of Texas MD Anderson Cancer Center.**

ifosfamide group as compared with placebo. A subsequent randomized trial of adjuvant chemotherapy conducted by the EORTC randomized patients with intermediate- or high-grade STS to receive five cycles of doxorubicin 75 mg/m^2 and ifosfamide 5 g/m^2 vs no adjuvant therapy.[49] There was no observed benefit of adjuvant chemotherapy in regard to relapse-free survival or OS; however, this lack of benefit may have been due in part to an overestimate of the expected absolute benefit (powered to detect a 15% difference in 5-year OS) as well as the inclusion of patients with small tumors in whom the risks of relapse and death are lower. A subsequent risk stratified analysis of this trial using a validated nomogram (Sarculator) found that high-risk patients (those with a predicted OS <60%) derived a significant DFS and OS benefit from adjuvant chemotherapy supporting the role of chemotherapy among those with high-risk disease.[48] With a move toward subtype-specific treatment of STS, a recent international phase 3 trial evaluated the benefit of histotype-specific neoadjuvant chemotherapy compared with three cycles of standard chemotherapy consisting of epirubicin–ifosfamide among patients with localized myxoid liposarcoma, UPS, LMS, synovial sarcoma, or malignant peripheral nerve sheath tumors.[49] There was no improvement in DFS or OS with histotype-specific chemotherapy compared with anthracycline–ifosfamide within these five STS histologic subtypes.

Although the data regarding adjuvant therapy are conflicting, within our institution, we continue to offer adjuvant therapy with doxorubicin in combination with ifosfamide to healthy patients with intact organ function who have high-risk disease (tumor size >5 cm, high-grade histology, and deep soft tissue involvement).

Targeted Therapy

As in other tumor types, increased knowledge of cancer genomics and identification of oncogenic driver mutations in STS have led to much enthusiasm and investigation of molecular-based targeted therapies. A comprehensive review of targeted therapies under development for STS is beyond the scope of this chapter; therefore, the focus will be on currently approved therapies. Targeting cKIT with the tyrosine kinase inhibitor (TKI) imatinib in GISTs is perhaps the best-known and most successful example in sarcoma. Although targeted agents have shown promise in specific histologies, the multitargeted TKI pazopanib has shown activity across multiple subtypes of STS. Pazopanib is a small-molecule inhibitor with activity against VEGF1-3, PDGFRA, PDGFRB, and KIT. A phase II trial of pazopanib in advanced STS evaluating 12-week PFS as the primary end point showed benefit in LMS (44%), synovial sarcoma (49%), and other nonlipomatous STS (39%).[50] Subsequently, a placebo-controlled phase III trial of pazopanib in metastatic STS demonstrated a low response rate (partial response [PR], 6%) but significant improvement in PFS (4.6 months vs 1.6 months with placebo; HR, 0.31; P <.0001).[51] In a multivariate Cox model, favorable prognostic factors in patients treated with pazopanib were good performance status and low or intermediate tumor grade. Additional targeted therapies in STS are primarily being developed and studied in specific STS subtypes.

Metastatic Disease and Metastasectomy

Chemotherapy is the mainstay of therapy for patients with metastatic disease, although surgical resection of residual oligometastatic disease may be pursued on a case-by-case basis. Patients with metastatic disease involving multiple organs are generally incurable and considered appropriate for palliative systemic therapy. The subset of patients with lung-only metastatic disease, especially those with a greater than 12-month disease-free interval, have a favorable biology and prognosis and therefore should be considered for resection if feasible. This approach results in 3- to 5-year survival rate of up to 20%. The sequencing of chemotherapy is similar to that used for patients with localized disease. In a study conducted at MDACC, patients with metastatic disease showed a 57% response rate to doxorubicin (75–90 mg/m^2) and ifosfamide (10 g/m^2).[52] If patients fail this regimen, the choice of treatment depends on the histology of the tumor, performance status, and comorbid conditions.

Specific Soft Tissue Sarcomas

Vascular Sarcomas

Vascular sarcomas are tumors that originate from or differentiate toward the endothelium with varying malignant potential. Although epithelioid hemangioendotheliomas (EHEs) have an intermediate malignant potential and indolent clinical course, angiosarcomas, at the other end of the spectrum, have a highly malignant biologic behavior with early propensity for distant metastasis and dismal outcomes. These tumors also differ in their response to chemotherapy and targeted therapy and, therefore, are discussed separately below.

EHEs are considered to be of intermediate malignant potential with development of metastasis and recurrence. They typically are associated with a blood vessel, usually a medium-sized or large vein. EHE most commonly occurs in the soft tissues, but liver, lung,

and bone may be sites of primary involvement. In more than 42% of patients with hepatic EHE, symptoms are often absent, and the lesions are discovered incidentally. Some patients experience constitutional symptoms such as fatigue, anorexia, nausea, and poor exercise tolerance. Most cases of EHE affecting soft tissues are localized, whereas multifocality is more common with EHE involving liver or lung, and these patients develop metastatic disease during the course of their illness. Multifocal or metastatic disease does not equate to mortality, and many patients can survive long term with metastatic disease. Sixty-three percent of patients with liver EHE and fewer than half of patients with metastatic EHE of soft tissues die from their disease.

Localized EHE of soft tissue should be treated with surgical resection with adequate margins. After resection, these tumors can recur locally in about 12% of patients.[53] Preoperative radiation therapy should be considered in patients in whom good margins are unlikely, and postoperative radiation therapy should be considered in cases in which the margins are positive and no preoperative radiation was administered. Localized EHE does not require the use of chemotherapy or targeted therapies.

Metastatic EHE of soft tissue may be followed without therapy until there is evidence of progressive disease on serial imaging over a 3-month period. When systemic therapy is needed, conventional chemotherapy and antiangiogenic therapy may be considered. Systemic therapy options include gemcitabine, taxanes, and doxorubicin. Targeted therapy with bevacizumab (PR, 29%; stable disease, 57%; and progressive disease, 14%),[54] and sorafenib (30.7% without progression at 9 months)[55] has been reported to have utility in patients with metastatic EHE.

Angiosarcomas are highly malignant tumors with endothelial differentiation with a propensity for recurrence and distant metastasis. These tumors are extremely rare, representing fewer than 2% of all sarcomas, and can develop de novo or in the setting of prior radiation therapy or chronic lymphedema. Because of their endothelial location, these tumors are particularly well poised for early dissemination and development of metastasis. Angiosarcoma has a propensity for cutaneous involvement, and 60% of cases have skin or soft tissue involvement. Other sites of visceral involvement include spleen, liver, lung, pleura, heart, and gastrointestinal (GI) tract. Clinical behavior and response to therapy can vary from one site to another, with cardiac angiosarcomas carrying the worst prognosis.

Even when these tumors are nonmetastatic, multifocality is often present locally, resulting in high recurrence rates. Therefore, it is critical to approach localized disease with a multidisciplinary approach that combines chemotherapy, radiation, and surgery to produce better outcomes.[56] At our institution, we prefer to treat these patients with neoadjuvant chemotherapy followed by surgery and radiation. Chemotherapy can use either doxorubicin- or taxane-based approaches, both of which have excellent outcomes, and the choice of the regimen depends on the primary location of disease, histologic subtype, performance status of the patient, and potential for toxicity. For cutaneous angiosarcoma, taxanes are as good as doxorubicin-based approaches, but for visceral angiosarcoma, doxorubicin-based approaches may have better activity.

Patients with metastatic disease can be treated with single-agent or multiagent chemotherapy. Monotherapy with doxorubicin (response rate, 29%–33%; PFS, 3–5 months) and paclitaxel (response rate, 18%–89%; PFS, 4–5 months) appears to have significant activity in patients with angiosarcomas.[57–59] Based on a retrospective study of 117 patients with metastatic angiosarcoma, weekly paclitaxel (response rate, 53%) may have comparable efficacy to doxorubicin as a single agent in patients with cutaneous angiosarcoma.[59] Doxorubicin may have advantages over paclitaxel in visceral angiosarcomas. Gemcitabine also appears to have single-agent activity (response rate, 64%; PFS, 7 months),[60] but this drug is more commonly used in combination with taxanes.

The most commonly used combination therapies in angiosarcoma are doxorubicin–ifosfamide and gemcitabine–docetaxel. The doxorubicin–ifosfamide combination is preferred for visceral angiosarcomas and has better durability than any other treatment for angiosarcoma, with a median PFS of 5.4 months.[57] The gemcitabine–docetaxel combination appears to have good activity both in the visceral and cutaneous angiosarcomas.

Antiangiogenic therapies with activity in angiosarcomas include bevacizumab (PR, 9%; stable disease, 48%; median PFS, 12 weeks),[54] sunitinib,[61] and sorafenib (CR, 3%; PR, 11%; stable disease, 57%; median PFS, 3.2 months).[62] Although responses with targeted therapies appear to be low compared with conventional chemotherapy, this may be a result of using an unselected study population for treatment.

Leiomyosarcoma

LMS is a common STS subtype and can anywhere in the body. The site of origin and grade are important prognostic factors and also guide treatment. Patients with vascular-origin LMS have a worse prognosis than those with nonvascular LMS. Additionally, patients with uterine LMS tend to fare better than those with extrauterine LMS, although this may be in part due to a higher rate of complete resection in uterine LMS.[63] LMS is responsive to multiple chemotherapeutic

agents used in STS but has been shown to be less responsive to ifosfamide-containing regimens than single-agent doxorubicin.[64] A recent retrospective study conducted by the EORTC sought to identify the optimal treatment for patients with advanced LMS comparing doxorubicin–dacarbazine, doxorubicin–ifosfamide, and single-agent doxorubicin as first-line treatment.[38] Doxorubicin–dacarbazine was associated with the highest objective response rate compared with doxorubicin–ifosfamide and single-agent doxorubicin (30.9% vs 19.5% and 25.6% respectively) and showed favorable PFS. Gemcitabine is also active in the treatment of LMS. A subtype-specific phase II trial of gemcitabine versus gemcitabine in combination with docetaxel in metastatic or relapsed LMS[65] showed significant response rates with both single-agent gemcitabine and the combination (19% vs 24%, respectively) in patients with uterine LMS. In the nonuterine LMS subgroup, combination therapy resulted in higher objective response rates (14% vs 5%) and prolonged PFS (6.3 vs 3.8 months). Options for third-line therapy include trabectedin or pazopanib. Hormonal treatment may be considered for patients with uterine LMS but is typically reserved for patients with ER/PR+, low-volume, indolent disease given its limited activity. In the largest retrospective study of aromatase inhibitors in uterine LMS, response rates included PR in 9% and stable disease in 32%. Patients with hormone receptor–positive disease demonstrated better PFS.[66] The treatment algorithm for advanced LMS should take into account the site of origin (uterine vs extrauterine) and patient-specific factors (see Fig. 50–1).

Liposarcoma

Liposarcomas represent the second most common STS. There are several histologic subtypes of liposarcoma with unique clinical and biological features. Myxoid liposarcoma represents the most common subtype of liposarcoma. Other subtypes include well-differentiated, dedifferentiated, and pleomorphic liposarcoma. Myxoid liposarcomas often occur in the third through fifth decades of life, generally develop in the extremities, and harbor a balanced translocation $t^{12;16}$(q13;p11) resulting in the oncoprotein FUS-DDIT3, which is considered pathognomonic for the disease.[67,68] Although regarded a low-grade tumor, local recurrence and distant metastasis occur in about 30% of patients. Sites of metastasis include the lungs and soft tissue regions such as the axilla, the retroperitoneum, the pleural lining, the pericardium, and occasionally the spine. A variant of myxoid liposarcoma, round cell liposarcoma, is considered to be a more aggressive. An increase in round cell percentage correlates to metastasis and poor survival in myxoid liposarcomas.[67] Treatment options for myxoid liposarcoma depend on its size, location, and presence of adverse prognostic features such as the presence of round cell changes. Surgery and radiation are the mainstays of treatment; however, given the chemosensitive nature of myxoid liposarcoma, neoadjuvant or adjuvant chemotherapy is considered for patients with large or borderline resectable tumors as well as those at high risk of metastatic disease recurrence. Reports from MDACC using doxorubicin-based chemotherapy yield response rates of 44%. Trabectedin has been shown to be active in myxoid liposarcoma across multiple trials.[41,69] Aside from binding to the minor groove of DNA and forming covalent adducts and displacement of transcription factors, this agent is thought to promote differentiation of myxoid liposarcoma lipoblasts.

Surgery is the mainstay of treatment for patients with well-differentiated and dedifferentiated liposarcoma; however, recurrence rates are high, especially in the retroperitoneum. Benefit from chemotherapy has been reported to be minimal, with objective response rates of approximately 12%.[70] In a recent review of 89 patients with dedifferentiated liposarcoma of the retroperitoneum treated at MDACC, response rates were higher (23% by RECIST) with a clinical benefit rate (PR + stable disease >6 months) of 37%, suggesting a potential role for chemotherapy in select patients with unresectable or borderline resectable disease.[71] Doxorubicin-based regimens are typically preferred as first-line treatment, with gemcitabine–docetaxel, trabectedin, and eribulin also having activity in advanced or metastatic liposarcoma (see Fig. 50–1).

Alveolar Soft Parts Sarcoma

ASPS is a rare STS subtype predominantly affecting adolescents and young adults and accounting for fewer than 1% of all STS. Although the disease course is indolent with a prolonged natural history, ASPSs have a high rate of metastasis and a median OS of approximately 90 months. Although lung metastases are most common, ASPS can also metastasize to the brain, an otherwise uncommon site for sarcoma. In a review of our institutional experience with ASPS, 65% of patients presented with stage IV disease. Among those with localized disease at presentation, 5-year OS was 88%, whereas those who presented with metastatic disease had a median OS of 40 months and 5-year OS of 20%.[72] Despite its propensity for metastasis, ASPS is resistant to conventional chemotherapy. Highly vascular, these tumors are characterized by an unbalanced translocation t(X;17)(p11:q25), resulting in the ASPL-TFE3 fusion protein and overexpression of *MET*, leading to angiogenesis. Tyrosine kinase receptor inhibitors with activity against the vascular endothelial growth factor receptors such as cediranib[73] and sunitinib[74] have demonstrated activity against

several phase II studies with response rates exceeding 30% and with control rates of greater than 80% at 6 months. Interestingly, ASPS has been shown to be responsive to immune checkpoint inhibitors. We were the first to demonstrate activity of nivolumab and ipilimumab in ASPS.[75] Additionally, a phase II study of axitinib in combination with pembrolizumab demonstrated activity against ASPS with a response rate of 54.5% and a median PFS at 3 months of 72.7%.[76] Although the immune microenvironment has yet to be comprehensively defined for this rare form of sarcoma, several studies suggest the presence of programmed cell death protein 1–expressing tumor infiltrating lymphocytes, molecular evidence of mismatch-repair deficiencies, and possible immunogenicity associated with the breakpoint of the fusion protein.[77] Despite this evidence of activity, clinical trials are still ongoing, and there is yet to be an approval by the FDA for the use of immune checkpoint inhibitors in the treatment of patients with advanced or metastatic ASPS. As such, ASPS patients requiring medical management of their advanced or metastatic disease should be considered for clinical trials.

Tenosynovial Giant Cell Tumor and Pigmented Villonodular Synovitis

Tenosynovial giant cell tumor (TGCT), previously called pigmented villonodular synovitis, is characterized by hypervascular proliferative synovium with an accumulation of polyclonal macrophages, hemosiderin deposition (detectable on imaging), and multinucleated giant cells. Consequently, joint destruction by inflammatory infiltrates results in pain, swelling, and limitation of movement. Most commonly, TGCT involves a single joint such as the knee or ankle but can occur anywhere that synovium is present. Surgically resectable disease, especially in the frontline setting, should be managed using surgery as the mainstay of treatment. Patients who develop recurrent disease or present with diffuse-type disease that is not surgically resectable without considerable morbidity should be considered for targeted therapy. TGCT harbors a clonal population of cells that have the *CSF1-COL6A3* translocation, which results in overproduction of CSF1 that recruits inflammatory cells into the joint. The pathogenic mechanism opens up a unique opportunity to treat these patients with unresectable disease with a CSF1R inhibitor. Pexidartinib is an orally bioavailable agent that is FDA approved for use in this rare disease. Pexidartinib produced a response rate of 39% compared with 0% in the placebo arm of ELIVEN, a randomized phase III trial comparing the activity of the drug with placebo.[78] Pexidartinib has the potential to produce rare but potentially fatal hepatotoxicity through ductopenia that requires use of this drug to be monitored closely using the Turalio Risk Evaluation and Mitigation Strategies program. It is particularly important to administer the drug on an empty stomach because dietary fat increases the absorption of the drug and increases the likelihood of hepatotoxicity. Other CSF1R inhibitors such as imatinib and emactuzumab have shown activity in TGCT and may also have a role in treatment, but their use remains investigational.

Follow-up Management

The major goals of follow-up surveillance and management should be early identification of potentially curable recurrences, identification of treatment-related complications, and patient reassurance. Surveillance of patients treated for STS is based on known prognostic factors, outcomes in individual subsets of patients, and patterns of tumor recurrence. Similarly, the screening, evaluation, and management of late effects related to chemotherapy and radiation are based on the specific regimens received and the site and dose of radiation.

For patients with low-risk T1 primary STS who have undergone treatment with curative intent and have no evidence of disease, follow-up should include a history and physical examination, cross-sectional imaging of the tumor bed to evaluate for local recurrence, and routine chest radiography for surveillance of metastatic disease.[79] For tumors of the head and neck and extremities, MRI is appropriate; for tumors of the chest, abdomen, and retroperitoneum, CT scans are appropriate. The routine use of chest CT for evaluation of metastatic disease in low-risk STS has been studied and found not to be cost effective. The NCCN guidelines recommend follow-up with annual scanning of the primary site for at least 5 years; however, often these patients are seen every 3 to 4 months in the immediate postoperative period for the first 2 years, then every 4 to 6 months for the next 2 years, and yearly thereafter.[28]

Patients with high-risk T2 (>5 cm) STS are at a greater risk for distant lung metastases. In patients with high-risk tumors who have undergone treatment with curative intent and have no evidence of gross disease, follow-up should include a history and physical examination, cross-sectional imaging of the tumor bed, and routine chest radiography or chest CT for surveillance of metastatic disease. These patients are followed in the same manner as low-risk patients, with follow-up visits with the above studies every 3 months for the first 1 to 2 years, then visits every 4 months for the next 1 to 2 years, followed by visits every 6 months for 1 to 2 years and yearly visits thereafter. As for local recurrence surveillance, the cross-sectional imaging is omitted after 5 years

because most local recurrences appear within 5 years of initial treatment.

Gastrointestinal Stromal Tumors

GISTs are the most common mesenchymal tumors of the GI tract.[80] Previously, they were often designated smooth muscle tumors of the GI tract, specifically, GI LMS, leiomyoblastoma, LMS, and leiomyomas. Investigators discovered that GISTs express the KIT (CD-117) receptor tyrosine kinase and possibly originate from the interstitial cell of Cajal, the intestinal pacemaker cell responsible for peristalsis.[81] These tumors most commonly arise in the stomach (60%–70%), followed by small intestine (20%–30%), colon and rectum (5%), and esophagus (<5%), although they can arise anywhere in the GI tract, omentum, or peritoneum. The liver, peritoneum, and bone are the most common sites of metastatic disease; however, there are reports of associated central nervous system, lymph node, lung, and other metastases.[82] The incidence of GIST is equal in men and women; it generally peaks between the fourth and sixth decades of life, and patients are more commonly of European descent. Presenting symptoms often represent the site of tumor origin but may be vague, including abdominal pain, anorexia, weight loss, and dyspepsia. GI bleed presenting as anemia or near syncope is also common.

Historically, the mainstay of treatment for GIST was surgical resection. Conventional chemotherapy or radiotherapy has not been effective in the treatment of GIST. The identification of specific oncogenic driver mutations involving *KIT* and *PDGFRA* has led to the development and approval of multiple TKIs that have greatly improved the prognosis of patients with high-risk localized and metastatic GIST. Before the availability of TKIs, median OS was approximately 18 months. In the era of TKIs, this has improved to around 5 years.[83]

Molecular profiling of patients with GIST has now become standard of care because the mutational status has important implications in regard to diagnosis, prognosis, and guiding treatment decisions. Approximately 70% to 80% of GISTs harbor a *KIT* gene mutation, with another 5% to 8% with *PDGFRA* mutations and the remaining 12% to 15% deemed wild-type GIST.[84] Wild-type GIST constitutes a heterogeneous group, with additional mutations identified in succinate dehydrogenase (*SDH*), *BRAF* V600E, and *RAS*, among others. Deletions in exon 11 are the most common *KIT* mutation and portend a more aggressive disease course with shorter OS and higher risk of recurrence. Internal tandem repeats involving exon 11, however, are associated with gastric GIST and tend to be more indolent. Exon 9 mutations have been associated with GIST of the small intestine and a clinically aggressive course. *PDGFRA* mutations can occur in multiple exons (12, 14, and 18) and are observed primarily in gastric GIST.

Imatinib mesylate, an oral TKI that selectively inhibits BCR-ABL, KIT, and PDGFR, is approved for adjuvant therapy and for unresectable or metastatic GIST. Early trials with imatinib showed objective response rates of 53% to 69% and significant improvement in 5-year OS of about 50%.[85] These trial results led to two phase III trials (EORTC 62005 and SWOG S0033) that were designed to compare imatinib at two dose levels (400 mg/day vs 800 mg/day).[86,87] In both studies, the higher-dose arm failed to show a statistically significant difference in response or OS compared with the standard dose; however, PFS was superior for exon 9 mutant patients in the higher-dose arm. GISTs with exon 11 mutations are more responsive to imatinib therapy compared with exon 9 mutations.[88] Patients with non-KIT non-PDGFRA mutated or wild-type GIST rarely show significant or sustained response to imatinib. In one study, investigators randomized patients who had control of disease at 3 years with imatinib to either continue or discontinue treatment.[89] The 2-year PFS was 80% in the continuous treatment cohort compared with 16% in the treatment interruption group. Further randomization at 3 years to either continue for 5 years or stop revealed similar results. It is therefore recommended that patients with advanced or metastatic GIST should avoid interruption and keep taking imatinib until PD or true intolerance.

Imatinib has also shown efficacy in the adjuvant setting.[90] As in the metastatic setting, the optimal duration of adjuvant imatinib therapy has not been well established. A randomized trial comparing 1 year versus 3 years of adjuvant imatinib therapy for patients with *KIT*-positive resected GIST showed benefit to longer duration of adjuvant therapy.[91] Patients receiving 36 months of adjuvant imatinib had longer recurrence-free survival (5-year recurrence-free survival, 65.6% vs 47.9%; HR, 0.46; P <.001) and improved 5-year OS (92% vs 81.7%; HR, 0.45; P =.02). A single-arm study of 5 years of adjuvant imatinib in intermediate- and high-risk GIST reported a 5-year RFS of 90% and OS of 95%.[92]

Approximately 10% of patients with GIST have primary resistance to imatinib, with higher rates seen in exon 9 mutated and wild-type GIST. Secondary resistance is often caused by new mutations in the *KIT* gene involving exon 13 or exon 17.[93] Sunitinib, a multikinase inhibitor that targets VEGF, appears to have activity in patients with primary resistance and secondary *KIT* mutations.[94,95] The overall objective response rate, however, was less than 10%. Several additional targeted therapies targeting the KIT and PDGFRA pathways have also been evaluated. Nilotinib, a second-generation TKI, was evaluated as

third-line therapy after imatinib and sunitinib and showed a low response rate of 3%.[96] Regorafenib, a multitargeted TKI, has shown better efficacy in patients after failure of both imatinib and sunitinib. In a phase II trial, an objective response rate of 12% and clinical benefit rate (PR or stable disease >16 weeks) of 79% were observed in patients.[97] The phase 3 GIST - regorafenib in progressive disease (GRID) trial randomized patients with metastatic GIST who had failed imatinib and sunitinib to either regorafenib or placebo. Median PFS was 4.8 months versus 0.9 months in favor of regorafenib, resulting in FDA approval of this agent.[98] About 5% to 6% of patients with GIST have a primary PDGFRA D842V mutation, which is known to be resistant to all the currently approved TKIs. Avapritinib is a selective and potent inhibitor of PDGFRA loop mutations that recently received FDA approval in 2020 based on an 8% CR and 82% PR with a 12-month PFS of 85%.[99]

Response evaluation in GIST uses the Choi criteria rather than the standard RECIST measures used in most other solid tumors. PET imaging may also be used and was initially noted to show treatment response at an earlier time point compared with standard CT imaging. Certain molecular events, such as apoptosis, occur early on and may partially explain the rationale behind early PET response related to imatinib.[100] Our institution also demonstrated that RECIST criteria may underestimate early tumor response seen in GIST. Patients who respond to imatinib clinically may show a decrease in tumor size, or a decrease in tumor radiodensity by CT radiography, or both. Further analysis of patients treated with imatinib at MDACC revealed that when tumor density is taken into account, sensitivity of CT imaging is comparable to PET response.[101,102] These data culminated in the development of the Choi criteria of response assessment (Table 50–3). These criteria have been prospectively validated and are considered in response assessment in current trials of GIST. It is our experience that decisions to discontinue therapy should not be based solely on CT radiography or PET imaging but instead should also take into consideration the patient's overall clinical condition.

In summary, the frontline therapy for patients with newly diagnosed, metastatic GIST is imatinib at 400 mg/day. Patients with exon 9 mutations should have therapy initiated with imatinib at 800 mg/day. Imatinib should be continued indefinitely or until progression, as defined by Choi criteria. CT imaging is used to assess response initially at 2 months and then at 3-month intervals for at least the first 2 years. At the time of progression, if tolerable, we increase the dosage of imatinib to a total of 800 mg/day. If or when this strategy fails, we proceed to second-line therapy sunitinib and subsequent third-line therapy with regorafenib. For patients with isolated or resectable metastatic disease, surgery and/or hepatic artery embolization or radiofrequency ablation is offered if feasible. For resectable GIST patients with high-risk features, such as a high mitotic count or large tumor size, adjuvant imatinib for at least 3 years should be administered to increase recurrence-free survival. The optimal duration of imatinib use in the adjuvant setting beyond 3 years remains unknown.

TABLE 50–3 Choi Response Criteria

Response	Response Definition
Complete response (CR)	Disappearance of all disease No new lesions
Partial response (PR)	A decrease in size of >10% or a decrease in CT density (HU) >15% No new lesions No obvious progression of non-measurable disease
Stable disease (SD)	Does not meet the criteria for CR, PR, or PD No symptomatic deterioration attributed to tumor progression
Progression of disease (PD)	An increase in unidimensional tumor size of >10% and did not meet criteria for PR by CT density Any new lesions, including new tumor nodules in a previous cystic tumor

CT, computed tomography; HU, Hounsfield unit.

BONE SARCOMA

Bone sarcomas are rare tumors, making up fewer than 0.2% of all cancers. In 2020, an estimated 3600 new cases of bone sarcomas were estimated to be diagnosed in the United States, and 1720 deaths from these cancers were expected.[1] The most common malignant tumor of bone is osteosarcoma followed by chondrosarcoma and then the Ewing family of tumors (EFT), which includes sarcoma and peripheral primitive neuroectodermal tumors (PNETs). UPS of bone (previously termed malignant fibrous histiocytoma), fibrosarcoma, chordoma, and giant cell tumor of bone are rare bone tumors and account for fewer than 5% of all primary malignant bone tumors. EFT tends to occur more frequently in children and adolescents, whereas osteosarcoma has a biphasic pattern of incidence that peaks in adolescents with the growth of long bones and has a second peak in older adults with tumors arising in association with Paget

TABLE 50–4 Features of Common Bone Tumors

Type	Frequency (%)	Age Distribution (years)	Gender	Common Sites	Radiologic Features	Pathologic Features
Osteosarcoma	45	10–20	M > F	Metaphysis	Sunburst calcifications	Spindle cells, osteoid matrix
UPS of bone	8	20–80	M > F	Long bones	Radiolucent with ill-defined margins	Pleomorphic spindle cells, no osteoid
Chondrosarcoma	22	20–80	M > F	Pelvis or shoulder girdles	Lobulated appearance	Lobules, chondroid matrix
Ewing or PNET	15	10–20	F > M	Diaphysis	Lytic with soft tissue component	Small round blue cells

F, female; M, male; PNET, primitive neuroectodermal tumor; UPS, undifferentiated pleomorphic sarcoma.

disease or as a secondary malignancy after therapeutic radiation. Chondrosarcomas are usually seen in adult patients after the fifth decade of life, with fewer than 5% of cases occurring in pediatric patients, in whom the tumors tend to be of a higher grade malignancy. Features of common bone tumors are listed in Table 50–4.

Clinical Presentation

The clinical presentation of any bone tumor depends on its location. Most osteosarcomas arise in the metaphyseal region of long bones, specifically the distal femur, proximal tibia, and proximal humerus. Approximately half of all osteosarcomas occur around the knee joint. Chondrosarcomas can also arise in any bone of the body; however, they generally occur in the pelvis and other flat bones. EFTs tend to occur in the diaphyseal portion of the long bones and in flat bones of the body (eg, the pelvis and scapula) but can involve any bone and occasionally arise in the soft tissue (termed *extraskeletal* or *extraosseous Ewing sarcoma*).

The most common presenting symptom is pain and swelling or a mass. Patients who have pelvic tumors may have neurologic impairment and severe pain, typically because these tumors are often not recognized until late in the disease course. In the case of EFT, patients often present with constitutional symptoms of night sweats and fevers.

Evaluation

Evaluation of suspected bone sarcoma should begin with a careful history, physical examination, and routine laboratory tests followed by imaging directed to the given complaint. The imaging of any bone tumor should begin with a plain film of the involved area. Radiography images are often helpful in the diagnosis of bone sarcomas; for example, osteosarcoma often has a "sunburst" appearance of calcification on x-ray imaging, which is virtually diagnostic (Fig. 50–3). The amount of calcification associated with osteosarcoma depends on the histologic subtype (eg, whereas osteoblastic osteosarcoma usually has very dense calcification, telangiectatic osteosarcoma is primarily lytic). Chondrosarcoma also has a distinct appearance on x-ray imaging, with destruction of the bone and endosteal scalloping of the bony cortex and a chondroid matrix, which appears lobulated (see Fig. 50–3). EFT has a typical "onion-skin" appearance on x-ray imaging (see Fig. 50–3). Additional initial imaging should include a CT scan, MRI, or both of the primary lesion to further evaluate involvement of the neurovascular structures, surrounding soft tissues, and adjacent joints and to better evaluate any associated soft tissue mass.

Biopsy of bone sarcomas is critical to the diagnosis, and careful planning is essential. When patients are diagnosed with bone sarcoma or the diagnosis is suspected, it is important to have a multidisciplinary team approach with physicians who are experienced in the treatment of patients with bone sarcomas. Core-needle biopsy has been shown to be accurate in making a diagnosis in up to 91% of cases.[103] An open biopsy should be performed only when core-needle biopsy is nondiagnostic. Current guidelines recommend either a core or open biopsy to confirm the diagnosis before any surgical procedure. When surgery is ultimately performed, care should be taken to assure that the biopsy tract is completely resected.

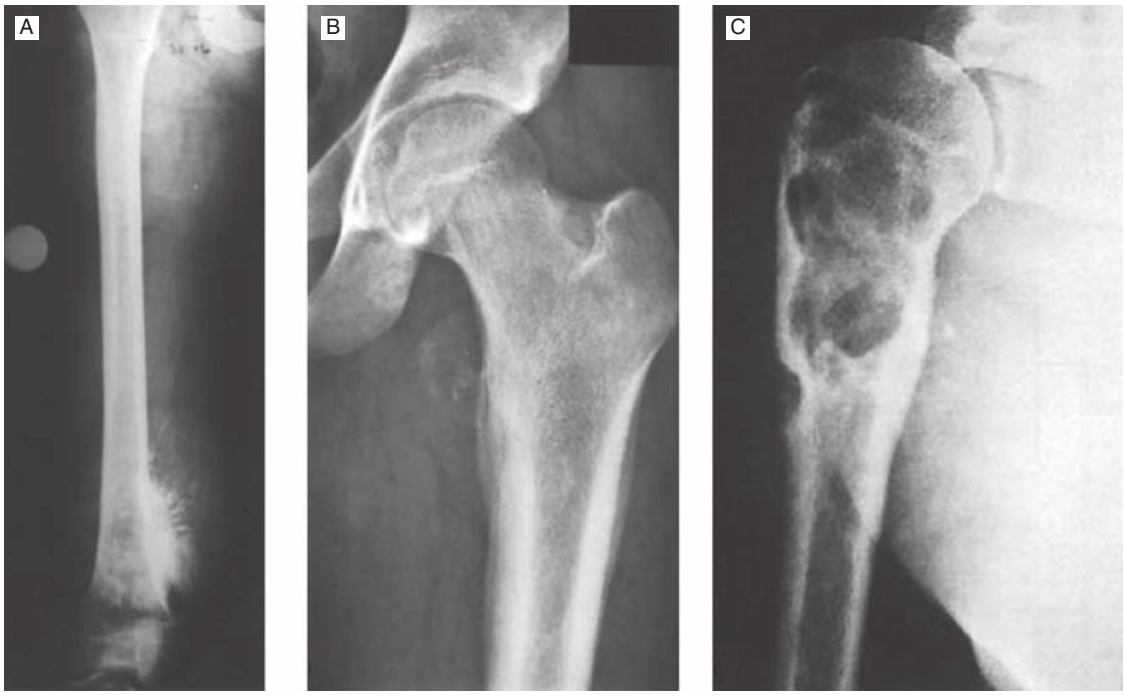


FIGURE 50–3 X-ray imaging of osteosarcoma, Ewing sarcoma, and chondrosarcoma. **A.** The typical "sunburst" appearance of osteosarcoma. **B.** The "onion-skin" appearance often seen in Ewing sarcoma. **C.** The lobulated appearance of chondrosarcoma.

Complete staging should include chest radiography, CT scan of the chest, and bone scan to evaluate for metastatic disease. Chest imaging is warranted in all patients because the most common site of metastasis from bone sarcoma is the lungs. A bone scan should be included in the workup for metastatic disease in patients with bone sarcoma to evaluate for distant bone metastases or skip metastases. For patients with EFT, an MRI of the spine should also be performed because of the risk of bone marrow metastases. We do not routinely obtain bone marrow biopsy in the staging evaluation of EFT, preferring the use of MRI because marrow involvement has been shown to highly correlate with bone metastasis.[104]

PET-CT is frequently used in the initial diagnostic evaluation, staging, and response assessment for bone sarcomas. However, fluorodeoxyglucose (FDG) uptake alone is not adequate for characterization of primary bone tumors; morphologic evaluation is key.[105] PET-CT imaging can also play an important role in response assessment because bone sarcomas do not demonstrate typical RECIST responses to chemotherapy. Multiple studies have reported the utility of PET-CT in evaluating chemotherapy response in osteosarcoma and EFTs.[106,107] In one study of osteosarcoma, a 25% to 50% reduction of SUV after 1 week of neoadjuvant chemotherapy has been shown to correlate with greater than 90% tumor necrosis on pathologic evaluation.[108] At our center, we routinely use PET-CT in the evaluation and response assessment for osteosarcoma and EFTs.

Pathology

There are multiple histologic subtypes of bone sarcoma, with the most common cytogenetic and molecular aberrations summarized in Table 50–5. Osteosarcoma can be broken down into two major categories: conventional osteosarcoma and variant osteosarcoma. Conventional osteosarcoma, which includes osteoblastic, chondroblastic, and fibroblastic subtypes, comprises approximately 60% to 75% of all osteosarcomas, whereas the 11 variants comprise the other 35% to 40%. These classifications are made based on the histologic features of the tumor, such as the amount of matrix present within the tumor and whether bone or cartilage is predominant. The classification of osteosarcoma variants often relies more on clinical features such as the site of disease (eg, jaw, skull, pelvis), the setting in which the disease presents (eg, postradiation, Paget disease, multifocal, retinoblastoma), and the morphology (eg, telangiectatic, small cell, and surface lesions such as parosteal, periosteal, and high-grade surface osteosarcoma). High-grade osteosarcomas demonstrate significant genomic instability and therefore possess complex and heterogeneous chromosomal alterations. *TP53* alterations are common and found in the vast majority of all osteosarcomas followed in frequency by

TABLE 50–5 Selected Genetic Alterations in Bone Tissue Sarcomas

Tumor	Cytogenetic Abnormality	Gene Product
Aneurysmal bone cyst	t(16;17)(q22;p13) t(1;17)(p34.3;p13) t(3;17)(q21;p13) t(9;17)(q22;p13) t(17;17)(q21;p13)	*CDH11-USP6* *THRAP3-USP6* *CNBP-USP6* *OMD-USP6* *COL1A1-USP6*
Chondrosarcoma or chondroma		*IDH1* or *IDH2* Point mutation
Ewing sarcoma and PNET family	t(11;22)(q24;q12) t(21;22)(q22;q12) t(7;22)(p22;q12) t(2;22)(q33;q12) t(17;22)(q12;q12) inv(22)(q12;q12) t(16;21)(p11;q22)	*EWS1-FLI1* *EWS1-ERG* *EWSR1-ETV1* *EWSR1-FEV* *EWSR1-E1AF* *EWSR1-ZSG* *FUS-ERG*
Fibrous dysplasia	Activating oncogenic mutations	*GNAS1*
Mesenchymal chondrosarcoma	t(8;8)(q13;q21)	*HEY1-NCOA2*
Osteosarcoma, low-grade (parosteal and intramedullary)	12q14-15 (ring chromosomes, giant marker chromosomes)	Amplification of *CDK4, MDM2, HMGA2, GLI*, and *SAS*
Osteosarcoma		Frequent *TP53* alterations; multiple genetic aberrations, including copy number alterations

PNET, primitive neuroectodermal tumor.

mutations in the tumor suppressor gene *RB1*. Copy number loss or gain in multiple chromosomes as well as amplifications in the *MDM2* gene, *CDK4*, *MYC*, and *VEGF* have been described.[109] To date, contemporary next-generation sequencing studies of osteosarcomas has yet to identify recurrent actionable molecular targets.

UPS of bone (previously termed *malignant fibrous histiocytoma of bone*) is a rare high-grade bone sarcoma accounting for fewer than 2% of all primary bone malignancies. It is similar to UPS of soft tissue histologically and can often appear to as the high-grade component of dedifferentiated chondrosarcoma. UPS is thought to be part of a spectrum of osteosarcoma in which the spindle cells do not produce apparent osteoid visible by light microscopy; however, a subset of these tumors produce osteoid in response to preoperative chemotherapy and may be subsequently reclassified as osteosarcomas.

Chondrosarcomas are malignant tumors of bone characterized by cartilaginous matrix formation. These tumors produce chondroid matrix and can arise from benign processes such as enchondromas or osteochondromas. Chondrosarcoma is characterized by the permeation of cartilage into the bone marrow. This process is considered pathognomonic for chondrosarcoma. Dedifferentiated chondrosarcoma represents a unique subset of conventional chondrosarcomas typified by a low-grade conventional chondrosarcoma juxtaposed with a high-grade soft tissue component. Several less common variants exist, including mesenchymal chondrosarcoma and clear cell chondrosarcoma. Next-generation sequencing has identified somatic mutations in isocitrate dehydrogenase 1 and 2 (*IDH1/2*) in central conventional chondrosarcomas and dedifferentiated chondrosarcomas.[110] This finding may aid in distinguishing chondrosarcoma from chondroblastic osteosarcoma and could serve as a unique therapeutic target.[111]

EFTs represent a completely separate histology and are grouped with the PNETs because of their similarities in histology, immunohistochemical staining, and molecular genetics. This family of tumors includes Ewing tumors of bone, extraosseous Ewing tumors, PNETs, and Askin tumors (PNET of the chest wall). These tumors are often referred to as "small round blue cell tumors" because, under a microscope, the cells contain scanty cytoplasm and round to oval nuclei with fine chromatin that are tightly packed together. The ESFTs possess recurrent translocations involving the *EWS* gene. The translocation $t^{11;22}$(q24;q12) *EWS-FLI-1* fusion was the first described and most common translocation. Several additional translocations have also been identified (see Table 50–5).

Bone sarcomas are classified as either high- or low-grade lesions, similar to the three-tier grading system of

STS. Grading is an important factor that helps to determine the overall stage, expected natural history, and prognosis. Finally, the pathologist should be provided with the diagnostic imaging and x-ray findings because these provide important information to assist in making a final diagnosis in bone sarcomas.

Staging and Prognosis

There are two widely accepted staging systems, that of the AJCC and that of the Musculoskeletal Tumor Society.[17,112] In a comparison of these systems, there was no significant difference between them, and neither had any notable advantage.[113] At MDACC, instead of routinely using a staging system, we prefer to emphasize prognostic factors (eg, size of the primary, location and extent of bone involvement, soft tissue involvement, histologic grade, and presence or absence of distant metastases). The prognosis of patients with bone sarcomas largely depends on the specific histology, grade, and location, as well as the presence and location of metastatic disease. In addition to the clinical and pathologic prognostic features assessed at diagnosis, pathologic treatment response assessed as the percentage of tumor necrosis after preoperative chemotherapy is the most well-established prognostic factor for patients with high-grade osteosarcoma.

Treatment

The treatment of bone sarcomas is best accomplished by a multidisciplinary team comprising medical oncologists, surgical oncologists, radiologists, pathologists, and radiation oncologists working together to provide comprehensive care. The treatment required depends on the tumor type, location, and extent of disease. Treatment algorithms for high-grade bone sarcomas and Ewing sarcoma are show in Figures 50–4 and 50–5.

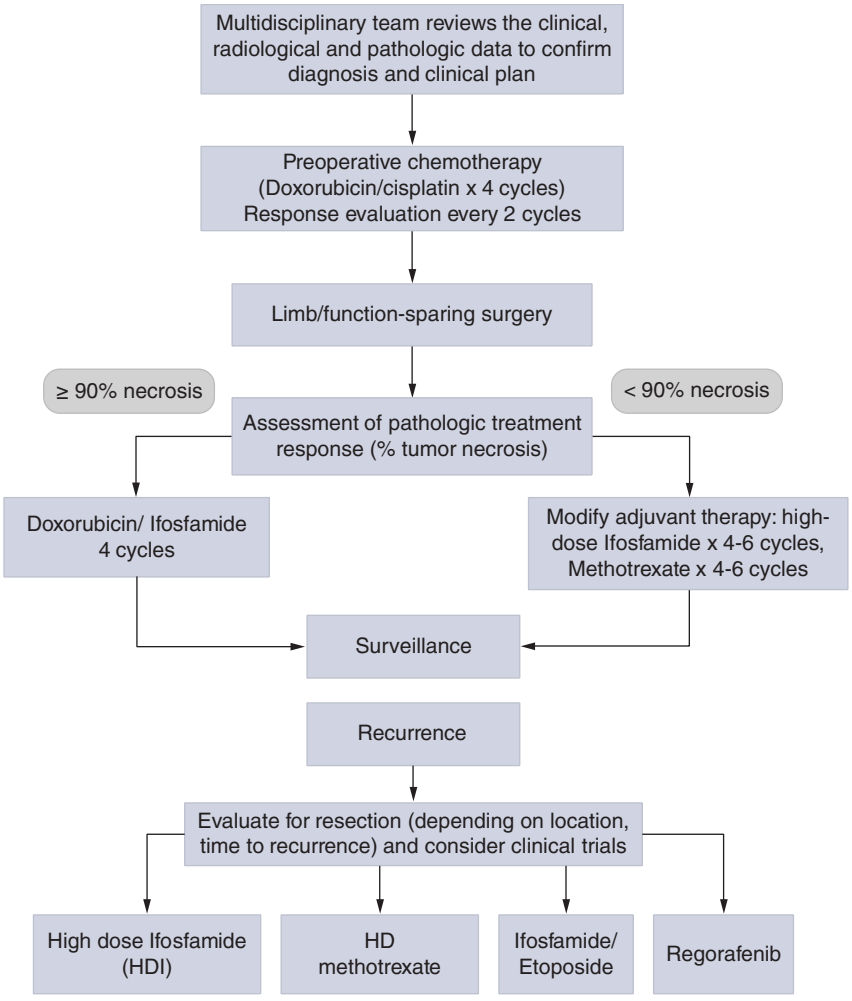


FIGURE 50–4 Treatment approach for patients with high-grade primary bone sarcomas.

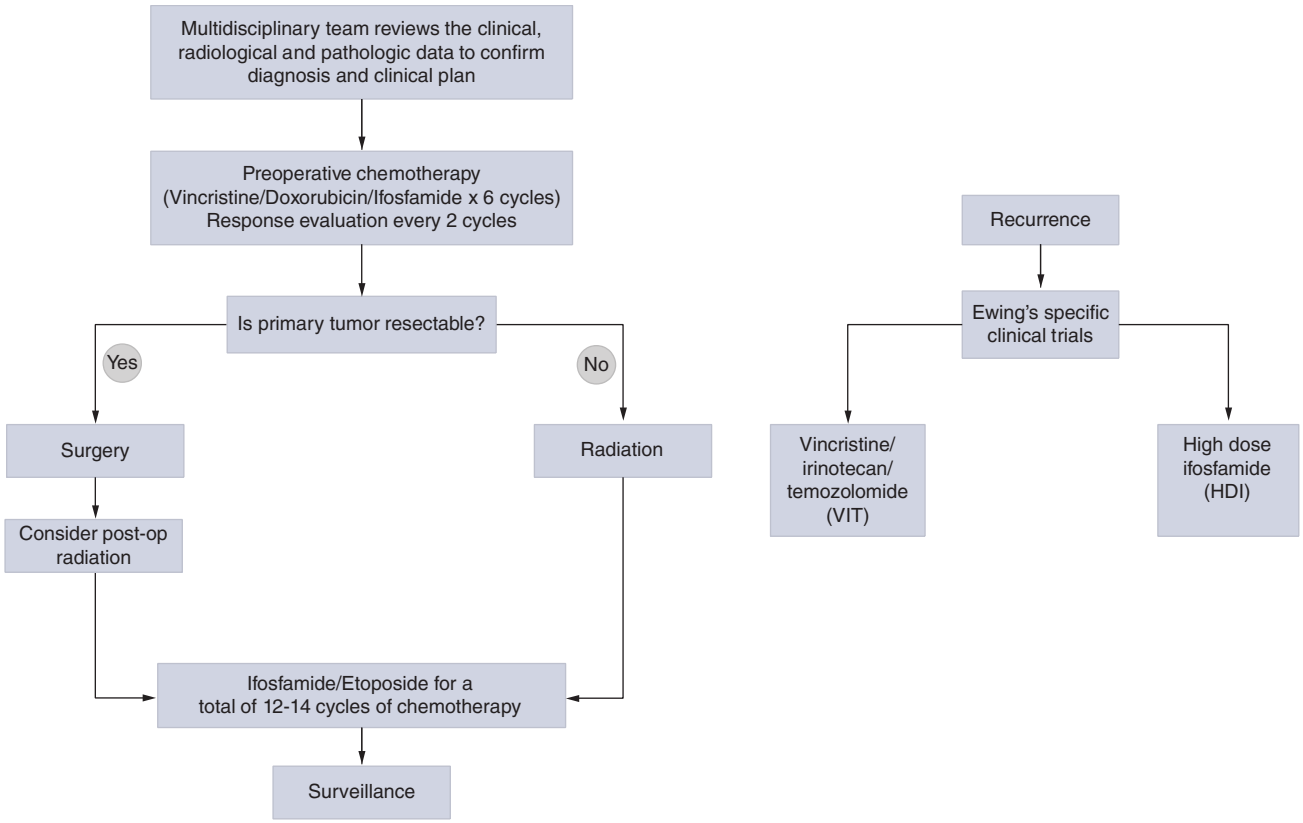


FIGURE 50–5 **Treatment approach for patients with Ewing sarcoma family tumors.**

Osteosarcoma

Osteosarcoma is the prototype of most other bone sarcomas. Chemotherapy is the mainstay of treatment for osteosarcoma, which is considered a systemic disease because most patients have micrometastatic disease at presentation. This is evidenced by the historic long-term survival rate of less than 20% in patients treated with surgery alone compared with the nearly 70% cure rate among patients with localized osteosarcoma of an extremity treated with aggressive combination chemotherapy followed by surgery.[114]

At MDACC, adult patients with conventional high-grade osteosarcoma of an extremity receive treatment consisting of preoperative chemotherapy followed by limb-sparing surgery followed by postoperative chemotherapy (see Fig. 50–4). The postoperative therapy is tailored based on the knowledge of the percent necrosis found in the pathologic specimen after surgery. This approach is based on a series of patients treated within our center in which tailored postoperative therapy demonstrated improved survival and differs from the current standard treatment of pediatric osteosarcoma.[115]

The most active agents for the treatment of patients with osteosarcoma are cisplatin, doxorubicin, ifosfamide, and high-dose methotrexate. Among pediatric patients with osteosarcoma, a combination of high-dose methotrexate, doxorubicin, and cisplatin (MAP) chemotherapy remains the standard of care within the United States. For adult patients, we use a preoperative regimen of doxorubicin (75–90 mg/m^2 as continuous infusion over 72 hours) in combination cisplatin (120 mg/m^2).[116] At resection after preoperative chemotherapy, the percentage of tumor necrosis is the single most important predictor of long-term DFS and OS. Generally, patients with 90% or greater tumor necrosis after preoperative chemotherapy have a 5-year continuous DFS of approximately 80%.[117] The 5-year continuous DFS of patients with less than 90% tumor necrosis after preoperative chemotherapy is significantly worse, ranging from 13% up to 67% depending on the postoperative chemotherapy regimen. To address this, we analyzed a consecutive series of 123 patients with osteosarcoma of the extremity treated within our center who were divided into three cohorts based on the time period in which they

were treated and the postoperative chemotherapy given. All patients received preoperative doxorubicin and cisplatin induction. Patients received the sequential addition of high-dose methotrexate (8 g/m^2) and then methotrexate plus ifosfamide postoperatively in the second and third groups depending on the time period in which they were treated. Among patients with 90% or greater tumor necrosis, relapse-free survival was not significantly different among the three groups. In patients with poor response, with less than 90% tumor necrosis, the addition of methotrexate and then methotrexate plus ifosfamide improved the 5-year relapse-free survival from 13% to 34% and 67%, respectively.[115] A recent updated analysis of adult osteosarcoma patients treated with this modified approach at MDACC confirmed the long-term survival of patients with poor response to preoperative doxorubicin and cisplatin and went on to receive postoperative therapy with high-dose ifosfamide and high-dose methotrexate.[118]

For patients who achieve 90% or greater tumor necrosis with four cycles of doxorubicin and cisplatin preoperatively, we recommend four additional cycles of doxorubicin (75 mg/m^2) combined with ifosfamide (10 g/m^2). For those with less than 90% tumor necrosis after preoperative doxorubicin and cisplatin, we favor six cycles of high-dose ifosfamide and six cycles of high-dose methotrexate given sequentially.

The role of postoperative switch therapy or intensified therapy guided by histologic response to preoperative chemotherapy remains controversial in osteosarcoma. In the European and American Osteosarcoma Studies (EURAMOS-1) study, 618 children and young adults with high-grade osteosarcoma who received preoperative methotrexate, doxorubicin, and cisplatin (MAP) with 10% or greater viable tumor at surgery were randomized one to one after surgery to receive either continuation of MAP or intensification with the addition of ifosfamide and etoposide to the same MAP backbone (MAPIE).[119] Intensification with MAPIE failed to show an advantage in terms of event-free survival (HR, 1.01) and OS (HR, 0.99) and was associated with additional toxicity at a median follow-up period of 4.5 years.

Patients with high-grade osteosarcomas of other sites are treated in a similar fashion; however, their overall outcome is worse than that of patients with extremity tumors. This may be due in part to difficulties in achieving a negative surgical margin of resection owing to anatomic constraints. Patients with low-grade and variant osteosarcomas—such as well-differentiated intramedullary osteosarcoma, parosteal osteosarcoma, and jaw osteosarcoma typically arising in the mandible, which have a lower tendency to produce distant metastases—are treated with surgical resection with negative margins alone without routine use of adjuvant chemotherapy. If surgical resection with negative margins cannot be achieved in osteosarcoma of the jaw, preoperative chemotherapy should be considered. Postoperative radiation therapy has been shown to reduce local recurrence and improve survival for patients with craniofacial and jaw osteosarcomas with positive resection margins.[120] Patients with intermediate-grade periosteal osteosarcoma should also receive preoperative chemotherapy.

UPS of bone is treated according to the same basic principles as conventional osteosarcoma. In a series of patients treated at MDACC, about 35% of patients with an initial diagnosis of UPS of bone based on biopsy were subsequently reclassified as osteosarcoma or other bone sarcomas at the time of resection after preoperative chemotherapy.[121] For patients with confirmed UPS of bone, the median OS for patients with localized disease was 5.2 years compared with 1.7 years for patients with metastatic disease at diagnosis. Importantly, among patients with localized disease, treatment with preoperative doxorubicin and cisplatin was associated with significantly better OS (HR, 0.23). The European Osteosarcoma Intergroup had similar results in studies using doxorubicin and cisplatin preoperatively and postoperatively, with 5-year PFS and OS rates of 56% and 59%, respectively.[122]

Metastatic and Recurrent Disease

Approximately 10% to 20% of patients with osteosarcoma present with metastatic disease. The lung is the most common site of metastasis in osteosarcoma; however, osteosarcoma can also metastasize to almost any bone in the body. Lymph node metastases are rare. Patients who have resectable pulmonary metastases are treated with curative intent with primary chemotherapy, as described earlier, followed by surgical resection of all lesions either at the same time or in staged operations. With this approach, patients have a 15% to 30% chance of long-term DFS and potential cure. Patients with bone or other unresectable metastasis have a poorer prognosis, with therapy usually directed at palliation.

Relapse is seen in about 30% of patients presenting with localized disease and up to 80% of patients who present with primary metastatic disease. Patients with relapsed metastatic or locally recurrent disease are approached similarly to patients with primary metastatic disease with chemotherapy or resection (or both) when possible. Surgery alone is appropriate for patients with resectable lung metastasis and a favorable disease-free interval (typically >1–2 years after initial chemotherapy). This approach yields 5-year survival rate of 25% to 40% for patients who can be rendered surgically free of disease.[123] The prognosis for patients with recurrent unresectable disease remains

exceedingly poor, and treatment is focused on disease control and palliation.[124] Several agents have activity in relapsed or refractory osteosarcoma including ifosfamide alone or in combination with etoposide (IE), gemcitabine in combination with docetaxel, and more recently, VEGF-targeted TKIs. Regorafenib, a multitargeted antiangiogenic TKI, has shown activity in metastatic osteosarcoma in two recent placebo-controlled phase 2 trials. In the French REGOBONE study, 65% of patients treated with regorafenib were progression-free at 8 weeks compared with 0% of those receiving placebo.[125] Findings from the US-led SARC024 study were comparable, with an improvement in PFS (median progression-free survival [mPFS], 3.6 months regorafenib vs 1.7 months placebo).[126] For patients with late recurrences and a favorable initial treatment response, retreatment with a combination of the initial chemotherapy (methotrexate, doxorubicin, cisplatin) can also be considered.

Chondrosarcoma

Chondrosarcomas are resistant to most chemotherapeutic agents used for the treatment of bone sarcomas. Surgical resection is the primary treatment modality, regardless of the grade of the tumor. Patients with conventional chondrosarcoma with unresectable or metastatic disease should be enrolled onto clinical trials, and genomic profiling should be considered for potential target identification. Unlike other chondrosarcoma subtypes, patients with mesenchymal chondrosarcoma and dedifferentiated chondrosarcoma should be treated with multimodality therapy.

Dedifferentiated chondrosarcoma is associated with a low-grade chondrosarcoma component as well as an area of high-grade STS, which may resemble other bone sarcomas.[127] They are associated with a much more aggressive clinical course and generally require urgent treatment to palliate tumor-related symptoms to hopefully extend survival. These tumors may respond to doxorubicin- and cisplatin-based chemotherapy and are treated in a similar manner as those with conventional osteosarcomas, although pathologic tumor necrosis at resection is frequently less than would be expected in conventional osteosarcomas. It is unclear if this measure is of the same prognostic significance as observed with osteosarcomas. Furthermore, tolerance to osteosarcoma regimens is generally less optimal compared with younger patients affected by osteosarcoma. Patients with relapsed or refractory disease should be considered for clinical trials and molecular testing. Approximately 60% of dedifferentiated chondrosarcomas harbor mutations in exon 4 of the *IDH1* gene, which makes IDH oncometabolite inhibitors an attractive option to consider.[128] Interestingly, dedifferentiated chondrosarcomas have been shown to harbor an inflamed phenotype with the presence of CD8+ T-cells and programmed cell death ligand 1 (PD-L1) expression involving the dedifferentiated portions of the tumor samples.[129] In addition, several reports suggest possible efficacy of immune checkpoint inhibitors.[130,131] Clinical trials specific to this rare malignancy are still needed to confirm this activity.

Mesenchymal chondrosarcomas are a rare variant that present in the jaw, spinal column, and ribs with lytic lesions on x-ray examination. The histology consists of a biomorphic appearance of benign to low-grade cartilaginous components with poorly differentiated small cell components.[132] The majority of these tumors harbor a unique *HEY1-NCOA2* fusion, which is thought to affect Notch signaling.[133] Patients with mesenchymal chondrosarcomas typically respond to chemotherapy; a recent series of 54 patients with localized disease treated with combination chemotherapy demonstrated a reduced risk of fracture (HR, 0.482; 95% CI, 0.213–0.996; P =.046) and death (HR, 0.445; 95% CI, 0.256–0.774; P =.004).[134] For this reason, we typically treat patients with mesenchymal chondrosarcoma in a similar fashion as those with Ewing sarcoma. In our experience, responsive tumors typically exhibit more calcification with an associated decrease in FDG avidity (when PET-CT is used for response assessment), and they are less apt to show decreases in tumor size as opposed to Ewing sarcomas, which typically exhibit dramatic volumetric response and reduction in tumor size.

Ewing Sarcoma

Like patients with osteosarcoma, those with Ewing sarcoma and the PNET family of tumors are treated primarily with chemotherapy before surgery because of the high likelihood of micrometastatic disease at the time of diagnosis. These tumors are highly chemosensitive and responsive to the following chemotherapeutic agents: doxorubicin, dactinomycin, ifosfamide, cyclophosphamide, vincristine, and etoposide. The most commonly used combinations are vincristine, doxorubicin, and cyclophosphamide (VAC); IE; and vincristine, doxorubicin, and ifosfamide (VAI). Multiple trials have shown that with these combinations of chemotherapy, survival rates greater than 50% can be achieved. At MDACC, for adult patients with EFT, we typically give vincristine (up to 2 mg) with doxorubicin (75–90 mg/m^2) and ifosfamide (10 g/m^2) as our preferred preoperative chemotherapy regimen. This is followed by surgical resection, if possible, or radiation therapy. Ewing sarcoma is very radiosensitive; often, when surgical resection is not an option or positive margins remain, consolidative radiation therapy

is used. After definitive resection, tumor necrosis is assessed, and postoperative therapy is modified as needed (see Fig. 50–5). In adults with Ewing sarcoma, this approach has yielded favorable outcomes compared with historic control participants.[135] Treatment with VAI was associated with a radiologic response in 84% of patients. Five-year OS was highest for patients with localized disease (68% vs 10%) and those with favorable tumor necrosis after neoadjuvant VAI (5-year OS, 84% for those with ≥95% tumor necrosis vs 53% for those with <95% tumor necrosis). A separate retrospective review of 66 patients from our institution treated with chemotherapy and R0 resection similarly identified histologic response (necrosis ≤95%), radiographic response by RECIST, and metastasis to be independent predictors of outcome.[136]

Metastatic and Recurrent Disease

Patients with metastatic or recurrent Ewing sarcoma are treated in a similar manner as metastatic or recurrent disease in osteosarcoma with chemotherapy being a mainstay of treatment. Patients who have lung metastasis at the time of presentation are treated as outlined earlier with chemotherapy, surgery, and/or radiation with curative intent. Patients with recurrent or metastatic disease after primary therapy are treated on the basis of their disease-free interval, location, and extent of disease. Given its rarity and limited therapeutic options available, we prefer treatment on Ewing sarcoma–specific clinical trials when available. If there is a long disease-free interval (>12 months), retreatment with previous chemotherapeutic regimens, preferably at higher-dose intensity (eg, high-dose ifosfamide), is reasonable. For patients with a shorter interval between therapy and recurrence or metastasis, second-line options include vincristine, irinotecan, and temozolomide or cyclophosphamide with topotecan. Recent studies have evaluated the activity of VEGF-targeted TKIs with varying activity, including pazopanib, regorafenib,[137] and cabozantinib.[138]

Giant Cell Tumor of Bone

Giant cell tumor of bone a rare primary bone malignancy of osteoblastic lineage that often contains osteoclast-like giant cells surrounded by stromal cells. The stromal cells are considered to be the neoplastic cells for this disease that recruit a population of non-neoplastic multinucleated giant cells.[139] This tumor generally involves the ends of long bones, including the distal femur, proximal tibia, and distal radius. Although considered benign, these tumors have a propensity for local recurrence, and approximately 3% metastasize to the lung parenchymal tissue. These tumors may result in pain, swelling, or decreased range of motion. Giant cell tumors appear as lytic, eccentrically located lesions in the epiphyses of a long bone on x-ray imaging. The primary treatment of giant cell tumors of bone consists of surgical intervention, either wide excision or intralesional curettage and cementation. Radiation therapy can be used as primary treatment or after surgery and has been shown to improve local control and DFS but has also been associated with an increased risk of malignant transformation.[140] When the primary location precludes surgical resection because of morbidity or patients develop distant metastatic disease, consideration is given to systemic therapy). Denosumab, an antibody to the receptor activator of nuclear factor kappa-B (RANK) ligand, which inhibits osteoclastic function and increases calcification, has been shown to improve pain in patients with recurrent or metastatic giant cell tumor. In a phase II study of denosumab in unresectable or recurrent giant cell tumor, treatment with denosumab resulted in tumor response in 86% of evaluable patients (defined as elimination of >90% of giant cells or no radiographic progression of target lesion for ≤25 weeks).[141] These results led to an FDA approval of denosumab for treatment of patients with giant cell tumor of bone in adults or skeletally mature adolescents who have unresectable disease or in whom surgery may result in significant morbidity. More recently, denosumab has been used as a neoadjuvant with one open-label phase 2 trial of 222 patients demonstrating native joint preservation in 96% of patients who were planned to have a joint or prosthesis replacement and 86% of patients who were originally planned to have a joint resection or joint fusion.[142] For patients with unresectable disease, we currently use denosumab as a frontline option, though there are still circumstance when we consider embolization or cryoablation on a case-by-case basis.

Follow-up Management

Regular and long-term follow-up is essential for patients with bone sarcoma. Patients are followed at MDACC with radiographs and physical examination every 3 months for the first 2 years, every 4 months for the next 2 years, every 6 months for the next 2 years, and then yearly thereafter. Surveillance includes high-quality chest imaging with either chest radiography or chest CT in high-risk patients, plain films of the primary tumor site to evaluate for recurrence and stability of any prosthesis, and routine laboratory studies. Bone scans, PET-CT scans, or both are useful in patients with specific symptoms or history of bony metastasis but are otherwise not routinely used for surveillance. Monitoring should also include an assessment of the potential late effects of chemotherapy, including anthracycline-induced cardiomyopathy, nephrotoxicity, neuropathy, and secondary malignancies.

MD ANDERSON PRACTICE TIPS

- Successful treatment of patients with soft tissue and bone sarcomas relies on multidisciplinary care, including radiology, pathology, medical, surgical, orthopedic, and radiation oncology. Treatment in experienced large-volume sarcoma centers has been associated with improved outcomes and should be considered when feasible.
- We recommend the use of neoadjuvant or adjuvant chemotherapy with doxorubicin and ifosfamide in patients with high-risk soft tissue sarcoma of the extremity, with the specific risks and benefits assessed for each individual patient.
- Within our center, treatment of stage III soft tissue sarcoma consists of neoadjuvant chemotherapy with doxorubicin and ifosfamide followed by preoperative radiation and surgical resection.
- Anthracyclines in combination with ifosfamide remain the standard frontline therapy for most patients with soft tissue sarcoma. Second-line chemotherapy regimens should be selected based on the histologic subtype and patient-specific factors.
- Treatment of bone sarcomas in adults presents additional challenges compared with the pediatric population. For adults with localized osteosarcoma, we favor neoadjuvant chemotherapy with doxorubicin and cisplatin. Postoperative adjuvant chemotherapy is tailored to histologic response based on percent tumor necrosis. For adults with Ewing sarcoma, we use WAI as frontline therapy.
- Surgical resection should be considered for patients with oligometastatic disease. Aggressive surgical management of pulmonary metastases is associated with improved survival in both soft tissue and bone sarcomas, particularly among patients with a prolonged disease-free interval.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70:7-30.
2. Zahm SH, Fraumeni J. The epidemiology of soft tissue sarcoma. *Semin Oncol*. 1997;24:504-514.
3. Kleinerman RA, Tucker MA, Abramson DH, et al. Risk of soft tissue sarcomas by individual subtype in survivors of hereditary retinoblastoma. *J Natl Cancer Inst*. 2007;99:24-31.
4. Helman LJ, Meltzer P. Mechanisms of sarcoma development. *Nat Rev Cancer*. 2003;3:685-694.
5. Ballinger ML, Goode DL, Ray-Coquard I, et al. Monogenic and polygenic determinants of sarcoma risk: an international genetic study. *Lancet Oncol*. 2016;17:1261-1271.
6. Lazar A, Abruzzo LV, Pollock RE, et al. Molecular diagnosis of sarcomas: chromosomal translocations in sarcomas. *Arch Pathol Lab Med*. 2006;130:1199-1207.
7. Coindre JM, Pelmus M, Hostein I, et al. Should molecular testing be required for diagnosing synovial sarcoma? A prospective study of 204 cases. *Cancer*. 2003;98:2700-2707.
8. de Alava E, Kawai A, Healey JH, et al. EWS-FLI1 fusion transcript structure is an independent determinant of prognosis in Ewing's sarcoma. *J Clin Oncol*. 1998;16:1248-1255.
9. van Doorninck JA, Ji L, Schaub B, et al. Current treatment protocols have eliminated the prognostic advantage of type 1 fusions in Ewing sarcoma: a report from the Children's Oncology Group. *J Clin Oncol*. 2010;28:1989.
10. Stegmaier S, Poremba C, Schaefer KL, et al. Prognostic value of PAX–FKHR fusion status in alveolar rhabdomyosarcoma: a report from the cooperative soft tissue sarcoma study group (CWS). *Pediatr Blood Cancer*. 2011;57:406-414.
11. Doebele RC, Davis LE, Vaishnavi A, et al. An oncogenic NTRK fusion in a patient with soft-tissue sarcoma with response to the tropomyosin-related kinase inhibitor LOXO-101. *Cancer Discov*. 2015;5:1049-1057.
12. Folpe AL, Lyles RH, Sprouse JT, et al. (F-18) fluorodeoxyglucose positron emission tomography as a predictor of pathologic grade and other prognostic variables in bone and soft tissue sarcoma. *Clin Cancer Res*. 2000;6:1279-1287.
13. Herrmann K, Benz MR, Czernin J, et al. 18F-FDG-PET/CT Imaging as an early survival predictor in patients with primary high-grade soft tissue sarcomas undergoing neoadjuvant therapy. *Cancer Res*. *Clin Cancer Res*. 2012;18:2024-2031.
14. Kilpatrick SE, Cappellari JO, Bos GD, et al. Is fine-needle aspiration biopsy a practical alternative to open biopsy for the primary diagnosis of sarcoma? Experience with 140 patients. *Am J Clin Pathol*. 2001;115:59-68.
15. Moch, Holger. "Soft Tissue and Bone Tumours WHO Classification of Tumours/Volume 3." *WHO Classification of Tumours* 3 (2020).
16. Guillou L, Coindre JM, Bonichon F, et al. Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 adult patients with soft tissue sarcoma. *J Clin Oncol*. 1997;15:350-362.
17. Amin M, Edge S, Greene F, eds. *AJCC Cancer Staging Manual*. 8th edition. Springer; 2017.
18. Coindre JM, Terrier P, Guillou L, et al. Predictive value of grade for metastasis development in the main histologic types of adult soft tissue sarcomas: a study of 1240 patients from the French Federation of Cancer Centers Sarcoma Group. *Cancer*. 2001;91:1914-1926.
19. Callegaro D, Miceli R, Bonvalot S, et al. Development and external validation of two nomograms to predict overall survival and occurrence of distant metastases in adults after surgical resection of localised soft-tissue sarcomas of the extremities: a retrospective analysis. *Lancet Oncol*. 2016;17:671-680.
20. Gronchi A, Miceli R, Shurell E, et al. Outcome prediction in primary resected retroperitoneal soft tissue sarcoma: histology-specific overall survival and disease-free survival nomograms built on major sarcoma center data sets. *J Clin Oncol*. 2013;31:1649-1655.
21. Behranwala KA, A'Hern R, Omar A-M, Thomas JM. Prognosis of lymph node metastasis in soft tissue sarcoma. *Ann Surg Oncol*. 2004;11:714-719.
22. Zagars GK, Ballo MT, Pisters PW, et al. Prognostic factors for patients with localized soft-tissue sarcoma treated with conservation surgery and radiation therapy: an analysis of 1225 patients. *Cancer*. 2003;97:2530-2543.
23. Zagars GK, Ballo MT, Pisters PW, et al. Preoperative vs. postoperative radiation therapy for soft tissue sarcoma: a retrospective comparative evaluation of disease outcome. *Int J Radiat Oncol Biol Phys*. 2003;56:482-488.
24. Weber DC, Malyapa R, Albertini F, et al. Long term outcomes of patients with skull-base low-grade chondrosarcoma and chordoma patients treated with pencil beam scanning proton therapy. *Radiother Oncol*. 2016;120:169-174.
25. Leiser D, Calaminus G, Malyapa R, et al. Tumour control and quality of life in children with rhabdomyosarcoma treated with pencil beam scanning proton therapy. *Radiother Oncol*. 2016;120:163-168.
26. Alektiar KM, Velasco J, Zelefsky MJ, et al. Adjuvant radiotherapy for margin-positive high-grade soft tissue sarcoma of the extremity. *Int J Radiat Oncol Biol Phys*. 2000;48:1051-1058.
27. Folkert MR, Singer S, Brennan MF, et al. Comparison of local recurrence with conventional and intensity-modulated radiation therapy for primary soft-tissue sarcomas of the extremity. *J Clin Oncol*. 2014;32:3236.
28. National Comprehensive Cancer Network. Clinical practice guidelines in oncology (NCCN guidelines) soft tissue sarcoma version 2.National Comprehensive Cancer Network; 2019. 2020.
29. Slater JD, McNeese MD, Peters LJ. Radiation therapy for unresectable soft tissue sarcomas. *Int J Radiat Oncol Biol Phys*. 1986;12:1729-1734.
30. Farooqi A, Mitra D, Guadagnolo BA, Bishop AJ. The evolving role of radiation therapy in patients with metastatic soft tissue sarcoma. *Curr Oncol Rep*. 2020;22:1-8.
31. Ning MS, Deegan BJ, Ho JC, et al. Low incidence of late failure and toxicity after spine stereotactic radiosurgery: secondary analysis of phase I/II trials with long-term follow-up. *Radiother Oncol*. 2019;138:80-85.
32. O'Bryan RM, Baker LH, Gottlieb JE, et al. Dose response evaluation of adriamycin in human neoplasia. *Cancer*. 1977;39:1940-1948.
33. Patel SR, Vadhan-Raj S, Papadopolous N, et al. High-dose ifosfamide in bone and soft tissue sarcomas: results of phase II and pilot studies—dose-response and schedule dependence. *J Clin Oncol*. 1997;15:2378-2384.
34. Patel SR, Vadhan-Raj S, Burgess MA, et al. Results of two consecutive trials of dose-intensive chemotherapy with doxorubicin and ifosfamide in patients with sarcomas. *Am J Clin Oncol*. 1998;21:317-321.
35. Judson I, Verweij J, Gelderblom H, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. *Lancet Oncol*. 2014;15:415-423.
36. Elias A, Ryan L, Sulkes A, et al. Response to mesna, doxorubicin, ifosfamide, and dacarbazine in 108 patients with metastatic or unresectable sarcoma and no prior chemotherapy. *J Clin Oncol*. 1989;7:1208-1216.
37. Vadhan-Raj S, Patel S, Burgess M. Phase II trial of adriamycin (A), ifosfamide (I), mesna (M) uroprotection, cadarbazine (D) (MAID) with pixy321 (GM-CSF/IL-3 fusion protein) or G-CSF in patients (pts) with soft tissue sarcoma (STS). *Proc Am Soc Clin Oncol*. 1996;15:525.

38. D'Ambrosio L, Touati N, Blay JY, et al. Doxorubicin plus dacarbazine, doxorubicin plus ifosfamide, or doxorubicin alone as a first-line treatment for advanced leiomyosarcoma: a propensity score matching analysis from the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. *Cancer*. 2020;126(11):2637-2647.
39. Patel SR, Gandhi V, Jenkins J, et al. Phase II clinical investigation of gemcitabine in advanced soft tissue sarcomas and window evaluation of dose rate on gemcitabine triphosphate accumulation. *J Clin Oncol*. 2001;19:3483-3489.
40. Maki RG, Wathen JK, Patel SR, et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002 [corrected]. *J Clin Oncol*. 2007;25:2755-2763.
41. Di Giandomenico S, Frapolli R, Bello E, et al. Mode of action of trabectedin in myxoid liposarcomas. *Oncogene*. 2014;33:5201-5210.
42. Demetri GD, Chawla SP, von Mehren M, et al. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules. *J Clin Oncol*. 2019;27:4188-4196.
43. Demetri GD, von Mehren M, Jones RL, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. *J Clin Oncol*. 2016;34:786.
44. Ratan R, Patel SR. Trabectedin and eribulin: where do they fit in the management of soft tissue sarcoma? *Curr Treat Options Oncol*. 2017;18:34.
45. Schöffski P, Chawla S, Maki RG, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. *Lancet*. 2016;387:1629-1637.
46. Demetri GD, Schöffski P, Grignani G, et al. Activity of eribulin in patients with advanced liposarcoma demonstrated in a subgroup analysis from a randomized phase III study of eribulin versus dacarbazine. *J Clin Oncol*. 2017;35:3433-3439.
47. Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. *Lancet*. 1997;350:1647-1654.
48. Pasquali S, Pizzamiglio S, Touati N, et al. The impact of chemotherapy on survival of patients with extremity and trunk wall soft tissue sarcoma: revisiting the results of the EORTC-STBSG 62931 randomised trial. *Eur J Cancer*. 2019;109:51-60.
49. Gronchi A, Ferrari S, Quagliuolo V, et al. Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial. *Lancet Oncol*. 2017;18:812-822.
50. Sleijfer S, Ray-Coquard I, Papai Z, et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European Organisation for Research and Treatment of Cancer–Soft Tissue and Bone Sarcoma Group (EORTC study 62043. *J Clin Oncol*. 2009;27:3126-3132.
51. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2012;379:1879-1886.
52. Ratan R, Patel SR. Chemotherapy for soft tissue sarcoma. *Cancer*. 2016;122:2952-2960.
53. Mentzel T, Beham A, Calonje E, et al. Epithelioid hemangioendothelioma of skin and soft tissues: clinicopathologic and immunohistochemical study of 30 cases. *Am J Surg Pathol*. 1997;21:363-374.
54. Agulnik M, Yarber JL, Okuno SH, et al. An open-label, multicenter, phase II study of bevacizumab for the treatment of angiosarcoma and epithelioid hemangioendotheliomas. *Ann Oncol*. 2013;24:257-263.
55. Ray-Coquard I, Italiano A, Bompas E, et al. Sorafenib for patients with advanced angiosarcoma: a phase II trial from the French Sarcoma Group (GSF/GETO). *Oncologist*. 2012;17:260.
56. Torres KE, Ravi V, Kin K, et al. Long-term outcomes in patients with radiation-associated angiosarcomas of the breast following surgery and radiotherapy for breast cancer. *Ann Surg Oncol*. 2013;20:1267-1274.
57. Fury MG, Antonescu CR, Van Zee KJ, et al. A 14-year retrospective review of angiosarcoma: clinical characteristics, prognostic factors, and treatment outcomes with surgery and chemotherapy. *Cancer J*. 2005;11:241-247.
58. Skubitz KM, Haddad PA. Paclitaxel and pegylated-liposomal doxorubicin are both active in angiosarcoma. *Cancer*. 2005;104:361-366.
59. Italiano A, Cioffi A, Penel N, et al. Comparison of doxorubicin and weekly paclitaxel efficacy in metastatic angiosarcomas. *Cancer*. 2012;118:3330-3336.
60. Stacchiotti S, Palassini E, Sanfilippo R, et al. Gemcitabine in advanced angiosarcoma: a retrospective case series analysis from the Italian Rare Cancer Network. *Ann Oncol*. 2012;23:501-508.
61. Lu HJ, Chen PC, Yen CC, et al. Refractory cutaneous angiosarcoma successfully treated with sunitinib. *Br J Dermatol*. 2013;169:204-206.
62. Maki RG, D'Adamo DR, Keohan ML, et al. Phase II study of sorafenib in patients with metastatic or recurrent sarcomas. *J Clin Oncol*. 2009;27:3133.
63. Farid M, Ong WS, Tan MH, et al. The influence of primary site on outcomes in leiomyosarcoma: a review of clinicopathologic differences between uterine and extrauterine disease. *Am J Clin Oncol*. 2013;36:368-374.
64. Sleijfer S, Ouali M, van Glabbeke M, et al. Prognostic and predictive factors for outcome to first-line ifosfamide-containing chemotherapy for adult patients with advanced soft tissue sarcomas: an exploratory, retrospective analysis on large series from the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG). *Eur J Cancer*. 2010;46:72-83.
65. Pautier P, Floquet A, Penel N, et al. Randomized multicenter and stratified phase II study of gemcitabine alone versus gemcitabine and docetaxel in patients with metastatic or relapsed leiomyosarcomas: a Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) French Sarcoma Group Study (TAXOGEM study). *Oncologist*. 2012;17:1213.
66. O'Cearbhaill R, Zhou Q, Iasonos A, et al. Treatment of advanced uterine leiomyosarcoma with aromatase inhibitors. *Gynecol Oncol*. 2010;116:424-429.
67. Kilpatrick SE, Doyon J, Choong PF, et al. The clinicopathologic spectrum of myxoid and round cell liposarcoma: a study of 95 cases. *Cancer*. 1996;77:1450-1458.
68. Riggi N, Cironi L, Provero P, et al. Expression of the FUS-CHOP fusion protein in primary mesenchymal progenitor cells gives rise to a model of myxoid liposarcoma. *Cancer Res*. 2006;66:7016-7023.
69. Le Cesne A, Blay JY, Judson I, et al. Phase II study of ET-743 in advanced soft tissue sarcomas: a European Organisation for the Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group trial. *J Clin Oncol*. 2005;23:576-584.
70. Italiano A, Toulmonde M, Cioffi A, et al. Advanced well-differentiated/dedifferentiated liposarcomas: role of chemotherapy and survival. *Ann Oncol*. 2012;23:1601-1607.
71. Livingston JA, Bugano D, Barbo A, et al. Role of chemotherapy in dedifferentiated liposarcoma of the retroperitoneum:

defining the benefit and challenges of the standard. *Sci Rep*. 2017;7:1-8.
72. Portera CA Jr, Ho V, Patel SR, et al. Alveolar soft part sarcoma: clinical course and patterns of metastasis in 70 patients treated at a single institution. *Cancer*. 2001;91:585-591.
73. Judson I, Morden JP, Kilburn L, et al. Cediranib in patients with alveolar soft-part sarcoma (CASPS): a double-blind, placebo-controlled, randomised, phase 2 trial. *Lancet Oncol*. 2019;20:1023-1034.
74. Stacchiotti S, Negri T, Zaffaroni N, et al. Sunitinib in advanced alveolar soft part sarcoma: evidence of a direct antitumor effect. *Ann Oncol*. 2011;22:1682-1690.
75. Conley AP, Trinh VA, Zobniw CM, et al. Positive tumor response to combined checkpoint inhibitors in a patient with refractory alveolar soft part sarcoma: a case report. *J Glob Oncol*. 2018;4:1-6.
76. Wilky BA, Trucco MM, Subhawong TK, et al. Axitinib plus pembrolizumab in patients with advanced sarcomas including alveolar soft-part sarcoma: a single-centre, single-arm, phase 2 trial. *Lancet Oncol*. 2019;20:837-848.
77. Salah S, Lewin JH, Davidson S, et al. Immunoprofiling in alveolar soft part sarcoma. *J Clin Oncol*. 2017;35(15 suppl):11059.
78. Tap WD, Gelderblom H, Palmerini E, et al. Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised phase 3 trial. *Lancet*. 2019;394:478-487.
79. Patel SR, Zagars GK, Pisters PW. The follow-up of adult soft-tissue sarcomas. *Semin Oncol*. 2013;30:413-416.
80. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. *Hum Pathol*. 2002;33:459-465.
81. Kindblom LG, Remotti HE, Aldenborg F, et al. Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. *Am J Pathol*. 1998;152:1259-1269.
82. DeMatteo RP, Lewis JJ, Leung D, et al. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg*. 2000;231:51-58.
83. Blanke CD, Demetri GD, von Mehren M, et al. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. *J Clin Oncol*. 2008;26:620-625.
84. Corless CL, Barnett CM, Heinrich MC. Gastrointestinal stromal tumours: origin and molecular oncology. *Nat Rev Cancer*. 2011;11:865-878.
85. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med*. 2002;347:472-480.
86. Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. *Lancet*. 2004;364:1127-1134.
87. Blanke CD, Rankin C, Demetri GD, et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. *J Clin Oncol*. 2008;26:626-632.
88. Heinrich MC, Owzar K, Corless CL, et al. Correlation of kinase genotype and clinical outcome in the North American Intergroup phase III trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 study by Cancer and Leukemia Group B and Southwest Oncology Group. *J Clin Oncol*. 2008;26:5360-5367.
89. Le Cesne A, Ray-Coquard I, Bui BN, et al. Discontinuation of imatinib in patients with advanced gastrointestinal stromal tumours after 3 years of treatment: an open-label multicentre randomised phase 3 trial. *Lancet Oncol*. 2010;11:942-949.
90. Dematteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2009;373:1097-1104.
91. Joensuu H, Eriksson M, Sundby Hall K, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. *JAMA*. 2012;307:1265-1272.
92. Raut CP, Espat NJ, Maki RG, et al. Efficacy and tolerability of 5-year adjuvant imatinib treatment for patients with resected intermediate-or high-risk primary gastrointestinal stromal tumor: the PERSIST-5 clinical trial. *JAMA Oncol*. 2018;4:e184060-e184060.
93. Antonescu CR, Besmer P, Guo T, et al. Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. *Clin Cancer Res*. 2005;11:4182-4190.
94. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet*. 2006;368:1329-1338.
95. Heinrich MC, Maki RG, Corless CL, et al. Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. *J Clin Oncol*. 2008;26:5352-5359.
96. Sawaki A, Nishida T, Doi T, et al. Phase 2 study of nilotinib as third-line therapy for patients with gastrointestinal stromal tumor. *Cancer*. 2011;117:4633-4641.
97. George S, Wang Q, Heinrich MC, et al. Efficacy and safety of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of imatinib and sunitinib: a multicenter phase II trial. *J Clin Oncol*. 2012;30(19):2401-2407.
98. Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381:295-302.
99. Heinrich MC, Jones RL, von Mehren M, et al. Avapritinib in advanced PDGFRA D842V-mutant gastrointestinal stromal tumour (NAVIGATOR): a multicentre, open-label, phase 1 trial. *Lancet Oncol*. 2020;21:935-946.
100. McAuliffe JC, Hunt KK, Lazar AJ, et al. A randomized, phase II study of preoperative plus postoperative imatinib in GIST: evidence of rapid radiographic response and temporal induction of tumor cell apoptosis. *Ann Surg Oncol*. 2009;16:910-919.
101. Choi H, Charnsangavej C, Faria SC, et al. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. *J Clin Oncol*. 2007;25:1753-1759.
102. Benjamin RS, Choi H, Macapinlac HA, et al. We should desist using RECIST, at least in GIST. *J Clin Oncol*. 2007;25:1760-1764.
103. Adams SC, Potter BK, Pitcher DJ, Temple HT. Office-based core needle biopsy of bone and soft tissue malignancies: an accurate alternative to open biopsy with infrequent complications. *Clin Orthop Relat Res*. 2010;468:2774-2780.
104. Kopp LM, Hu C, Rozo B, et al. Utility of bone marrow aspiration and biopsy in initial staging of Ewing sarcoma. *Pediatr Blood Cancer*. 2015;62:12-15.
105. Costelloe CM, Chuang HH, Madewell JE. FDG PET/CT of primary bone tumors. *AJR Am J Roentgenol*. 2014;202:W521-W531.
106. Hawkins DS, Schuetze SM, Butrynski JE, et al. [18F] Fluorodeoxyglucose positron emission tomography predicts outcome for Ewing sarcoma family of tumors. *J Clin Oncol*. 2005;23:8828-8834.
107. Hawkins DS, Conrad EU 3rd, Butrynski JE, et al. [F-18]-fluorodeoxy-D-glucose–positron emission tomography response is

associated with outcome for extremity osteosarcoma in children and young adults. *Cancer*. 2009;115:3519-3525.
108. Brenner W, Bohuslavizki KH, Eary JF. PET imaging of osteosarcoma. *J Nucl Med*. 2003;44:930-942.
109. Wu C-C, Livingston JA. Genomics and the immune landscape of osteosarcoma. In: *Current Advances in the Science of Osteosarcoma*. Springer; 2020:21-36.
110. Amary MF, Bacsi K, Maggiani F, et al. IDH1 and IDH2 mutations are frequent events in central chondrosarcoma and central and periosteal chondromas but not in other mesenchymal tumours. *J Pathol*. 2011;224:334-343.
111. Kerr DA, Lopez HU, Deshpande V, et al. Molecular distinction of chondrosarcoma from chondroblastic osteosarcoma through IDH1/2 mutations. *Am J Surg Pathol*. 2013;37:787-795.
112. Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. *Clin Orthop Relat Res*, 1980;153:106-120.
113. Heck RK Jr, Stacy GS, Flaherty MJ, et al. A comparison study of staging systems for bone sarcomas. *Clin Orthop Relat Res*. 2003;415:64-71.
114. Jaffe N, Patel SR, Benjamin RS. Chemotherapy in osteosarcoma. Basis for application and antagonism to implementation; early controversies surrounding its implementation. *Hematol Oncol Clin North Am*. 1995;9:825-840.
115. Benjamin RS, Patel S.. Pediatric and adult osteosarcoma: comparisons and contrasts in presentation and therapy. In: *Pediatric and Adolescent Osteosarcoma*. Springer; 2010:355-363.
116. Benjamin R, Wagner M, Livingston J, et al. Chemotherapy for bone sarcomas in adults: the MD Anderson experience. Paper presented at: *American Society of Clinical Oncology Meeting*; 2015;e656-e660.
117. Raymond AK, Chawla SP, Carrasco CH, et al. Osteosarcoma chemotherapy effect: a prognostic factor. *Semin Diagn Pathol*. 1987;4:212-236.
118. Wagner MJ, Livingston JA, Patel SR Benjamin RS. Chemotherapy for bone sarcoma in adults. *J Oncol Pract*. 2016;12:208-216.
119. Marina NM, Smeland S, Bielack SS, et al. Comparison of MAPIE versus MAP in patients with a poor response to preoperative chemotherapy for newly diagnosed high-grade osteosarcoma (EURAMOS-1): an open-label, international, randomised controlled trial. *Lancet Oncol*. 2016;17:1396-1408.
120. Guadagnolo BA, Zagars GK, Raymond AK, et al. Osteosarcoma of the jaw/craniofacial region: outcomes after multimodality treatment. *Cancer*. 2009;115:3262-3270.
121. Livingston JA, Posey K, Wang WL, et al. Chemotherapy in the treatment of high grade undifferentiated pleomorphic sarcoma of bone. Paper presented at: CTOS Annual Meeting Rome, Italy; 2018.
122. Bramwell VH, Steward WP, Nooij M, et al. Neoadjuvant chemotherapy with doxorubicin and cisplatin in malignant fibrous histiocytoma of bone: a European Osteosarcoma Intergroup study. *J Clin Oncol*. 1999;17:3260-3269.
123. Bielack SS, Kempf-Bielack B, Branscheid D, et al. Second and subsequent recurrences of osteosarcoma: presentation, treatment, and outcomes of 249 consecutive cooperative osteosarcoma study group patients. *J Clin Oncol*. 2009;27:557-565.
124. Lagmay JP, Krailo MD, Dang H, et al. Outcome of patients with recurrent osteosarcoma enrolled in seven phase II trials through children's cancer group, pediatric oncology group, and children's oncology group: learning from the past to move forward. *J Clin Oncol*. 2016;34:3031-3038.
125. Duffaud F, Mir O, Boudou-Rouquette P, et al. Efficacy and safety of regorafenib in adult patients with metastatic osteosarcoma: a non-comparative, randomised, double-blind, placebo-controlled, phase 2 study. *Lancet Oncol*. 2019;20:120-133.
126. Davis LE, Bolejack V, Ryan CW, et al. Randomized double-blind phase II study of regorafenib in patients with metastatic osteosarcoma. *J Clin Oncol*. 2019;37:1424-1431.
127. Frassica FJ, Unni KK, Beabout JW, Sim FH. Dedifferentiated chondrosarcoma. A report of the clinicopathological features and treatment of seventy-eight cases. *J Bone Joint Surg Am*. 1986;68:1197-1205.
128. Schaap FG, French PJ, Bovée JV. Mutations in the isocitrate dehydrogenase genes IDH1 and IDH2 in tumors. *Adv Anat Pathol*. 2013;20:32-38.
129. Kostine M, Cleven AH, de Miranda NF, et al. Analysis of PD-L1, T-cell infiltrate and HLA expression in chondrosarcoma indicates potential for response to immunotherapy specifically in the dedifferentiated subtype. *Mod Pathol*. 2016;29:1028-1037.
130. Paoluzzi L, Cacavio A, Ghesani M, et al. Response to anti-PD1 therapy with nivolumab in metastatic sarcomas. *Clin Sarcoma Res*. 2016;6:24.
131. Tawbi HA, Burgess M, Bolejack V, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. *Lancet Oncol*. 2017;18:1493-1501.
132. Nakashima Y, Unni KK, Shives TC, et al. Mesenchymal chondrosarcoma of bone and soft tissue. A review of 111 cases. *Cancer*. 1986;57:2444-2453.
133. Wang L, Motoi T, Khanin R, et al. Identification of a novel, recurrent HEY1-NCOA2 fusion in mesenchymal chondrosarcoma based on a genome-wide screen of exon-level expression data. *Genes Chromosomes Cancer*. 2012;51:127-139.
134. Frezza AM, Cesari M, Baumhoer D, et al. Mesenchymal chondrosarcoma: prognostic factors and outcome in 113 patients. A European Musculoskeletal Oncology Society study. *Eur J Cancer*. 2015;51(3):374-381.
135. Wagner MJ, Gopalakrishnan V, Ravi V, et al. Vincristine, ifosfamide, and doxorubicin for initial treatment of Ewing sarcoma in adults. *Oncologist*. 2017;22:1271.
136. Pan HY, Morani A, Wang WL, et al. Prognostic factors and patterns of relapse in Ewing sarcoma patients treated with chemotherapy and R0 resection. *Radiat Oncol Biol Phys*. 2015;;92(2):349-357.
137. Attia S, Bolejack V, Ganjoo KN, et al. A phase II trial of regorafenib (REGO) in patients (pts) with advanced Ewing sarcoma and related tumors (EWS) of soft tissue and bone: SARC024 trial results. *J Clin Oncol*. 2017;35(15 suppl):11005.
138. Italiano A, Mir O, Mathoulin-Pelissier S, et al. Cabozantinib in patients with advanced Ewing sarcoma or osteosarcoma (CABONE): a multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2020;21:446-455.
139. Huang L, Xu J, Wood DJ, Zheng MH. Gene expression of osteoprotegerin ligand, osteoprotegerin, and receptor activator of NF-κB in giant cell tumor of bone: possible involvement in tumor cell-induced osteoclast-like cell formation. *Am J Pathol*. 2000;156:761-767.
140. Bhatia S, Miszczyk L, Roelandts M, et al. Radiotherapy for marginally resected, unresectable or recurrent giant cell tumor of the bone: a rare cancer network study. *Rare Tumors*. 2011;3(4):e48.
141. Thomas D, Henshaw R, Skubitz K, et al. Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study. *Lancet Oncol*. 2020;11:275-280.
142. Rutkowski P, Ferrari S, Grimer RJ, et al. Surgical downstaging in an open-label phase II trial of denosumab in patients with giant cell tumor of bone. *Ann Surg Oncol*. 2015;22:2860-2868.

This page intentionally left blank

Section XIII

Other Tumors and Cancer Topics of Interest

Section Editor: Alyssa G. Rieber

51 Endocrine Malignancies

52 The Acquired Immunodeficiency Syndrome–Related Cancers

53 Carcinoma of Unknown Primary

54 Pediatric Cancers

55 Cancer Genomics

56 Immuno-Oncology

57 Targeted Therapy in Cancer

58 Viral Infections in Patients with Cancer

59 Fungal Infections in Patients with Cancer

60 Endocrine and Metabolic Complications of Cancer Therapy

61 Oncologic Emergencies

62 Oncocardiology

63 Pulmonary Complications of Cancer Therapy

64 Cancer-Associated Thrombosis

This page intentionally left blank

51 Endocrine Malignancies

Ha Nguyen
Mouhammed Amir Habra

KEY CONCEPTS

- Thyroid carcinoma is the most common endocrine malignancy. Recent advances in molecular profiling identified actionable mutations, leading to the availability of multiple FDA-approved drugs. The current treatments target angiogenesis (sorafenib and lenvatinib) or can be mutation specific (larotrectinib targeting *NTRK* gene fusion and selpercatinib targeting *RET* gene fusions).
- Anaplastic thyroid carcinoma (ATC) has very poor prognosis, but the clinical outcomes appear to be improving with a multidisciplinary approach utilizing targeted therapy, immunotherapy, radiotherapy, and surgery when feasible.
- In cases with suspected parathyroid carcinoma, comprehensive surgery by an experienced team remains the mainstay of therapy, although the role of adjuvant radiation and targeted therapy remains unclear.
- Genetic counseling and testing is needed in all cases of pheochromocytoma/paraganglioma, even in the absence of family history of these tumors
- The management of metastatic pheochromocytoma/paraganglioma should be in the context of a multidisciplinary and experienced team. Resection of the primary tumor when feasible is associated with improved outcome. Iobenguane I 131 is FDA approved for patients with metastatic pheochromocytoma/paraganglioma that retain metaiodobenzylguanidine avidity, whereas traditional cytotoxic chemotherapy can be offered to select patients with rapidly progressing disease, especially in the presence of excess catecholamines. The role of targeted therapy is evolving, and extreme care must be exerted when using these drugs in patients with metastatic pheochromocytoma because they could exacerbate preexisting hypertension.
- The combined use of mitotane with cytotoxic chemotherapy (etoposide, doxorubicin, cisplatin) is associated with a suboptimal response rate of 23% and represents the first-line systemic therapy in advanced adrenocortical carcinoma. Single-agent immune checkpoint inhibitors are associated with lower response rates based on small clinical trials.

THYROID CANCER

Introduction

Thyroid cancer is the most common endocrine malignancy. The incidence of thyroid cancer in the United States has slightly declined over the past 5 years and in 2020, approximately 52,890 new cases of thyroid carcinoma were estimated to be diagnosed in the United States, accounting for 3% of all new malignancies, with women accounting for almost 76% of all cases.[1] Thyroid cancer occurs less frequently in children compared with adults, with a peak incidence of around 50 years. Despite this, overall long-term survival remains favorable. Histologic types (Table 51–1) include those that derive from the follicular epithelial cells (papillary and follicular), which account for the majority of thyroid cancers, and from the parafollicular C cells (medullary). Other thyroid tumors, including primary lymphomas of the thyroid, which are usually metastases from other primary sites, are also rarely encountered.

EVALUATION OF SOLITARY THYROID NODULES

Introduction

Thyroid cancer usually presents as a nodule identified on physical examination or discovered incidentally on imaging studies performed for unrelated reasons.

Table 51–1 Types of Thyroid Cancer

Type	Frequency	Prognosis (10-year Overall Survival)
Originating From Follicular Cells		
Papillary	80%	93%
Follicular	11%	85%
Hürthle cell	3%	76%
Anaplastic (undifferentiated)	2%	14%
Originating From C Cells		
Medullary	4%	75%

Data from Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995. *Cancer*. 1998;83(12):2638-2648.

However, most thyroid nodules are benign, with about 10% to 15% found to be malignant on biopsy.[2] The main diagnostic challenge is accurately differentiating benign from malignant disease to ensure appropriate definitive therapy and avoid unnecessary treatments.

Diagnosis

Clinically palpable nodules are found in approximately 5% of the population. With widespread use of different imaging modalities, thyroid nodules are reported to appear in up to 60% of the population.[3] Benign and malignant nodules are almost always clinically indistinguishable. Features indicating increased likelihood of carcinoma are summarized in Table 51–2. Initial evaluation and treatment of patients presenting with thyroid nodules is detailed in Fig. 51–1.

Thyroid ultrasonography (US) with fine-needle aspiration (FNA) and cytologic examination is the modality of choice for evaluating nodules with suspicious characteristics. Papillary, medullary, and anaplastic carcinomas can be readily diagnosed by FNA or biopsy, but distinguishing benign from malignant follicular lesions proves to be more difficult. Histologic examination showing capsular or vascular invasion is necessary to classify a lesion as malignant. Because follicular adenoma and carcinoma cannot be differentiated cytologically, they are grouped as "indeterminate or suspicious follicular neoplasms." The rate of carcinoma for suspicious follicular neoplasms is about 20%. The incidence of malignancy increases with larger nodule size, male sex, and increasing age. Testing for molecular markers should be considered for patients with indeterminate or suspicious follicular neoplasm on cytology.[4,5] Five percent to 10% of the time, the FNA will yield "inadequate diagnostic material," and this necessitates repeat aspiration. The majority (85%–95%) of thyroid nodules are benign. Radionuclide scans usually show malignant lesions as hypofunctioning or "cold," although 85% of "cold" nodules are still benign.

Table 51–2 Clinical Features Associated with Increased Risk of Malignancy

Age <20 years
Presence of cervical lymphadenopathy
History of radiation to the head and neck during childhood
Family history of medullary thyroid cancer or MEN types 2A and 2B
Hard, fixed nodule
Recent nodule growth
Hoarseness of voice (indicating invasion of recurrent laryngeal nerve)

MEN, multiple endocrine neoplasia.

DIFFERENTIATED THYROID CANCER

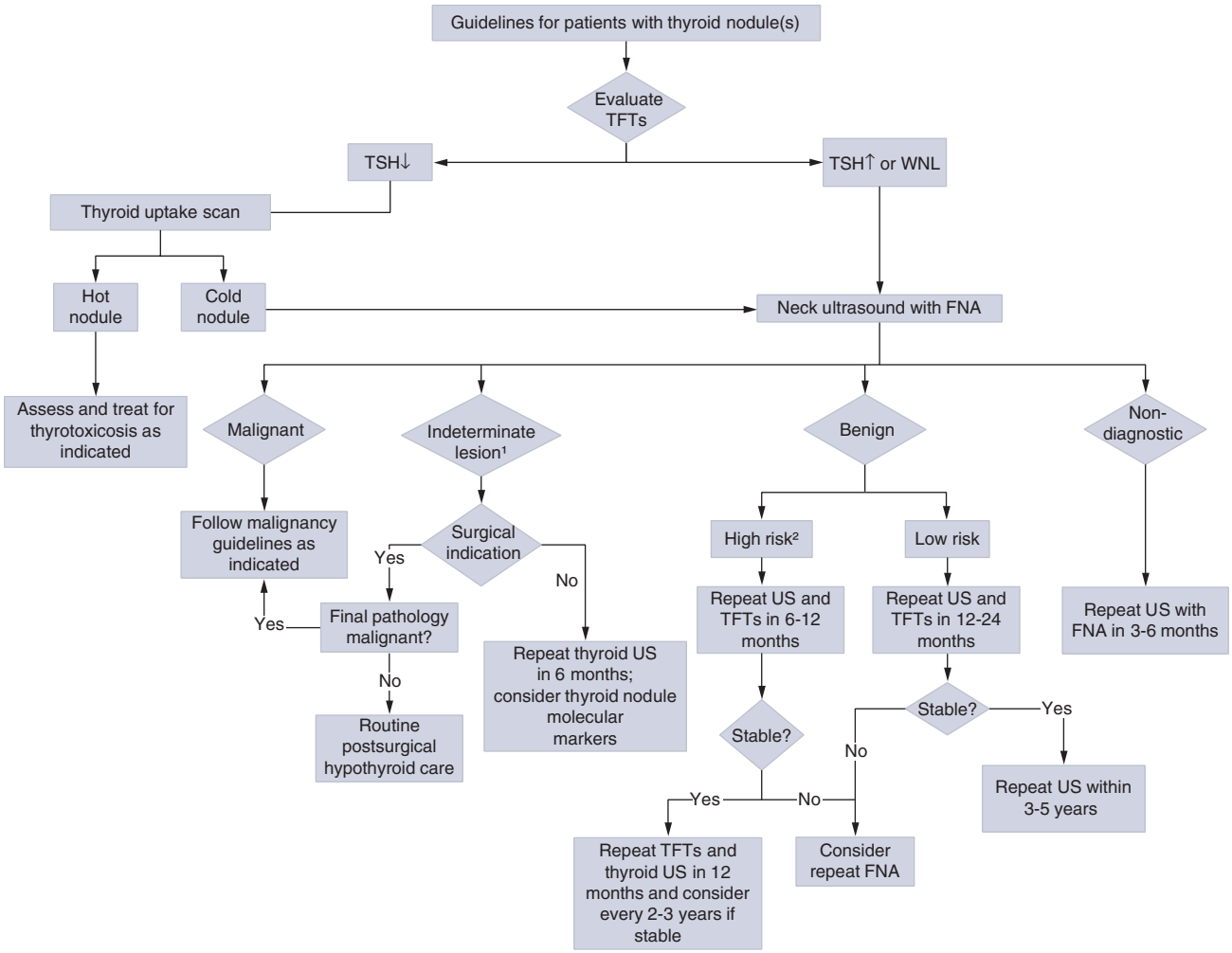
Introduction

Differentiated thyroid cancer (DTC) includes papillary, follicular, and poorly differentiated histology types and comprises about 90% of all thyroid cancers. The factors associated with increased risk of thyroid carcinoma are summarized in Table 51–3.

Traditionally, exposure to ionizing radiation, family history, and genetic syndromes have been the main risks associated with DTC.[6] In addition, a meta-analysis of 21 observational studies suggests an association with obesity (adjusted relative risk [RR] 1.33; 95% CI 1.24–1.42).[7] On average, thyroid tumors can be recognized 10 years after radiation exposure, but can be seen for as long as 30 years. Malignancy occurs in up to 30% of cases with head or neck irradiation. Exposure to external sources of radiation after the Chernobyl nuclear accident led to a three- to 75-fold increase in the incidence of papillary thyroid carcinoma (PTC) in fallout regions, especially in younger children.[6] Familial PTC is reported in 5% of all patients with PTC and may portend a more aggressive disease course. In addition, DTC has also been associated with other tumors, particularly breast and renal cancers.[8]

Pathogenesis

Understanding the follicular cell tumorigenesis pathways is central to the development of novel therapies to treat thyroid cancer. The MAPK pathway is the main oncogenic propagator of PTC. *BRAF* and *RAS* genes in this pathway normally code for growth and function in normal and tumor cells. Chromosomal rearrangements of the gene encoding the transmembrane



[1]Includes: suspicious for papillary, follicular neoplasm or lesion, Hürthle cell neoplasm, or lesion or atypical cells of undetermined significance.
[2]History of radiation exposure to the head and neck or family history of thyroid cancer.

FIGURE 51–1 Evaluation of thyroid nodules. FNA, fine-needle aspiration; TFT, thyroid function test; TSH, thyroid-stimulating hormone; US, ultrasound; WNL, within normal limits.

Table 51–3 Risk Factors Associated with Differentiated Thyroid Carcinoma

Exposure to ionizing radiation, especially during childhood
Familial adenomatous polyposis (Gardner syndrome)
Carney complex
Werner syndrome
Cowden syndrome (phosphatase and tensin homolog [PTEN]-hamartoma tumor syndrome)
Pendred syndrome
Familial papillary thyroid cancer

Data from Nose V. Familial follicular cell tumors: classification and morphological characteristics. *Endocr Pathol.* 2010;21(4):219-226; and Ivanov VK, Kashcheev VV, Chekin SY, et al. Radiation-epidemiological studies of thyroid cancer incidence in Russia after the Chernobyl accident (estimation of radiation risks, 1991-2008 follow-up period). *Radiat Prot Dosimetry.* 2012;151(3):489-499.

tyrosine kinase receptors RET and TRK have been implicated as an early step in the development of these tumors. Mutations in either *BRAF* (40%–60%) or *RAS* (10%–15%) or *RET/PTC* rearrangements (10%–15%) are present in most DTCs (Fig. 51–2).[9]

Activating *RET* mutations may be the result of ionizing radiation and were the most common mutations found in the Chernobyl radiation-induced thyroid carcinomas.[10] *BRAF* mutation has been implicated in more aggressive disease and greater mortality from PTC.[11]In addition, when present in combination with *BRAF*, a recent novel driver, telomerase reverse transcriptase (*TERT*) mutation, which is implicated in advanced thyroid cancer, results in the most aggressive PTC with the highest recurrence rate.[12] Of follicular thyroid cancers, 30% are driven by Pax8-peroxisome

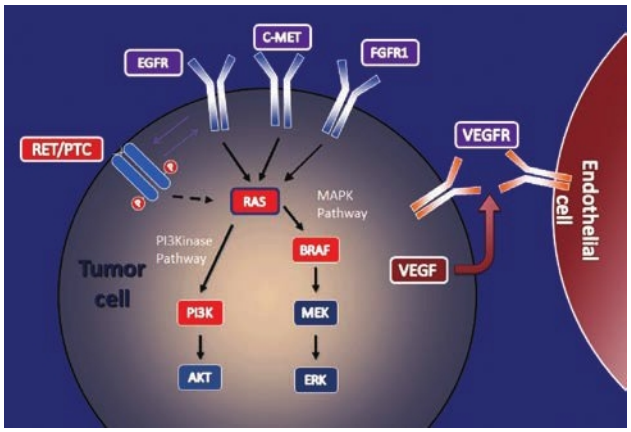


FIGURE 51–2 **Tumorigenesis of thyroid cancer. Used with permission from Dr. Steven I. Sherman.**

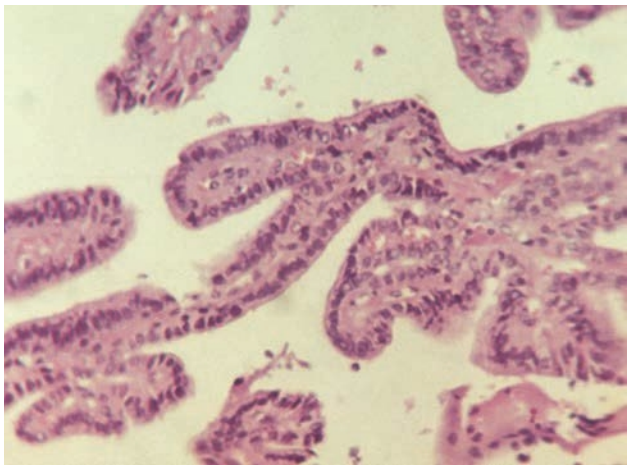


FIGURE 51–3 **Classic histology for papillary thyroid carcinoma.**

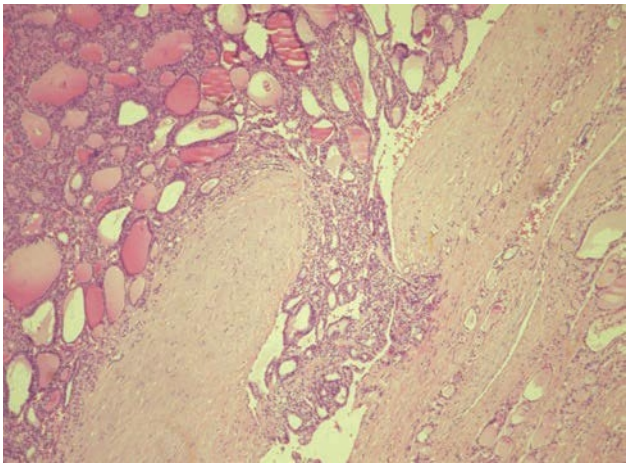


FIGURE 51–4 **Follicular carcinoma with invasion of capsule. Capsular and vascular invasion distinguish benign neoplasms from carcinoma.**

proliferator-activating receptor (*PPAR*)-γ rearrangements, and 10% to 15% are driven by *RAS* mutations.[9]

Thyroid tumor growth is dependent on angiogenesis, which is important for tumor cell growth, promotion, and development of metastases.[13] Vascular endothelial growth factor (VEGF), an important proangiogenic factor, binds to VEGF receptors. This then activates MAP-kinase signaling and promotes further tumor growth. VEGF receptors play a contributory role in the development and progression of thyroid cancer.

Diagnosis

Thyroid cancer is subdivided into well-differentiated neoplasms characterized by slow growth and high curability and a small group of poorly differentiated tumors with poor outcome. There are four major subtypes of thyroid cancer, which are based on morphology and biological behavior. This classification is advantageous because it relates morphology to methods of treatment and prognosis.

Histologic characteristics of conventional PTCs include numerous papillae lined by cuboidal to low columnar follicular cells with enlarged irregular nuclei with longitudinal grooves, intranuclear cytoplasmic pseudo-inclusions, and solitary or multiple marginally placed micronucleoli (Fig. 51–3). Follicular variants of PTC and other PTC variants are also recognized. Follicular tumors, although frequently encapsulated, can exhibit vascular and capsular invasion microscopically; it is this invasion that, when identified histopathologically, distinguishes benign neoplasms from malignant follicular neoplasms (Fig. 51–4). Hürthle cell carcinomas are considered a subtype of follicular cancer. Tall cell variants, columnar cell variants, Hürthle cell variant, and insular type are histologic subtypes that may portend a worse prognosis.

Staging

The TNM (tumor, node, metastasis) method may be most useful for prediction of disease-free survival and is generally used in our institution. Tumor size and presence of extrathyroidal invasion carry prognostic importance and thus should consistently be included in the pathologist's synoptic report. Anaplastic thyroid carcinoma (ATC) by convention is always stage IV (Tables 51–4 and 51–5).

Management

Surgical Management

Preoperative US of the entire neck (not just of the thyroid) is indicated to help identify the presence of nodal metastases and help the surgeon perform the

Table 51–4 Staging of Thyroid Carcinoma

Primary Tumor (T)	
Note: all categories may be subdivided into (a) solitary tumor and (b) multifocal tumor (the largest determines the classification).	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1a	Tumor ≤1cm in greatest dimension limited to the thyroid
T1b	Tumor >1 cm but ≤2 cm in greatest dimension limited to the thyroid
T2	Tumor >2 cm but ≤4 cm in greatest dimension limited to the thyroid
T3a	Tumor >4 cm limited to the thyroid
T3b	Gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid, or omohyoid muscles) from a tumor of any size
T4a	Gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve from a tumor of any size
T4b	Gross extrathyroidal extension invading prevertebral fascia or encasing the carotid artery or mediastinal vessels from a tumor of any size
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0a	One or more cytologically or histologically confirmed benign lymph nodes
N0b	No radiologic or clinical evidence of locoregional lymph node metastasis
N1	Regional lymph node metastasis
N1a	Metastasis to level VI or VII (pretracheal, paratracheal, or prelaryngeal/Delphian, or upper mediastinal) lymph nodes. This can be unilateral or bilateral disease.
N1b	Metastasis to unilateral, bilateral, or contralateral cervical neck lymph nodes (levels I, II, III, IV, or V) or retropharyngeal lymph nodes
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the *AJCC Cancer Staging System* (2020)

appropriate surgery. Total thyroidectomy was traditionally the standard of care in the majority of thyroid cancer cases. However, there is increasing evidence that thyroid lobectomy could be a reasonable option in certain group of patients with low-risk papillary or follicular carcinomas such as those younger than 45 years of age, those with intrathyroidal unifocal tumor, those with tumor smaller than 4 cm, and those with absence of nodal disease and no evidence of extrathyroidal extension.[14] Several studies have demonstrated excellent long-term clinical outcomes in properly selected patients eligible for thyroid lobectomy.[15,16] The rate of recurrent disease was less than 5%, readily detectable with long-term surveillance, and when properly treated, did not affect overall outcome (Fig. 51–5).[17]

Total thyroidectomy remains the treatment of choice in patients with higher risk of recurrence or death including primary tumor larger than 4 cm, presence of extrathyroidal extension, and regional or distant metastasis. However, patients with tumors between 1 and 4 cm with risk factors such as familial DTC, prior radiation therapy to the neck area, age older than 45 years, and presence of contralateral thyroid nodules may be considered to undergo total thyroidectomy to facilitate postoperative radioactive iodine (RAI) treatment or surveillance. Prophylactic central neck dissection remains controversial and is not always indicated. However, neck dissection should be performed on patients with identifiable nodal disease, because their presence affects recurrence. Calcium and parathyroid hormone levels should be monitored postoperatively because of the risk of hypoparathyroidism from either vascular damage intraoperatively or inadvertent removal.

Postoperative Iodine-131 Therapy (Radioactive Iodine Treatment)

Iodine-131 (^{131}I) is used as adjuvant therapy for thyroid carcinoma; iodine is preferentially taken up and

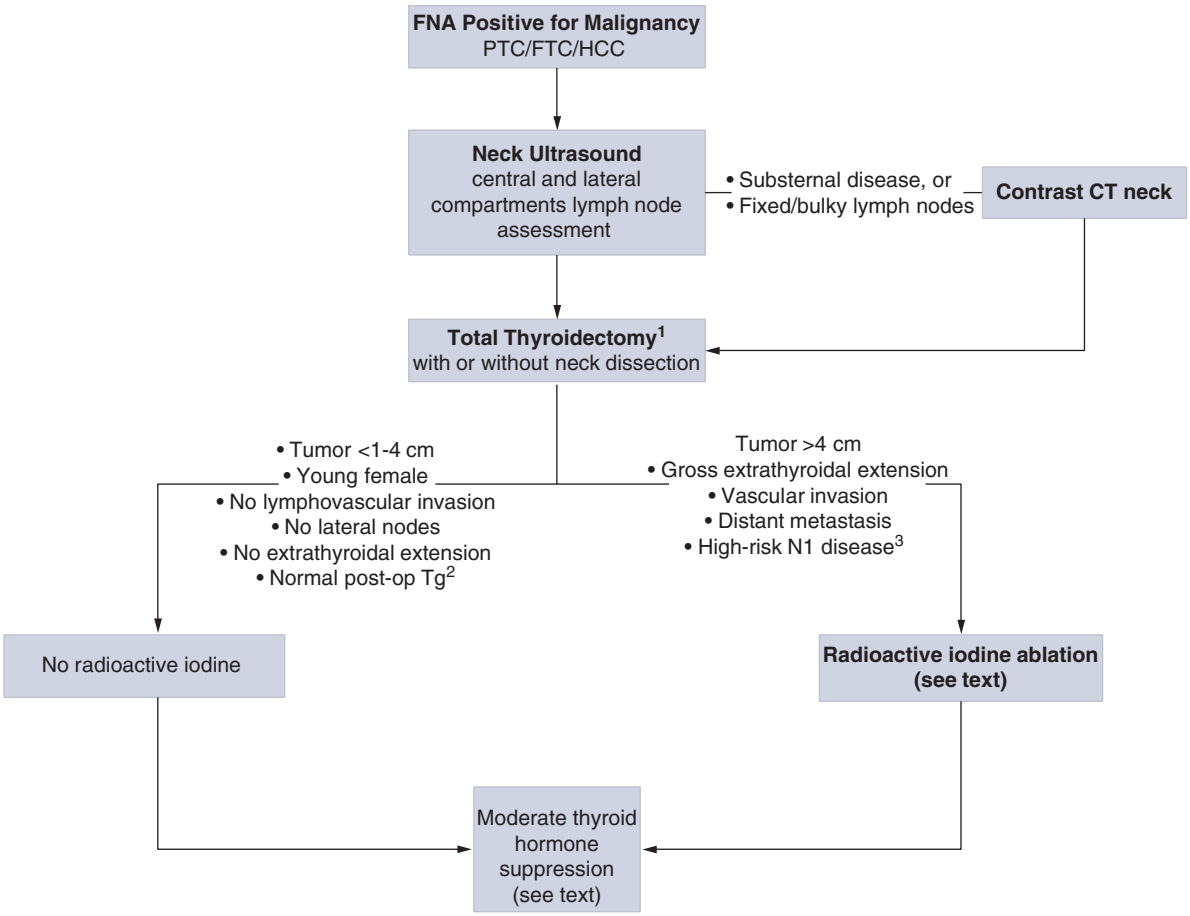
Table 51–5 Stage Grouping for Thyroid Carcinoma

Separate stage groupings are recommended for papillary or follicular, medullary, and anaplastic (undifferentiated) carcinomas.			
Papillary or Follicular (<55 Years)			
Stage I	Any T	Any N	M0
Stage II	Any T	Any N	M1
Papillary or Follicular (≥55 Years)			
Stage I	T1/T2	N0/NX	M0
Stage II	T1/T2	N1	M0
Stage II	T3a/T3b	Any N	M0
Stage III	T4a	Any N	M0
Stage IVA	T4b	Any N	M0
Stage IVB	Any T	Any N	M1
Medullary Carcinoma			
Stage I	T1	N0	M0
Stage II	T2–T3	N0	M0
Stage III	T1/T2/T3	N1a	M0
Stage IVA	T4a	Any N	M0
	T1/T2/T3	N1b	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1
Anaplastic Carcinoma			
All anaplastic carcinomas are stage IV.			
Stage IVA	T1–T3a	N0/NX	M0
Stage IVB	T1–T3a	N1	M0
Stage IVB	T3b	Any N	M0
Stage IVB	T4	Any N	M0
Stage IVC	Any T	Any N	M1

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the *AJCC Cancer Staging System* (2020)

trapped by the thyroid follicular cells as well as malignant counterparts. Iodine-131 destroys cells of follicular origin by first becoming concentrated in the cell where β rays are released, and the high-energy electrons spewed induce radiation cytotoxicity; simultaneously, γ rays are released that allow for detection of the emission by a camera. Therefore, postoperative examination with RAI scanning allows the identification of residual regional or distant foci of disease, and RAI can be used therapeutically to ablate such tumor deposits. The rationale for using ^{131}I as adjuvant therapy is as follows: (1) it destroys any residual microscopic foci of disease, (2) it increases specificity of subsequent ^{131}I scanning for detection of recurrent or metastatic disease by elimination of uptake by residual normal tissue, and (3) it improves the value of measurements of serum thyroglobulin (Tg) as a serum marker; hence, any elevation in Tg would be representative of recurrent or metastatic disease and not residual normal thyroid tissue. Combined retrospective data suggest that RAI ablation reduces long-term, disease-specific mortality in patients with primary tumors 4 cm in diameter or larger, those with multicentric disease, or those in whom there is evidence of soft tissue invasion at presentation.[18] Low-risk patients (Fig. 51–5) may not benefit from RAI, and selective use is advocated in these patients. The use of postoperative Tg measured 1 to 2 months after surgery is a useful tool to gauge residual or metastatic disease. Undetectable stimulated or unstimulated Tg indicates a very low likelihood of residual disease. Suppressed Tg levels lower than 0.2 ng/mL or stimulated Tg levels lower than 1 ng/mL are indicative for excellent response.[14] However, the decision to administer ^{131}I should not rely solely on the level of Tg.

Postoperatively, patients who require ^{131}I therapy may continue to take a thyroid supplement if recombinant human thyrotropin (rhTSH) is used or



[1]Consider lobectomy for small tumors <4 cm; no history of radiation; no gross extrathyroidal extension; no cervical lymph node disease; age <4; no family history.
[2]Nonstimulated Tg <5 ng/mL or stimulated Tg <10 ng/mL and negative Tg antibodies.
[3]High-risk N1 disease: >10 involved nodes if all are less than 5 mm; >5 involved nodes if most are 5-15 mm; or any single lymph node more than 15 mm.

FIGURE 51–5 Initial approach to management of differentiated thyroid cancer. CT, computed tomography; FNA, fine-needle aspiration; FTC, follicular thyroid carcinoma; HCC, Hürthle cell carcinoma; PTC, papillary thyroid carcinoma; Tg, thyroglobulin. Data from Tuttle RM, Sabra MM. Selective use of RAI for ablation and adjuvant therapy after total thyroidectomy for differentiated thyroid cancer: a practical approach to clinical decision making. *Oral Oncol*. 2013;49(7):676-683.

undergo thyroid hormone withdrawal in preparation for treatment.. During this time, patients should avoid iodine-rich food. Urinary iodine concentrations can be checked to assess total-body iodine content before RAI therapy. For maximum RAI uptake, thyroid-stimulating hormone (TSH) should be allowed to rise to more than 30 μIU/mL because this facilitates uptake of iodine by follicular cells. Increased iodine stores decrease RAI uptake. For patients in whom a preoperative contrast computed tomography (CT) was done, RAI therapy should be avoided for at least 2 months. A pretreatment scan using a 2- to 5-mCi ^{123}I or ^{131}I RAI scan for localization of uptake before ablation is recommended but not mandatory. Twenty-four to 96 hours after dosing, a whole-body scan showing less than 5% uptake is presumed to be normal residual tissue. An uptake of more than 5% indicates excessive thyroid tissue and warrants consideration for further surgical resection. The dose of RAI is determined by extent of residual disease: 30–100 mCi for adjuvant ablation, approximately 150 mCi for nodal disease, and 200 mCi or more for metastatic disease outside the lungs.[14] However, it is important to know that the routinely used ^{131}I doses are not administered from high-quality evidence. A post-treatment scan is performed to assess for further uptake of RAI that was not previously seen on the pretreatment scan (ie, regional or distant metastases). The post-treatment scan is a more sensitive technique to detect metastatic disease, because the ability to demonstrate RAI-avid lesions is directly proportional to the amount of RAI given (Fig. 51–6).

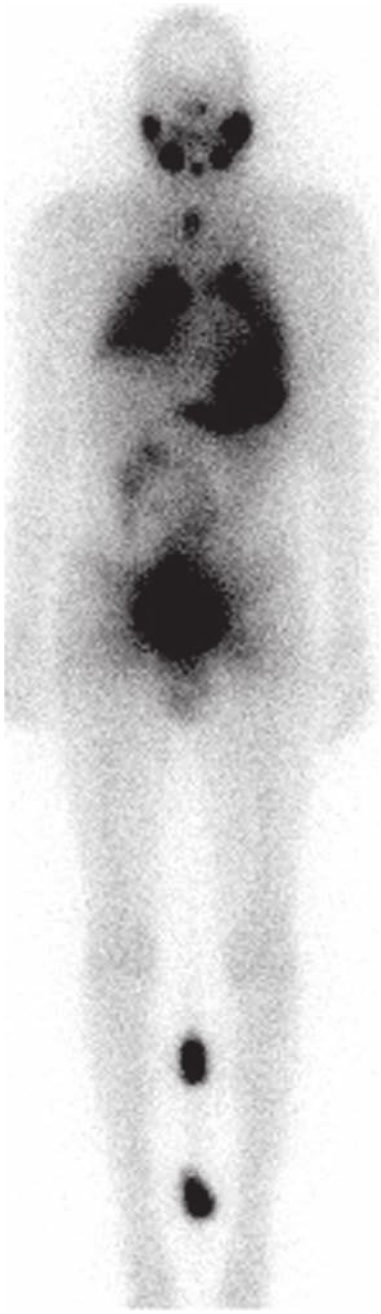


FIGURE 51–6 Whole-body scan with iodine-131 (^{131}I) showing multiple metastatic deposits in the neck and lungs, with physiologic uptake in the salivary gland, stomach, intestines, and bladder.

Short-term complications, although rare, include radiation thyroiditis, neck edema, sialadenitis, and tumor hemorrhage. These occur more often in the presence of bulky disease. Long-term complications, which increase with cumulative doses, include xerostomia, nasolacrimal duct obstruction, pulmonary fibrosis (if pulmonary metastasis is present and treated at high doses), and secondary malignancies such as acute myelogenous leukemia.[19] There are no reports of congenital abnormalities in children conceived after RAI treatment; however, most physicians recommend waiting for 6 months before conceiving. Radioactive iodine should not be given to pregnant women because of the potential teratogenic effects for the fetus's growth and thyroid development; all women of childbearing age must have a negative pregnancy test before receiving treatment.

Thyroid Hormone Therapy

Thyroid hormone replacement targeting TSH suppression has been shown to increase disease-free survival two- to threefold, especially in high-risk patients. It minimizes potential TSH-stimulated growth of thyroid cancer cells. Over-suppression of TSH to undetectable levels can present morbid consequences including osteopenia, atrial fibrillation, and possible cardiac hypertrophy. Moderate TSH suppression (subnormal but not undetectable) during follow-up was associated with better outcomes in all stages, including in patients with distant metastatic disease. For high-risk patients, moderate TSH suppression continued for the first 3 years after initial diagnosis may be indicated.

External Beam Radiotherapy

External beam radiotherapy (EBRT) plays a role in the treatment of PTC in certain subgroups of patients. Our institutional review of postoperative conformal EBRT in high-risk patients with DTC showed durable locoregional control in those with residual microscopic disease after initial surgery. However, patients with gross residual disease had significantly worse outcomes.[20] EBRT can be considered in aerodigestive invasion as adjuvant therapy after surgery.[14] Radiotherapy can also be a palliative local therapeutic option in RAI–nonavid, locally advanced or distant metastatic disease.

Management After Initial Therapy

Imaging

After initial therapy, patients with DTC need lifelong monitoring using both clinical and radiographic data. In high-risk patients, follow-up RAI scan 12 months after initial RAI ablation should be considered for reassessment of disease burden. The TSH should be allowed to increase to a value higher than 30 μIU/mL by either withdrawal of thyroid hormone or using rhTSH. Thyrotropin alfa, an rhTSH, administered as two injections on 2 consecutive days, may be used in lieu of standard thyroid hormone withdrawal to increase thyrotropin concentrations and for adequate stimulation of both RAI uptake for scanning and serum Tg concentrations. The use of rhTSH is of particular benefit for the patient in whom endogenous TSH levels cannot rise because

of hypopituitarism or in whom the clinician prefers to avoid prolonged hypothyroidism and its resultant complications caused by concurrent medical problems. Radioiodine scanning beyond this first follow-up scan needs to be individualized and is no longer routine for all patients with thyroid cancer, including high-risk patients.

Ultrasonography of the neck (thyroid bed and cervical neck compartments) with FNA of suspicious accessible lesions is used 6 to 12 months postoperatively as part of routine follow-up.

Other non–RAI imaging techniques include CT of the neck and chest, chest radiographs, fluorodeoxyglucose–positron emission tomography (FDG-PET) or PET, and magnetic resonance imaging (MRI). MRI and CT of the neck play important roles in the detection of recurrent disease; they are not as sensitive as US but are much less operator dependent. Chest CT shows both micronodular and macronodular pulmonary metastases. Fluorodeoxyglucose-PET/CT imaging is useful in patients with a Tg higher than 10 ng/mL who have negative RAI imaging but is not routinely used in follow-up of other patients with thyroid cancer.[14] Patients with DTC with little to no iodine activity generally have higher glucose metabolism and positivity on FDG-PET scans. Lack of iodine uptake denotes tumor dedifferentiation. Although PET is sensitive in detecting metastatic disease, it is not specific for thyroid cancer, and caution should be exercised when evaluating recurrent disease (Fig. 51–7). The use of CT imaging in conjunction with FDG-PET improves the sensitivity for small subcentimeter metastatic disease seen with DTC.

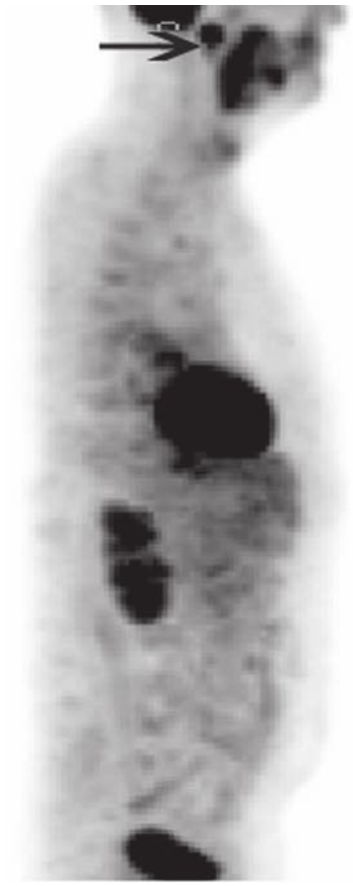


FIGURE 51–7 Positron emission tomography (PET) scan showing posterior pharyngeal metastatic papillary thyroid carcinoma. Thyroglobulin level was 35 ng/mL, and radioiodine whole-body scan was negative for disease.

Monitoring Serum Thyroglobulin

Thyroglobulin is a unique protein synthesized only by the thyroid follicular cells (both benign and differentiated malignant tissue) and, therefore, is a good biochemical test to assess for the presence of residual, recurrent, or metastatic disease. Dedifferentiated tumors lose the ability to secrete Tg, and it may not be used as a tumor marker. After total thyroidectomy with or without RAI ablation, the Tg falls to its nadir usually within 3 months but may take as long as 2 years. Subsequent Tg measurements (stimulated or unstimulated) are used to monitor for disease recurrence and should be repeated in the same laboratory to avoid erroneous misinterpretations of interassay variability. Simultaneously Tg and Tg antibody (TgAb) should always be measured together because TgAb can falsely lower the Tg concentrations in immunometric assays. These antibodies, which are present in approximately 25% of patients, interfere with the assay's ability to bind to Tg. Thyroglobulin measurements by radioimmunoassay or liquid chromatography tandem mass spectrometry are more resistant to interference by TgAb and are used when antibody presence is detected. The median time to TgAb disappearance after total thyroidectomy and RAI ablation is about 3 years.[21] Therefore, increases in TgAb after the nadir has been reached should alert the clinician to the possibility of recurrent disease. Although in general the diagnostic accuracy of serum Tg is higher after TSH stimulation than during thyroxine treatment, an unstimulated Tg measured by second-generation assays may be used to follow up patient treatment with stimulated Tg of less than 2 ng/mL with no evidence of recurrent disease on imaging.[22]

Metastatic Disease

Distant metastases are evident in about 15% of patients with DTC. Half of these patients have notable metastases at the time of initial presentation.[9] The most common sites of metastasis, in decreasing order of frequency, are the lungs, bones, and other soft tissues (Figs. 51–8A, B, and 51–9). Older patients have a higher

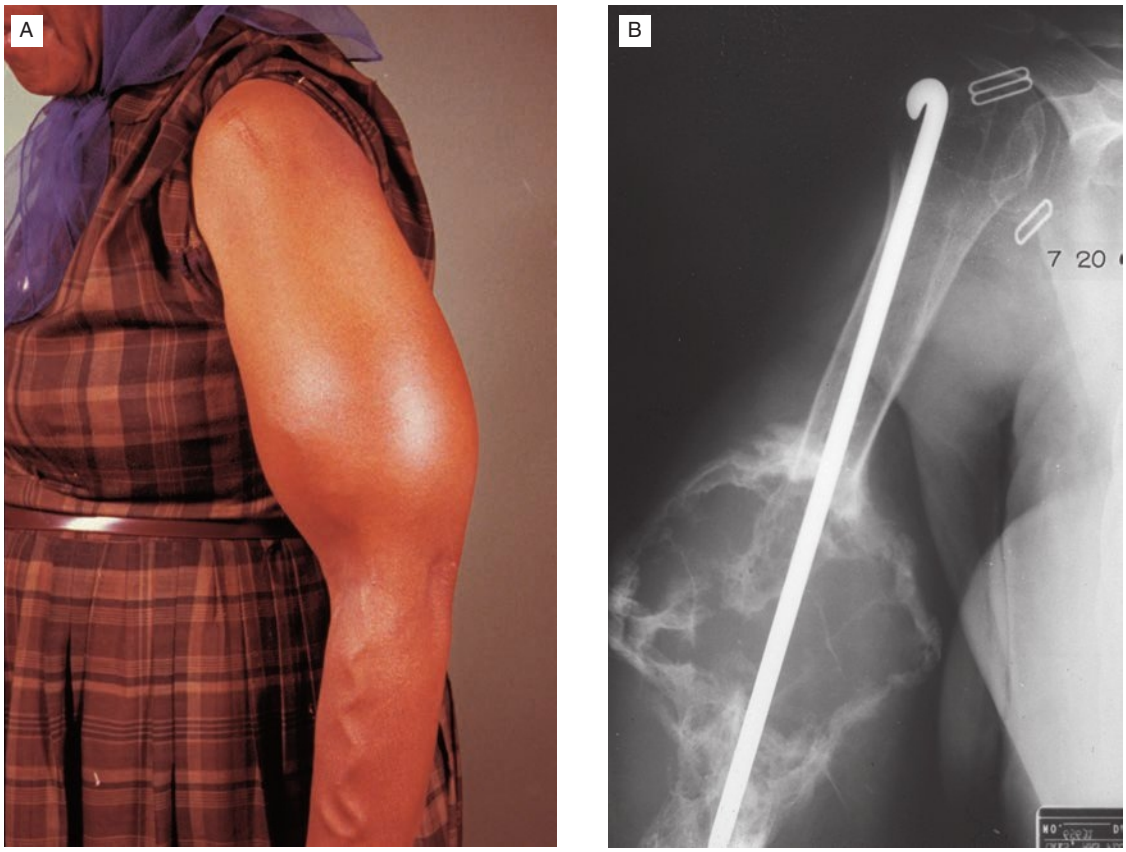


FIGURE 51–8 **A.** A woman with metastatic follicular thyroid carcinoma of the left humerus. **B.** Radiograph of metastatic follicular thyroid carcinoma of the left humerus in the same patient.



FIGURE 51–9 Patient with multiple metastatic deposits of papillary thyroid carcinoma to the skin.

risk for distant metastases. For resectable locoregional and isolated metastasis, surgery is preferred.

In those with iodine-avid unresectable disease or distant metastasis, ^{131}I treatment should be recommended, and higher doses (150–200 mCi) are typically used. Although this treatment may be repeated over time, caution and careful monitoring for side effects should be exercised. Moderate TSH suppression should also be continued in these patients. Metastases at different sites require management by multimodality approaches. Bone lesions may be surgically resected or treated with ^{131}I treatment or EBRT.[23] In follicular thyroid carcinoma, where the lesions are highly vascular, arterial embolization has been used anecdotally with successful reduction in pain at our institution. In addition, intravenous bisphosphonates (pamidronate or zoledronic acid) and denosumab are prescribed for painful bony metastases with some success. Experience at our institution also showed improved median survival for patients with one or more brain metastases after surgical resection. Stereotactic radiosurgery is also an option. We suggest a multidisciplinary approach and discussion with the surgeon, radiation oncologist, and endocrinologist about the risks and benefits of each modality in the management of metastatic disease.

Systemic Therapy

In patients with progressive metastatic disease that does not respond to standard therapy, long-term overall survival is less than 10%. For this subset of patients,

the understanding of the molecular model for thyroid cancer and the discovery of targeted therapies have led to a new era of treatment.[9] Consequently, two tyrosine kinase inhibitors (TKIs), sorafenib (2013) and lenvatinib(2015), have been approved by the FDA for the treatment of locally recurrent or metastatic, progressive DTC that is refractory to RAI treatment. Previously recommended cytotoxic therapies with agents such as doxorubicin have had poor outcomes with significant toxicities. TKIs target intercellular signaling pathways (MAPK pathway in the tumor cells) but also play a role in the surrounding tumor vasculature.[9] Trials evaluating the efficacy of the approved drugs have shown better progression-free survival (PFS) than in the placebo groups (5 months with sorafenib and 14.7 months with lenvatinib).[24,25] Lenvatinib had an overall response rate of 64.8% versus 1.5% in the placebo group (odds ratio [OR] 28.87, 95% CI 12.46–66.86). However, it is important to note the deleterious effects of these drugs, most commonly hypertension, gastrointestinal effects such as diarrhea, altered taste and stomatitis, palmar-plantar erythrodysesthesia syndrome (hand and foot syndrome), and weight loss. Recently, gene-specific therapies have received FDA approval for thyroid cancers harboring certain genetic mutations: larotrectinib (neurotrophic receptor tyrosine kinase [*NTRK*] gene fusion) (November 2018), dabrafenib and trametinib (*BRAF* V600E mutation in ATC) (May 2018), and selpercatinib (*RET* gene alterations) (May 2020).[26–28]

Indications for therapy include patients with progressive or symptomatic unresectable disease that is refractory to ^{131}I treatment. Patients with asymptomatic stable or very slowly progressive disease on thyroid hormone suppression therapy may be closely monitored. Before initiation of therapy, a comprehensive evaluation to ascertain appropriate selection of patients should be conducted. This should include a candid discussion with the patient and family about the benefits and risks of these agents. Furthermore, because of the life-threatening adverse effects of these drugs, only clinicians who are well versed in the use of these agents should initiate and monitor these patients. We have previously published an adverse event monitoring tool used at our institution to guide clinicians when starting patients on these agents.[29]

Differentiated Thyroid Carcinoma in Children

As in adults, PTC followed by follicular thyroid cancer occur most frequently in children. Exposure to radiation is the major risk factor. It is not unusual for children with PTC to present with multifocal disease with lymph node involvement, extrathyroidal extension, and pulmonary metastasis.[30] Despite this, children have high cure rates overall, with a 10-year survival rate of almost 100%. Those diagnosed before the age of 10 years, however, seem to have a higher risk of recurrence and death. The treatment of thyroid cancer in children mirrors that of adults. Total thyroidectomy (rarely lobectomy) with nodal dissection done at a high-volume center experienced with higher complication rates is recommended.[30] Postoperative universal RAI therapy is no longer advocated, and careful selection based on risk of recurrence, residual or distant disease remaining after surgery, and Tg levels is used to determine the need for therapy. Moderate TSH suppression (0.1–0.5 μIU/mL) with relaxation when there is no evidence of recurrent disease is suggested. Lifelong surveillance is essential in monitoring children for recurrent disease because recurrence may occur 20 to 30 years later. For the few children with progressive RAI-refractory DTC, referral to a center with pediatric endocrine neoplasia expertise for consideration for systemic therapy is recommended.

MEDULLARY THYROID CARCINOMA

Introduction

Medullary thyroid carcinomas (MTCs) are derived from C cells (calcitonin-secreting cells) that are part of the neural crest origin (see Table 51–1). The majority (75%) of patients with MTC have sporadic disease. The other 25 % have an inherited form that occurs as an autosomal dominant trait as part of the multiple endocrine neoplasia (MEN) clinical syndromes, MEN type 2A or type 2B, or familial MTC. In MEN 2A, MTC occurs in association with pheochromocytoma and multigland parathyroid tumors; MTC is usually the first manifested disease of the three components of this syndrome. In MEN 2B, MTC occurs in association with pheochromocytoma and mucosal neuromas (Figs. 51–10A, B) or neurofibromas and marfanoid habitus. Familial MTC is a variant of MEN 2A, where only MTC is clinically evident. Sporadic MTC in most patients presents in the fifth or sixth decade of life, with a male-to-female ratio of 1.4:1.[31]

Clinical Features and Diagnosis

The most common clinical presentation of sporadic MTC is a solitary thyroid mass found incidentally during routine examination. Other symptoms such as secretory diarrhea and facial flushing may also be seen with hormone overproduction. Fine-needle aspiration should be performed for suspicious nodules and once MTC is suspected, calcium, calcitonin, and carcinoembryonic antigen (CEA) levels should be obtained, as well as a screening for pheochromocytoma and a thorough



FIGURE 51–10 **A. Patient with multiple endocrine neoplasia (MEN) type 2B, with typical thickening of the palpebrum. Note also the ganglioneuroma on the left superior eyelid. B. Multiple ganglioneuromas on the tongue of a patient with MEN type 2B.**

history and physical examination done. Because about 6% of patients with sporadic MTC carry a germline *RET* mutation, genetic counseling and testing are offered to all patients with newly diagnosed apparent sporadic disease.[32] If pheochromocytoma is confirmed, appropriate control of catecholamine hypersecretion and removal should precede thyroid surgery.

Medullary thyroid cancer occurs as a solid mass or cluster of C-cell hyperplasia interspersed between



FIGURE 51–11 **Gross specimen of thyroid gland containing medullary thyroid carcinoma.**

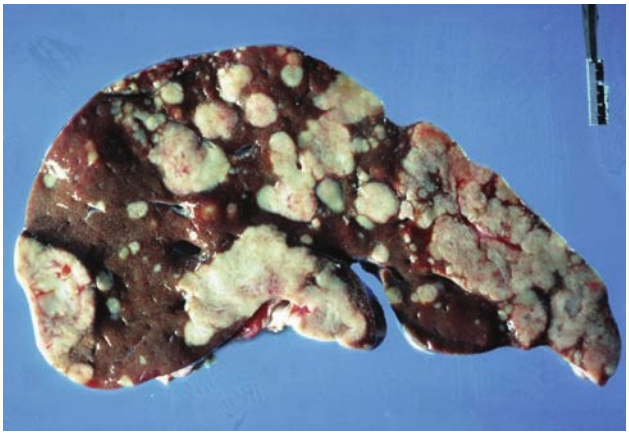


FIGURE 51–12 **Gross specimen of liver containing metastatic lesions of medullary thyroid carcinoma.**

normal thyroid follicles and can be visualized with calcitonin immunostaining (Fig. 51–11). It appears as variable amounts of fibrosis as well as deposits of amyloid in 60% to 80% of tumors. Notably, even the smallest visible tumors can be associated with metastases.

Metastases to cervical and mediastinal lymph nodes are found in about 50% of patients at the time of initial presentation. Distant metastases to the lungs, liver, bones, and adrenal glands most commonly occur late in the course of the disease (Fig. 51–12).

Inherited Medullary Thyroid Cancer

Inherited syndromes of MTC are all transmitted in an autosomal dominant form. In kindred with inherited MTC, prospective family screening is essential because of the 90% to 95% penetrance of the disease.[33] In these cases, MTC is usually present by the third to fourth decade of life. The mutation is detected in *RET* and can be identified in 98% of affected family members with

appropriate screening. Patients with MEN 2B tend to exhibit more locally aggressive MTC.[33] Screening with *RET* testing is recommended at less than 6 months of age for familial MTC, and MEN 2A screening is recommended by 5 years of age.[31]

Analysis of the *RET* gene should include the most common sites of mutation, exons 10 and 11 (C609, C611, C618, C620, C630, and C634) and RET codon mutations in exons 13, 14, 15, and 16.[34] With the substantial decrease in the expense of genetic sequencing in the last few years, some laboratories may sequence the entire RET coding region as the first step in screening. Appropriate genetic counseling must be a part of the initial evaluation, including the possibilities of errors in testing, the potential for discrimination, and changes that may occur in quality of life.

Management

Surgery

In MTC, there is a high propensity for bilateral disease in both the sporadic and familial forms, and therefore, the usual treatment is total thyroidectomy with central neck compartment dissection in all patients. In unilateral sporadic disease, if the primary tumor is greater than 1 cm or central compartment disease is present, strong consideration should be given to ipsilateral modified radical neck or mediastinal dissections, or both.[35] Bilateral neck dissections are usually performed in many institutions, including our own. Hypoparathyroidism and recurrent laryngeal nerve damage are the most frequently encountered complications in both children and adults. We recommend referral to centers with high volume and experienced surgeons to decrease these complications.

For carriers of a hereditary *RET* mutation, current guidelines recommend prophylactic total thyroidectomy at a certain age cut-off based on the risk of aggressive MTC disease in relationship with specific *RET* mutation. The ATA 2015 MTC guideline classified mutations M918T, C634F/G/R/S/W/Y, and A883F as highest-risk/high-risk mutations and others as moderate risk.[34] Of note, in many patients, C-cell hyperplasia and/or MTC is already present histologically at the time of surgery. There is also significant variability between families with similar mutations in terms of presentation, aggressiveness, and age of onset. Therefore, the timing of total thyroidectomy should involve a detailed and individualized discussion in addition to the available genotype-phenotype correlation data. As of this writing, total thyroidectomy is recommended in patients with MEN2B in the first year of life. Children with MEN2A carrying high-risk RET mutations should have total thyroidectomy by the age of 5 years. MEN2A moderate-risk RET mutations carriers may choose to have prophylactic total thyroidectomy during childhood or when the calcitonin level is elevated.

There is no role for thyroid hormone suppression therapy; hence, the goal should be to maintain the TSH and free thyroxine (T_4) concentrations within normal levels. There is also no role of RAI therapy in the treatment of MTC, and therefore, thyroid hormone replacement may be started immediately after surgery.

External Beam Radiotherapy

External beam radiotherapy should be considered for patients who are at high risk for locoregional recurrence, because of the improved relapse-free rate.[36] In general, 20 fractions totaling 40 Gy are given to the cervical, supraclavicular, and upper mediastinal lymph nodes over 4 weeks; subsequent booster doses of 10 Gy are then given to the thyroid bed, especially if there was gross residual disease.[35] External beam radiotherapy can also be given to treat painful skeletal metastases.

Monitoring and Follow-Up

Biochemical testing with serum calcitonin and CEA is used in the routine follow-up of patients with MTC. About 3 months postoperatively, these markers should be within the normal ranges (a nadir of 6 months has been reported). Patients with palpable recurrent/residual disease, in general, will have calcitonin levels of at least 10 pg/mL except for tumors that are dedifferentiated and no longer secrete calcitonin (these tumors usually secrete CEA). Monitoring calcitonin and CEA levels every 3 to 6 months to determine doubling times is helpful in assessing disease progression and pace of growth. Values of serum calcitonin higher than 100 pg/mL suggest residual neck disease or distant metastases, particularly in the liver, and these patients should be aggressively assessed clinically and radiographically.[35] Because of MTC's propensity to metastasize to the neck, mediastinum, liver, and bone, diagnostic imaging should include US of the neck, CT of the chest, MRI of the liver, and MRI of the spine. FDG- PET/CT and gallium-68 dotatate PET/CT can also be used in selected cases.[37]

Recurrent or Persistent Disease

Patients with stable and asymptomatic recurrent disease can be monitored closely without therapy. Once the disease is progressive, symptomatic treatment is recommended. For those with locoregional disease without metastases, surgery is preferred. Similar to metastatic DTC, treatment of individual metastatic sites causing symptoms or problems can be addressed individually (see earlier Differentiated

Thyroid Carcinoma section). As with DTC, the FDA has approved two TKIs, vandetanib (2011) and cabozantinib (2012), for progressive metastatic MTC. In May 2020, RET-specific inhibitor selpercatinib received FDA approval for RET-altered thyroid cancer, including MTC, after it showed durable efficacy with low-grade toxic effects in patients with and without previous vandetanib or cabozantinib treatment.[28] Initiation of these therapies should be done by clinicians who are well versed in using these agents and are able to monitor these patients closely.

ANAPLASTIC THYROID CARCINOMA

Introduction

ATC is a locally and systemically aggressive undifferentiated tumor with a disease-specific mortality rate approaching 100%. More than 90% of patients are over the age of 50 years, and more females than males are affected.

Diagnosis

ATC most commonly presents as rapid growth of a thyroid or neck mass. A history of longstanding thyroid enlargement is noted in about 80% of the patients. Fine-needle aspiration or surgical biopsy can usually establish the diagnosis. Preoperative imaging (CT of brain to pelvis including FDG-PET) to assess the extent of disease and planning for surgery and/or radiation therapy is recommended but should not delay therapy. Vocal cord paralysis is common in patients with ATC and should be assessed. ATC frequently arises from preexisting well-differentiated thyroid carcinoma, which supports the opinion that some ATCs develop by dedifferentiation from well-differentiated DTC (Fig. 51–13). Immunohistochemical staining for Tg, TTF1, and paired box protein Pax 8 (PAX8) should be used to aid in identifying better-differentiated sections.[38] However, because undifferentiated carcinoma cells lose their ability to synthesize Tg, Tg immunoreactivity in ATCs may be absent.

Therapy

Treatment is generally palliative in nature because ATC is rarely cured and almost always fatal. Death occurs from upper airway obstruction and suffocation in half of patients and complications of therapy or distant metastases in the others. A multidisciplinary thyroid cancer team approach is needed in the management of disease in these patients. The potential risks and benefits of all treatment modalities including palliative care should be discussed with the patient and family. Prognosis historically was dismal, with a median survival of 3 to 5 months and one-year survival of 20%.[39] Better survival rates were seen only in patients with well-localized anaplastic tumors. Favorable prognostic features seem to be: age younger than 60 years, tumor size less than 5 cm, extent of surgery, radiotherapy, chemotherapy, coexisting DTC, and absence of distant metastases.[40] Over the past decade, overall survival in ATC seems to be improving because of the availability of actionable mutations that can be targeted with small-molecule kinase inhibitors that are often combined with surgery, radiation, and immunotherapy through a multidisciplinary approach.[41]

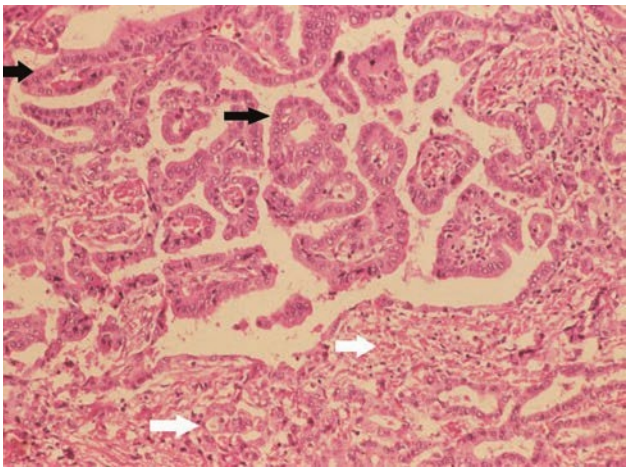


FIGURE 51–13 **Hematoxylin and eosin staining of thyroid illustrating papillary thyroid carcinoma (*black arrows*) in transition to anaplastic thyroid carcinoma (*white arrows*).**

For primary lesions with no distant metastases for which effective resection can be safely achieved, surgery is recommended as first-line treatment followed by adjuvant conformal radiotherapy with or without chemotherapy. In the presence of distant metastases, primary tumor resection should be considered to avoid invasion of surrounding structures. For unresectable lesions, neoadjuvant conformal radiotherapy with or without chemotherapy used to be considered first because this may render the tumor resectable.[38] Patients with poor performance status were often offered palliative doses of radiotherapy if tolerable. Recent advances in precision oncology have brought some impressive changes in the treatment paradigm of ATCs. The combination of dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) has shown strong clinical activity as well as tolerability in patients with *BRAF* V600E–mutant ATC. In a phase 2, open-label trial including 16 ATC patients who had undergone surgery, radiation, and systemic therapy, confirmed overall response rate to dabrafenib + trametinib was 69% with 12-month estimates of median duration of

response, PFS, and overall survival were 90%, 79%, and 80%, respectively.[27] In May 2018, this combination was granted the first FDA-approved treatment for patients with ATC. Immunotherapy may also play a role in the treatment of this aggressive cancer. Pembrolizumab as salvage therapy added at the time of progression on TKI has shown some benefits in a subset of patients.[42] Further research to explore other targeted therapies aiming at other driver mutations in ATC and a combination with immunotherapy is warranted. This novel molecular-based treatment together with a multidisciplinary approach appears to be associated with a higher survival rate, according to a large retrospective study from MDACC that included 479 patients with ATC over the span of 20 years. This has opened a new era in the treatment of ATCs, one of the most aggressive and lethal human cancers.[41]

PARATHYROID CARCINOMA

Introduction

Parathyroid carcinoma is a rare endocrine malignancy, with a prevalence of 0.005% of all cancers.[43] The etiology of parathyroid carcinoma remains largely unknown. No well-recognized risk factors have been identified. Predisposing factors identified with some cases are outlined in Table 51–6. Parathyroid carcinoma also occurs sporadically or as part of a genetic syndrome. Patients with parathyroid carcinoma are about a decade younger than patients with benign hyperparathyroidism. The disease occurs with similar frequency in both sexes.

Clinical Features

Hypercalcemia is common and ranges from mild to severe and may manifest with peripheral target organ complications such as kidney stones and osteoporosis. Parathyroid hormone levels are generally five times greater than normal, and patients may present with a discrete neck mass. However, parathyroid cancer is an uncommon cause of primary hyperparathyroidism. The presence of severe hypercalcemia (>12 mg/dL), extremely elevated parathyroid hormone, and a palpable neck mass should raise the suspicion for parathyroid carcinoma.[44]

Table 51–6 Risk Factors and Syndromes Associated with Parathyroid Carcinoma

Predisposing Factors
Prior diagnosis of thyroid cancer
Prior hyperfunctioning parathyroid gland
Secondary and tertiary hyperparathyroidism resulting from chronic renal failure and dialysis
Radiation exposure to the head and neck region
Genetic Syndromes
Multiple endocrine neoplasia type 1
Familial isolated hyperparathyroidism
Hereditary hyperparathyroidism–jaw tumor syndrome

Diagnosis

The presence of personal or family history of associated conditions and the constellation of clinical features described earlier significantly increase the likelihood of parathyroid cancer. Confirming the diagnosis before histologic confirmation remains challenging. Imaging modalities routinely used to aid diagnosis include parathyroid US and technetium-99m sestamibi. Chest CT and bone scintigraphy may also be useful for initial staging.[45] Fine-needle aspiration is not routinely recommended because of the risk of seeding the tumor and lack of sufficient sample to make a definitive diagnosis. Screening for mutations in the *CDC73* gene, which encodes parafibromin, a protein that inhibits its mitogenic function, is considered an integral part of the diagnostic workup of patients with sporadic or familial parathyroid cancer. Patients with familial hyperparathyroidism are also considered at high risk for *CDC73* mutation and should also be screened. Recent studies have provided useful data regarding genetic background in parathyroid carcinoma. The most common mutations reported were in the PI3K and TP53 pathways. Some other genetic alterations in the *KDM*, *TSC*, *RB1*, *NF1*, *KDR*, and *PTEN* genes have also been found.[46,47]

Pathology

Histopathologic diagnosis following the World Health Organization criteria is defined by the presence of capsular invasion and soft tissue invasion or histologic evidence of vascular invasion with or without invasion of vital organs or presence of locoregional or distant metastasis. The classic histopathologic criteria initially described by Schantz and Castleman, including the presence of a trabecular or lobular pattern, mitotic figures, thick fibrous bands, and capsular or blood vessel invasion, are also still used today (Fig. 51–14).[48]

However, in some cases, the histopathologic diagnosis remains challenging, and some highly differentiated tumors without distinct nuclear atypia or classic histopathologic criteria are initially considered to be adenomas but are later reclassified when recurrence or metastases appear. Immunohistochemical staining for parafibromin may increase the diagnostic accuracy,

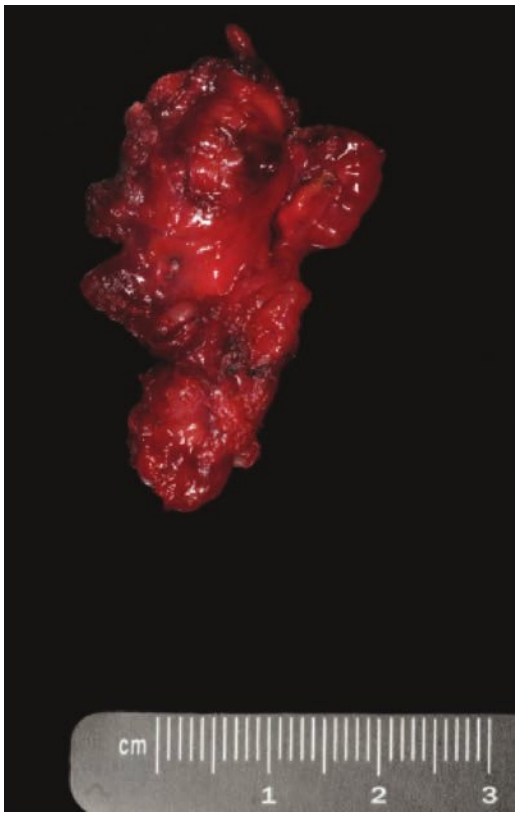


FIGURE 51–14 **Parathyroid gland carcinoma.**

and although not widely used, we have used this at our institution for various cases. Mutations in the *CDC73* gene are seen not only in the majority of patients with hyperparathyroidism–jaw tumor syndrome but also in cases of sporadic and familial parathyroid cancer.[49,50] Fifteen percent of the parathyroid tumors associated with hyperparathyroidism–jaw tumor syndrome are carcinomas.[51] On the contrary, mutations in *MEN1* seldom result in parathyroid carcinoma. To improve the accuracy of diagnosis of malignant parathyroid disease, pathologic specimens of suspected cases should be reviewed by experienced pathologists. As of this writing, we are exploring the role of molecular profiling of parathyroid cancer in prognostication and also to identify targetable mutations that could result in novel targeted therapies.

There no universally agreed upon staging criteria for parathyroid carcinoma.

The 5-year survival rate has improved over the years to approximately 85%, and the 10-year survival rate is approximately 50%.[42] Death usually results from hypercalcemia and its associated complications.

Management

Because of its rarity and unpredictable clinical course, a multidisciplinary approach to caring for the patient with parathyroid carcinoma that involves the endocrinologist, surgeon, oncologist, and radiotherapist offers the best chance for cure.

Preoperative suspicion and intraoperative identification of malignancy and appropriate initial surgery are critical to the choice of therapy for parathyroid carcinoma. Comprehensive resection of the tumor along with the ipsilateral lobe of the thyroid and abnormal or involved adjacent tissues (the so-called "en bloc" resection) is indicated.[52] Every effort should be made to maintain the integrity of the capsule to prevent seeding of tumor, because this will contribute to recurrence. Because this tumor does not typically metastasize to lymph nodes, routine lymph node dissection is not indicated unless involved by tumor. For recurrences, a wide excision of locally recurrent tumor and an aggressive surgical resection of metastases whenever possible are recommended. Although these repeat operations are not always curative, they usually offer palliation for the marked hypercalcemia (the cause of true morbidity in these patients) for a considerable although variable period. Nevertheless, surgical resection, where possible, remains the most effective treatment for both primary and recurrent disease.

Radiotherapy has not become the standard of care in patients with parathyroid carcinoma because it is difficult to prove its efficacy with such small numbers of patients being treated in reported series.[53] It may be considered in select patients at high risk of local relapse (those with gross or local invasion or tumor spillage intraoperatively) or those left with gross disease.

Chemotherapeutic agents with TKIs have shown some success in a few cases with radiographic and hormonal control. Case reports of patients with advanced parathyroid carcinoma achieving hormonal control and stable disease with sorafenib, cabozantinib, vandetanib and everolimus, temozolomide have been reported.[54] The exact mechanism of how TKIs were somewhat beneficial in selected patients is unclear. However, it could be from anti-angiogenic properties as well as bone resorption inhibition, which could be beneficial in parathyroid carcinoma with refractory hypercalcemia. Although selection bias was likely present, these cases suggest a possible role of targeted therapy in advanced parathyroid carcinoma, and further research is much needed.

Morbidity and mortality are generally caused by the effects of unremitting hypercalcemia rather than tumor growth. Medical treatments, especially in patients with unresectable disease, such as bisphosphonates, denosumab, or calcimimetics, offer only temporary and palliative control of hypercalcemia. Lifetime surveillance of serum calcium and parathyroid hormone levels is essential because of the protracted and unpredictable course of malignant parathyroid disease.

PHEOCHROMOCYTOMA AND PARAGANGLIOMA

Introduction

The term *pheochromocytoma* refers to a neoplasm derived from chromaffin cells. Although the majority of these tumors occur in the adrenal medulla, about 15% to 20% of cases arise from sympathetic or parasympathetic ganglia and are known as paragangliomas. Pheochromocytomas and paragangliomas are rare, with an estimated incidence of 0.95 per 100,000 person-years,[55] and they have a slight female predominance (54%).[56] Although pheochromocytoma is a possible cause of secondary hypertension, it represents less than 1% of cases. Nonetheless, it is important to consider this diagnosis in the proper clinical setting because it is potentially curable. Furthermore, failure to treat or improper treatment can lead to serious complications or death (Fig. 51–15).

The "rule of 10" is a classic teaching in regard to pheochromocytoma. This rule states that among pheochromocytomas, 10% are bilateral, 10% are extra-adrenal, 10% are familial, and 10% are malignant. However, this does not capture our current understanding. Data now suggest that nearly 25% of apparently sporadic pheochromocytomas are hereditary and associated with germline mutations such as *RET*, *VHL*, *SDHD*, and *SDHB*.[57] These are patients who were thought to have sporadic disease but have a higher risk of bilateral disease, malignancy, or extra-adrenal disease on the basis of their germline mutation.

Clinical Features

The presentation of pheochromocytomas and paragangliomas ranges from incidental discovery to cardiovascular shock and death. A classic presentation is described as spells of the five Ps: pressure (hypertension), pain (headache), palpitations, perspiration, and pallor. Although none of these signs and symptoms is universally present, it is reasonable to screen patients with hypertension and symptomatology suggestive of hyperadrenergic episodes. The spells can last from minutes to hours and may be triggered by exercise, stress, micturition, Valsalva maneuver, or anesthesia induction (Table 51–7).

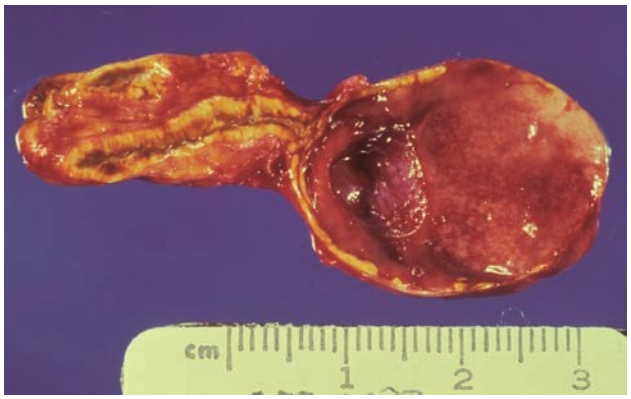


FIGURE 51–15 Adrenal gland with pheochromocytoma.

Table 51–7 Signs and Symptoms of Pheochromocytoma (List Not All Inclusive)

Hypertension	Anxiety
Headache	Constipation
Sweating	Nausea
Palpitations	Insulin resistance
Pallor	Orthostasis
Flushing	Weight loss

Additional findings include hyperglycemia (caused by suppression of insulin release), orthostasis/volume depletion (caused by vasoconstriction), and constipation/abdominal distention (a result of inhibition of gut motility). Rarely, there is cosecretion of other hormones resulting in distinct endocrine syndromes. These include vasoactive intestinal peptide causing Verner-Morrison syndrome, adrenocorticotropic hormone (ACTH) causing Cushing syndrome, growth hormone–releasing hormone causing acromegaly, and parathyroid hormone–related protein causing hypercalcemia (Figs. 51–16 and 51–17).[58]

Diagnosis

Laboratory

Biochemical testing is the cornerstone of diagnosis. Plasma-free metanephrines and 24-hour urine fractionated metanephrines are the two most commonly used laboratory tests to diagnose pheochromocytoma or paraganglioma. The high sensitivity and specificity of these tests are the main reasons they are preferred over alternatives such as plasma or urinary catecholamines, urinary total metanephrines, or urinary vanillylmandelic acid. Of course, note should be taken of any drugs or other factors that may cause false-positive results (Table 51–8).[59]

Even in patients without signs or symptoms of pheochromocytoma or paraganglioma, testing is suggested in the following situations: (1) features or family history suggestive of syndromes associated with pheochromocytoma listed in Table 51–9; (2) personal history of pheochromocytoma; or (3) adrenal incidentalomas.

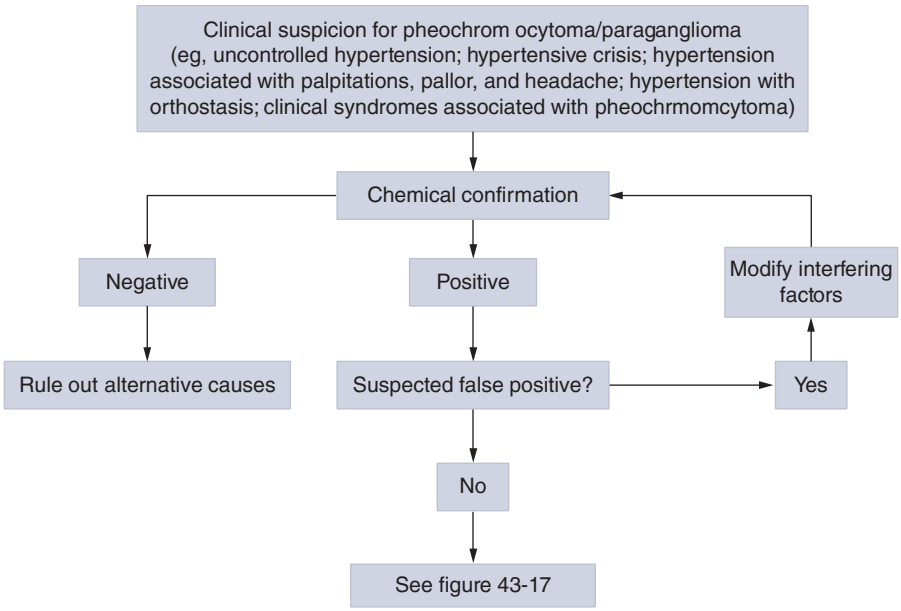


FIGURE 51–16 Biochemical confirmation of pheochromocytoma or paraganglioma.

Imaging

Imaging is not recommended for screening in the absence of biochemical evidence of pheochromocytoma or paraganglioma. However, once biochemical confirmation of the diagnosis is obtained, the next step is localization with imaging studies. Because the majority of pheochromocytomas and paragangliomas are located in the adrenal gland or elsewhere in the abdomen, cross-sectional imaging (CT or MRI) of the abdomen with attention to the adrenal glands has the highest yield. If an adrenal mass is not seen, the paraspinous region and urinary bladder should be carefully examined. Less commonly, extra-adrenal tumors may be located in the chest or the head and neck region.

There are certain imaging characteristics considered suggestive of pheochromocytoma or paraganglioma. Although helpful when present, their absence cannot be used to exclude the possibility that a mass is a pheochromocytoma or paraganglioma. On CT scan, they are usually heterogeneous with a density of greater than 10 Hounsfield units (HU) and delayed washout of contrast. On MRI, they are also usually heterogeneous and hyperintense on T2-weighted images with no dropout of signal on opposed phase imaging.[60] Functional imaging, such as meta-iodobenzylguanidine (MIBG) scintigraphy or PET scan, may be useful when cross-sectional imaging is nonlocalizing despite a high clinical suspicion. Because these tests are more often used to complement cross-sectional imaging when there is suspicion of metastases, they will be discussed in the section on malignant pheochromocytomas and paraganglioma (Figs. 51–18 and 51–19).

Genetics

Because pheochromocytoma and paraganglioma are associated with multiple familial syndromes (the majority of which are inherited in an autosomal dominant fashion), it is important to consider genetic testing. Features associated with familial cases include young age at diagnosis, positive family history, bilateral or multiple adrenal pheochromocytomas, and any paraganglioma. The syndromes in which pheochromocytomas or paragangliomas are seen include MEN type 2, familial paraganglioma syndromes, neurofibromatosis type 1, von Hippel–Lindau syndrome, Carney triad, and Carney-Stratakis syndrome (see Table 51–9).[61]

Although some clinicians recommend genetic testing only in patients with features suggesting a familial syndrome, others advocate more widespread testing because of a reported incidence of somatic mutations in more than 20% of patients with apparently sporadic disease. Genetic testing should be performed on all patients with pheochromocytoma or paraganglioma regardless of family history. In any case, patients should always meet with a knowledgeable genetic counselor to discuss the risks and benefits before and after any familial testing. When a decision is made to test, it is recommended that genetic testing be performed taking into account the most likely diagnoses rather than checking all mutations at once.

Therapy

Medical

Although surgery is the treatment of choice for pheochromocytoma or paraganglioma, patients must be

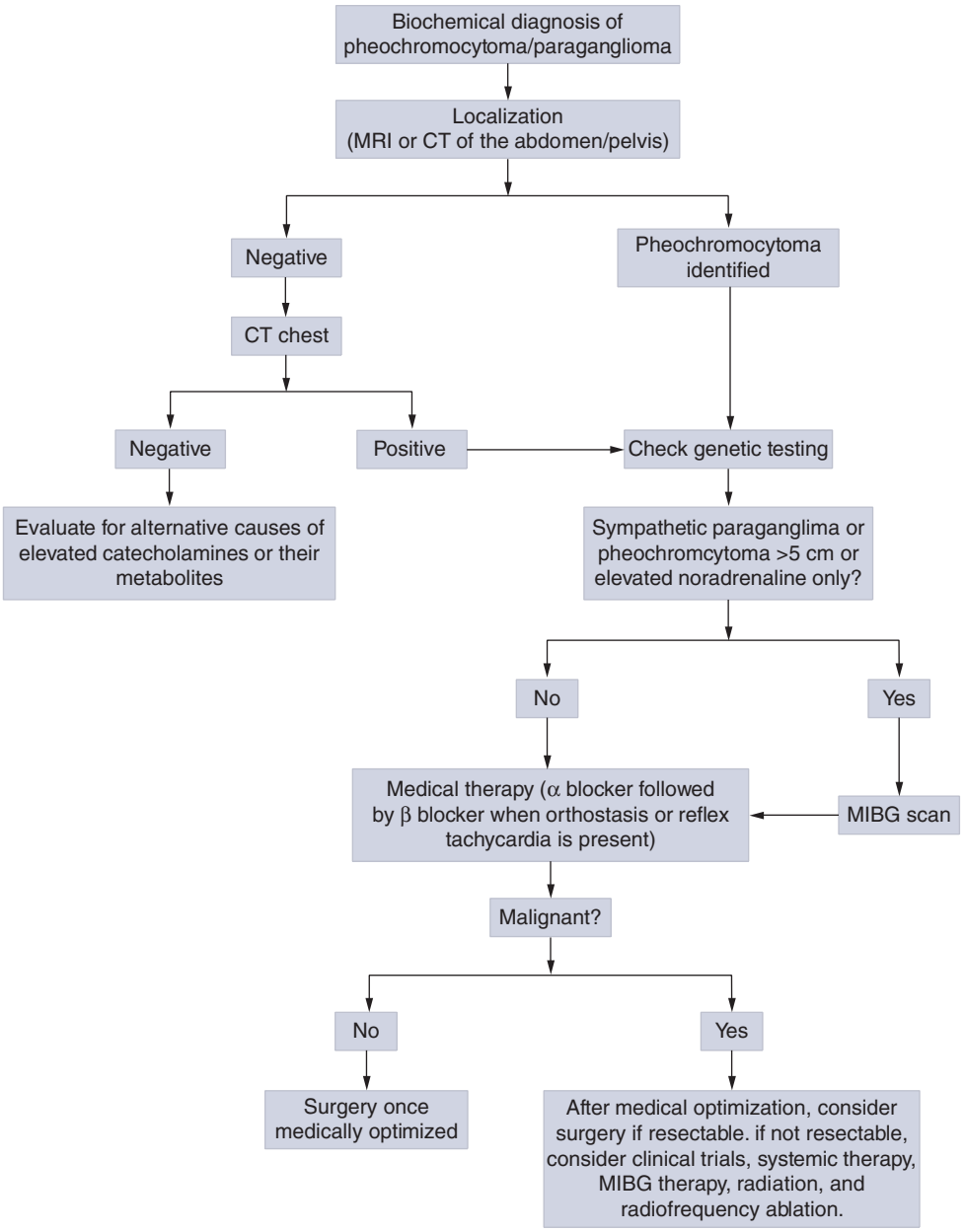


FIGURE 51–17 **Algorithm for clinical approach to pheochromocytoma or paraganglioma after biochemical confirmation. CT, computed tomography; MIBG, meta-iodobenzylguanidine; MRI, magnetic resonance imaging.**

medically optimized before surgery to reduce the risk of perioperative mortality. Preparation for surgery includes management of hypertension along with volume expansion. The first step is initiating α blockade with either a nonspecific α-blocker (phenoxybenzamine) or a selective α-1 blocker (eg, doxazosin, prazosin, or terazosin).[62] The dose is titrated until adequate control of hypertension is achieved without inducing severe orthostatic hypotension. Once the patient starts to develop orthostasis or reflex tachycardia, β blockade should be initiated. A high-sodium diet starting at the same time as α blockade is helpful for some patients to promote volume expansion. Medical optimization before surgery may be accomplished in 1 to 2 weeks. However, each patient is unique, and preparation may take longer for some patients.

It is of utmost importance to avoid β-blockers before achieving adequate α blockade because lone β blockade leaves α receptors unopposed and open for activation by circulating catecholamines. This situation could potentially promote a hypertensive crisis. Although it is not currently the standard of care, calcium channel blockers have also been effective in the preoperative management of these patients.

Table 51–8 Potential Sources of False-Positive Laboratory Results for Pheochromocytoma

Related to Time of Collection
Posture (fewer false positives if done supine after resting in a dark, quiet room for 30 minutes)
Exercise
Stress
Cold exposure
Hypoglycemia
Dietary or Habits
Caffeine
Nicotine
Alcohol
Ingestion of foods high in tyramine
Cocaine
Medications Listed Here are Those Most Frequently Encountered (Many are Test Dependent)
Tricyclic antidepressants (most other antidepressants can also interfere to a lesser degree)
Phenoxybenzamine
Labetalol
Acetaminophen
Amphetamines
Ephedrine
L-Dopa
Mesalamine
Sulfasalazine

Table 51–9 Syndromes Associated with Pheochromocytoma

Syndrome	Gene	Inheritance	Clinical Findings
MEN2a	*RET*	Autosomal dominant	Primary hyperparathyroidism, medullary thyroid carcinoma, Hirschsprung disease
MEN2b	*RET*	Autosomal dominant	Primary hyperparathyroidism, medullary thyroid carcinoma, mucosal ganglioneuromas, Marfanoid body habitus
Neurofibromatosis type 1	*NF1*	Autosomal dominant	Café-au-lait spots, axillary/inguinal freckling, neurofibromas, Lisch nodules, scoliosis, malignant nerve sheath tumors
von Hippel–Lindau syndrome	*VHL*	Autosomal dominant	Hemangiomas of the CNS, retinal angiomas, renal cell cancer, pancreatic neuroendocrine tumors, endolymphatic sac tumors
Carney triad	Unknown	Unknown	Gastrointestinal stromal tumors, pulmonary chondromas
Carney-Stratakis dyad	*SDHx*	Autosomal dominant	Gastrointestinal stromal tumors
Familial Paraganglioma Syndromes			
Paraganglioma syndrome 1	*SDHD*	Maternally imprinted	Head and neck parasympathetic paragangliomas (parent of origin effect—paternal), GIST, pituitary adenoma
Paraganglioma syndrome 2	*SDHAF2*	Maternally imprinted	Rare; head and neck parasympathetic paragangliomas (parent of origin effect—paternal)
Paraganglioma syndrome 3	*SDHC*	Autosomal dominant	Head and neck parasympathetic paragangliomas, GIST
Paraganglioma syndrome 4	*SDHB*	Autosomal dominant	Renal cell cancer, paragangliomas located in the chest/abdomen/pelvis, GIST, pituitary adenoma
Paraganglioma syndrome 5	*SDHA*	Autosomal dominant	Rare cause of PPGL; low penetrance; GIST, pituitary adenoma

CNS, central nervous system; GIST, gastrointestinal stromal tumor; MEN, multiple endocrine neoplasia.
Data from Waguespack SG, Rich T, Grubbs E, et al. A current review of the etiology, diagnosis, and treatment of pediatric pheochromocytoma and paraganglioma. *J Clin Endocrinol Metab*. 2010;95(5):2023-2037; Jimenez C, Cote G, Arnold A, Gagel RF. Review: should patients with apparently sporadic pheochromocytomas or paragangliomas be screened for hereditary syndromes? *J Clin Endocrinol Metab*. 2006;91(8):2851-2858; and Benn DE, Robinson BG, Clifton-Bligh RJ. 15 years of paraganglioma: clinical manifestations of paraganglioma syndromes types 1-5. *Endocr Relat Cancer*. 2015;22(4):T91-T103.

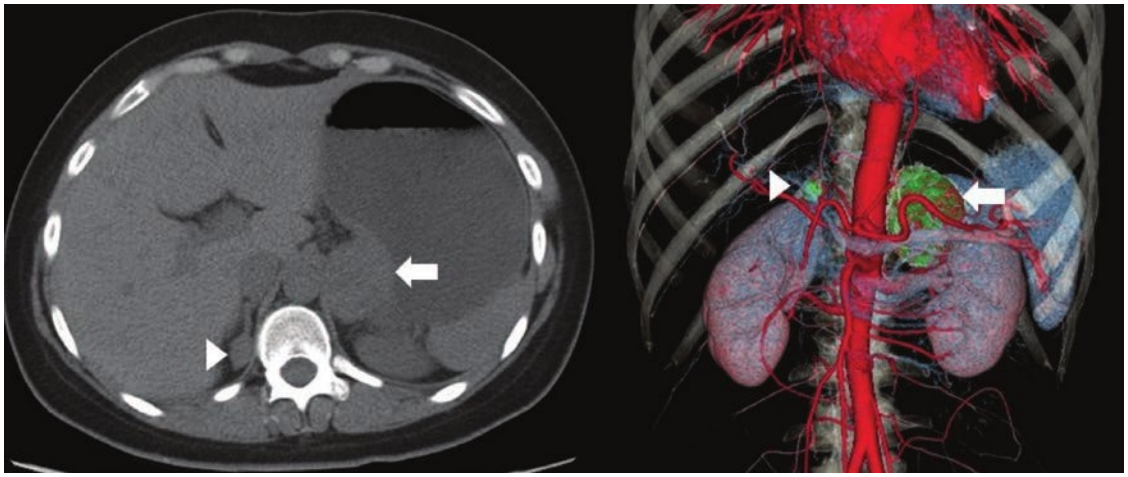


FIGURE 51–18 This is a patient with multiple endocrine neoplasia type 2A and bilateral adrenal pheochromocytomas. The computed tomography (CT) scan (*left*) and CT angiogram (*right*) show a 1.6-cm pheochromocytoma in the medial limb of the right adrenal gland (*white arrowheads*) and a 4.6-cm pheochromocytoma in the left adrenal gland (*white arrows*).

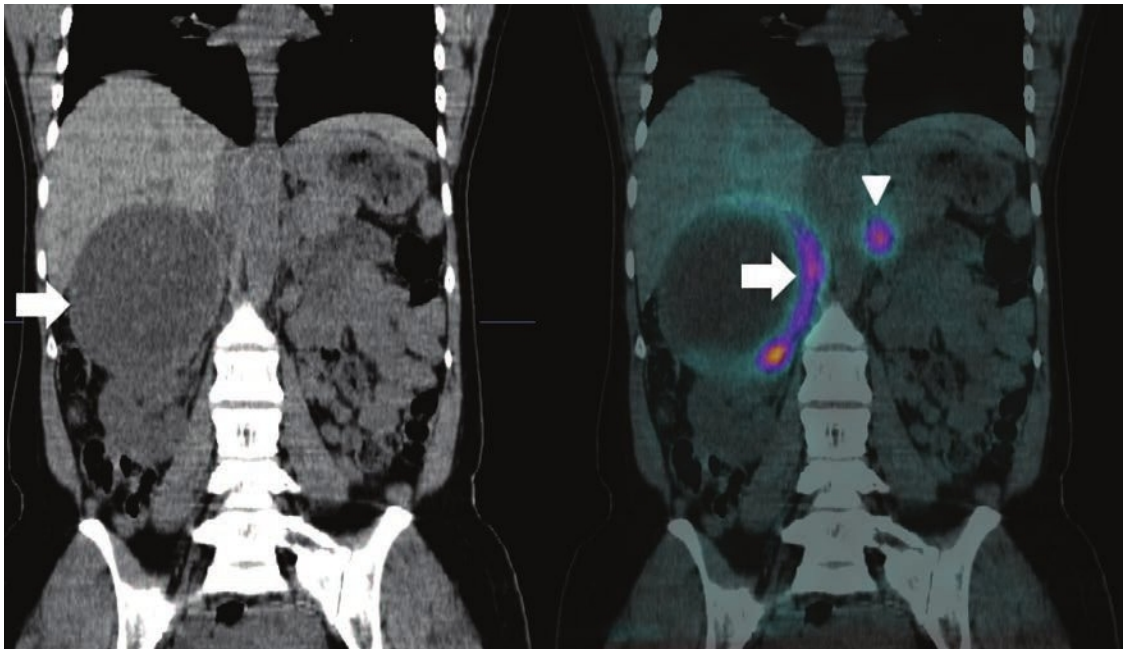


FIGURE 51–19 This is a patient with bilateral adrenal pheochromocytomas. These images are coronal views from a single photon emission computed tomography on the left and a meta-iodobenzylguanidine scan on the right. They show increased uptake in the periphery of a cystic right-sided adrenal pheochromocytoma (*white arrows*) as well as a smaller left-sided adrenal pheochromocytoma (*white arrowhead*).

Surgical

Surgical resection after appropriate medical therapy is the primary mode of treatment for benign pheochromocytoma or paraganglioma. For smaller tumors, minimally invasive surgeries can reduce blood loss and hospital length of stay. As a result, the preferred procedures are laparoscopic or posterior retroperitoneoscopic adrenalectomy. However, in some cases, a larger tumor or a lack of local surgical experience with these techniques may make an open procedure preferable.

Close hemodynamic monitoring with pre- and intraoperative volume repletion is important to avoid hypotension after tumor resection. Short-acting intravenous vasodilators (eg, nitroprusside, nitroglycerine, phentolamine) may be needed intraoperatively to

decrease the risk of precipitating a hypertensive crisis during tumor manipulation. Intravenous fluids should contain dextrose because patients are prone to hypoglycemia as a result of rebound insulin secretion after the precipitous drop in catecholamine levels after successful tumor resection. In patients who have pheochromocytoma associated with a germline mutation or bilateral adrenal disease, cortical-sparing adrenalectomy is the procedure of choice to minimize the risk of lifelong adrenal insufficiency. However, these patients require long-term follow-up because recurrence may develop many years after their primary surgery, and some may develop adrenal insufficiency despite a cortical-sparing technique.[63]

METASTATIC PHEOCHROMOCYTOMA

Introduction

Unfortunately, there are no reliable clinical or pathologic features of the primary tumor that have been shown to consistently identify malignant pheochromocytoma or paraganglioma. As a result, the diagnosis can only be made after the discovery of metastatic disease. The most common sites of metastasis are the axial skeleton, followed by the liver, lymph nodes, lungs, and peritoneum.[64] Although a generally quoted statistic is that 10% of pheochromocytomas are malignant, the risk of metastatic pheochromocytoma/paraganglioma is much higher and approaching 35% in all patients and close to 70% in patients with germline *SDHB* mutation.[65]

In a large retrospective review, it was found that almost half of patients with metastatic pheochromocytoma or paraganglioma are diagnosed with metachronous metastases (ie, they were thought to have benign disease until they were later found to have metastatic disease). This review identified tumor size (>5 cm) and site of primary tumor (infra-diaphragmatic para-aortic paraganglia or the mediastinum) as being associated with a higher incidence of malignancy. However, there were no criteria that reliably excluded the possibility of malignancy, and newly noted metastatic disease can be found up to 20 years after resection of an apparently benign pheochromocytoma. It is for these reasons that lifelong surveillance of patients with seemingly benign pheochromocytoma or paraganglioma is always recommended.[66]

Diagnosis

Because the diagnosis is made based on identification of metastatic disease, a combination of laboratory testing, imaging, and pathologic confirmation is generally relied upon. Typical staging studies include cross-sectional imaging (ie, CT or MRI) of the chest, abdomen, and pelvis. In the setting of malignant pheochromocytoma or paraganglioma, functional studies may be used to complement cross-sectional imaging. For example, MIBG scintigraphy has been used since 1981 to localize pheochromocytoma. Its usefulness is based on the fact that MIBG structurally resembles norepinephrine and is stored in the catecholamine-storage vesicles. For patients in whom dedifferentiation has occurred, as well as patients with an *SDHB* mutation, PET scans using FDG or Ga-dotatate have been a useful adjunct to cross-sectional imaging. Furthermore, 6-[^{18}F]fluorodopamine PET scanning may have a role in the future but is not widely available (Fig. 51–20).[67,68]

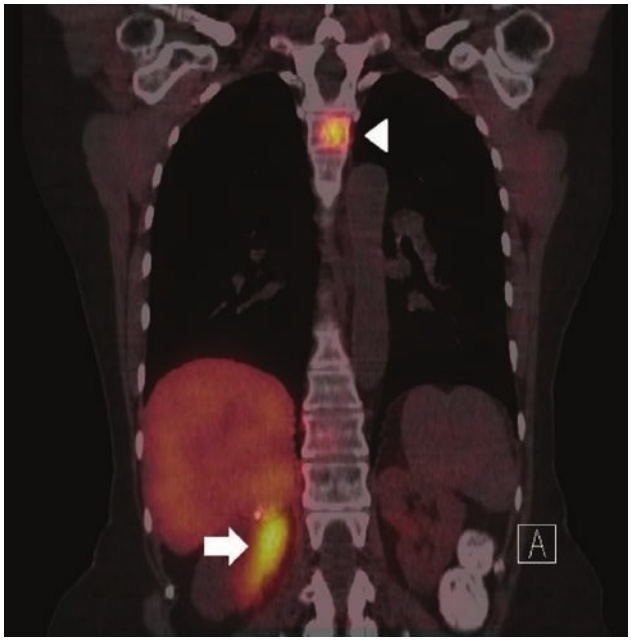


FIGURE 51–20 Meta-iodobenzylguanidine scan showing uptake in recurrent malignant pheochromocytoma in the right adrenal bed (*white arrow*), as well as metastatic disease in the T2 vertebral body (*white arrowhead*).

Given the rarity of this entity, mostly retrospective data exist regarding prognosis. In a meta-analysis, the 10-year mortality rate was 29%, with male patients and those presenting with synchronous metastases having a worse prognosis.[69] The American Joint Committee on Cancer's 8th edition of cancer staging used the TNM (T = primary tumor size, N = lymph node involvement, M = distant metastasis) staging system in metastatic pheochromocytoma/paraganglioma. In this system, tumors larger than 5 cm are associated with a worse prognosis compared with primary tumor smaller than 5 cm. Other important prognostic features include extra-adrenal location and the location of distant metastases.[70]

Therapy

Medical/Surgical

Medical therapy is recommended following the same process as for benign tumors. For patients whose disease is potentially curable, surgery via an open approach is the preferred strategy. In patients for whom surgical cure is not feasible, palliative surgery has been associated with improved survival and is recommended to assist with the control of catecholamine excess or for the prevention of complications related to the location of the disease.[71] Because skeletal metastases are commonly seen, it is important to consider antiresorptive therapy to reduce the risk of skeletal-related events and associated morbidity.

Radiation and Radiofrequency Ablation

If there is evidence of MIBG avidity, radiolabeled therapy can be used as a carrier for ^{131}I delivery as targeted therapy. Traditional MIBG has been associated with tumor response rates of about 30% and hormonal response in about 40% of treated patients.[72] Ultratrace iobenguane I-131 is produced using a solid-phase resin to reduce the percentage of unlabeled MIBG. Iobenguane I-131 is now FDA approved for patients 12 year and older with metastatic pheochromocytoma/paraganglioma that retain MIBG avidity. A multicenter, phase 2 trial reported the outcomes of 68 patients who received at least one iobenguane I-131 dose (~18.5 GBq) intravenously. More than 90% of evaluable patients had a partial response or stable disease within the first year and 25% had durable reduction in their antihypertensive therapy. Nausea, fatigue, and myelosuppression were the most common adverse events.[73]

Considering the neuroendocrine origin of pheochromocytoma/paraganglioma, somatostatin receptor expression is seen in the majority of these cases. The data about the efficacy of peptide receptor radionuclide therapy targeting somatostatin receptor in metastatic pheochromocytoma/paraganglioma are emerging. In 20 consecutive patients with metastatic pheochromocytoma/paraganglioma and high somatostatin receptor expression, ^{177}Lu-dotatate was associated with partial tumor response and blood pressure improvement in 29% and 57% of patients, respectively.[74]

External beam radiation therapy can also be used for symptomatic relief of metastases not amenable to surgical resection. Retrospective studies have demonstrated improvement in symptoms but no dramatic response of the tumor on imaging.[75] Radiofrequency ablation (RFA) has also been attempted in a limited number of patients with metastatic pheochromocytoma and can be considered as part of the treatment armamentarium.[76]

Chemotherapy

Traditional cytotoxic chemotherapy has been used with some success, though the survival benefit is unclear. The regimens most often used are CVD (cyclophosphamide, vincristine, and dacarbazine) and CVAD (cyclophosphamide, vincristine, doxorubicin, and dacarbazine). In a meta-analysis that included four studies (total 50 patients) with metastatic pheochromocytoma/paraganglioma, CVD chemotherapy was associated with complete response in 4%, partial response in 37%, and stable disease in 14% of treated patients and improvement of catecholamine excess in 54% of patients.[77]

Although initial reports using a multikinase inhibitor (sunitinib) suggested partial short-term responses in a very small number of patients, data regarding the long-term efficacy and validation of these findings are still lacking.[78] The data are more limited with other tyrosine kinas inhibitors. Pazopanib use in metastatic pheochromocytoma/paraganglioma was associated with significant toxicity and lack of efficacy based on a reported phase 2 study that enrolled six evaluable patients. In this small cohort, four patients had disease progression, one had grade 4 cardiomyopathy, and one withdrew from the study.[79] Cabozantinib is another multitarget kinase inhibitor and its efficacy in metastatic pheochromocytoma/paraganglioma is being studied in an ongoing phase 2 trial (NCT02302833).

Immunotherapy

Over the past decade, immune checkpoint inhibitors have transformed cancer care, and these drugs are now approved to treat a plethora of solid and hematologic malignancies. However, the role of immunotherapy in metastatic pheochromocytoma/paraganglioma is not yet defined. In a recently published phase 2 study, 11 patients with metastatic pheochromocytoma/paraganglioma received pembrolizumab 200 mg intravenously every 3 weeks. Only one patient had partial response and the clinical benefit rate was estimated to be around 73%.[80]

ADRENOCORTICAL CARCINOMA

Introduction

Adrenocortical carcinoma (ACC) is a rare malignancy with significant morbidity and mortality. A review of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database found the majority of patients (87%) were White and diagnosis occurred at an average age of 51 years. A bimodal distribution of incidence was seen in the first and fourth

Table 51–10 Clinical Syndromes Associated with Hormonally Functional Adrenocortical Carcinoma

Clinical Syndrome	Suggestive Clinical Features	Suggested Laboratory Workup
Cushing syndrome	Obesity, moon facies, purple striae, cervical fat pads, easy bruising, myopathy, hypertension, diabetes mellitus	Plasma electrolytes, plasma glucose, adrenocorticotropic hormone (ACTH), cortisol, 24-h urine-free cortisol
Virilizing syndrome	Hirsutism, clitoromegaly, temporal balding, increased muscle mass, amenorrhea, male precocious puberty, advanced bone age in children	Dehydroepiandrosterone sulfate (DHEAS), testosterone, 17-OH progesterone
Feminizing syndrome	Gynecomastia, loss of libido	Estradiol, prolactin, testosterone
Hyperaldosteronism	Hypertension, hypokalemia	Plasma renin activity, plasma aldosterone concentration, plasma electrolytes, 18-OH corticosterone
Mixed syndromes	Combinations of features above	Testing as appropriate based on clinical features

Data from Ayala-Ramirez M, Jasim S, Feng L, et al. Adrenocortical carcinoma: clinical outcomes and prognosis of 330 patients at a tertiary care center. *Eur J Endocrinol*. 2013;169(6):891-899.

decades of life. The age-adjusted annual incidence was 0.72 per million in the United States, and there was a slight female predominance (54%).[81]

A review of 330 patients seen at our institution found that 42% of cases were hormonally productive, but there have been studies reporting numbers as high as two-thirds of cases. The majority of cases (55%) were associated with hypercortisolemia, and smaller numbers were associated with hyperaldosteronism or hyperandrogenism. Furthermore, the production of multiple hormones was present in almost 20% of these patients.[82] The various syndromes seen with functioning adrenal cancers are presented in Table 51–10. ACC can be hormonally silent and discovered incidentally on imaging studies or may present with nonspecific symptoms such as back pain, abdominal discomfort, indigestion, or site-specific symptoms based on the location of metastatic disease.

Diagnosis

Laboratory

In addition to the evaluation of general laboratory tests, evaluation of hormonal levels should include serum cortisol, ACTH, 11-deoxycortisol, plasma renin activity, plasma aldosterone concentration, total testosterone (in women), dehydroepiandrosterone sulfate, and estradiol (in men and postmenopausal women). Further workup may be needed, including an overnight 1-mg dexamethasone suppression test or 24-hour urine-free cortisol test to evaluate cortisol production. In addition, urinary or plasma-free metanephrines must be assessed in every patient with an adrenal mass at baseline to rule out functioning pheochromocytoma (Fig. 51–21).

Imaging

Cross-sectional body imaging (CT or MRI) of the chest, abdomen, and pelvis is generally the first step in staging. On CT, ACC is usually a large, heterogeneous mass with attenuation values greater than 10 HU showing heterogeneous contrast enhancement, poor contrast washout, and necrosis. Special attention should be devoted to assessment for metastatic disease in the lungs, liver, bones, and regional lymph nodes. The MRI appearance of ACC is also heterogeneous and hyperintense on T2-weighted images. As seen on CT, contrast enhancement on MRI is heterogeneous with poor washout. Of note, MRI is particularly useful in assessing for tumor invasion of the inferior vena cava. Although FDG-PET scan is a sensitive tool for detecting malignant tissue, its low specificity limits its usefulness. However, FDG-PET can play an important role in the identification of metastatic disease in the setting of known ACC (Figs. 51–22 and 51–23).[83]

Pathology

The Weiss scoring system consists of nine pathologic criteria to aid in the diagnosis of ACC (Fig. 51–24). The criteria include: (1) mitotic rate greater than 5 mitoses per 50 high-power fields in the most active areas of the tumor, (2) atypical mitoses, (3) nuclear grade 3 or 4 tumor (Fuhrman method), (4) clear cells comprising 25% or less of the tumor, (5) tumor necrosis, (6) diffuse (solid) architecture in more than one-third of the tumor, (7) venous invasion, (8) invasion of sinusoidal structures, and (9) capsular invasion. The presence of three or more of these nine features is highly suggestive of ACC.[84] The staging of ACC is detailed in Table 51–11. Ki-67 expression is useful in assessing prognosis and

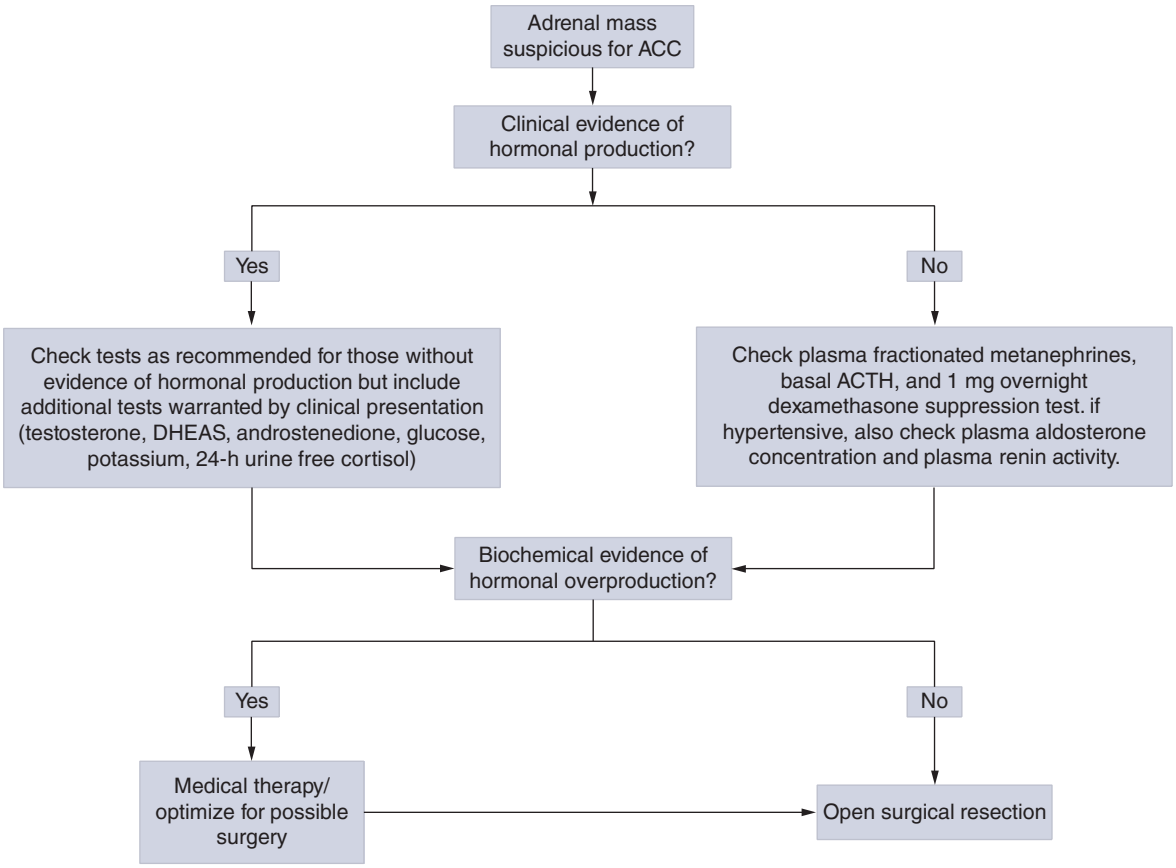


FIGURE 51–21 Hormonal testing for adrenocortical carcinoma (ACC). ACTH, adrenocorticotropic hormone; DHEAS, dehydroepiandrosterone sulfate.

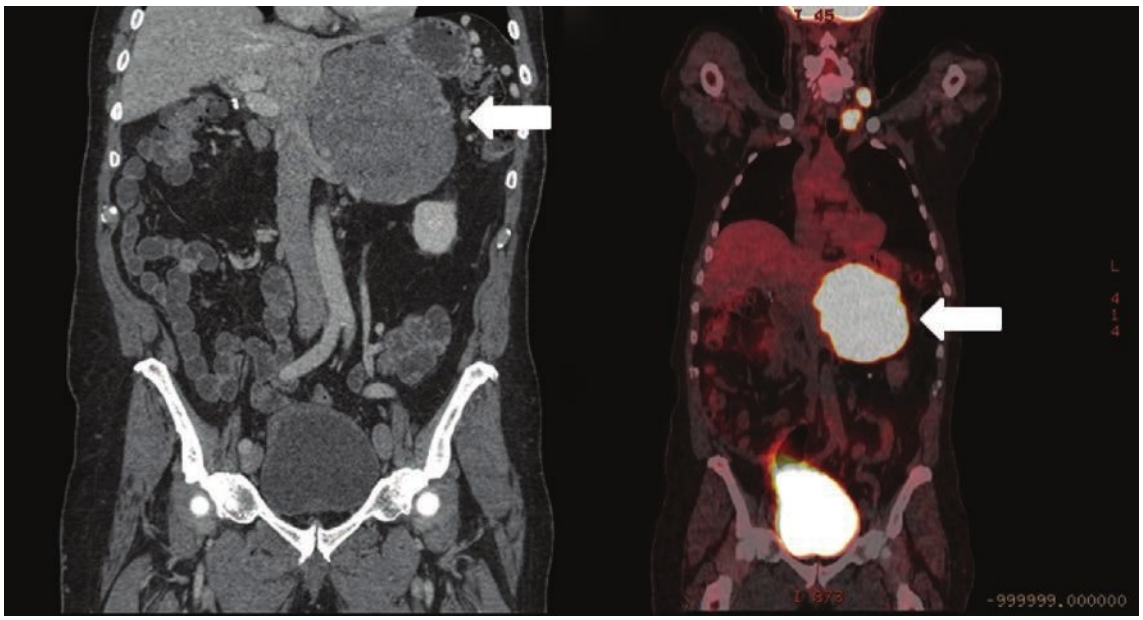


FIGURE 51–22 Coronal images from computed tomography (CT; *left*) and fluorodeoxyglucose–positron emission tomography/CT (*right*) showing left-sided adrenocortical carcinoma (*white arrows*).

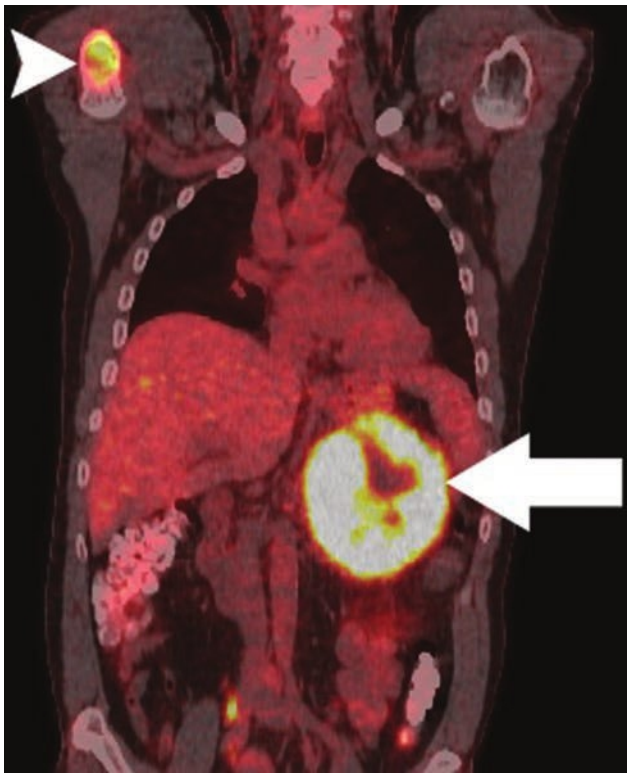
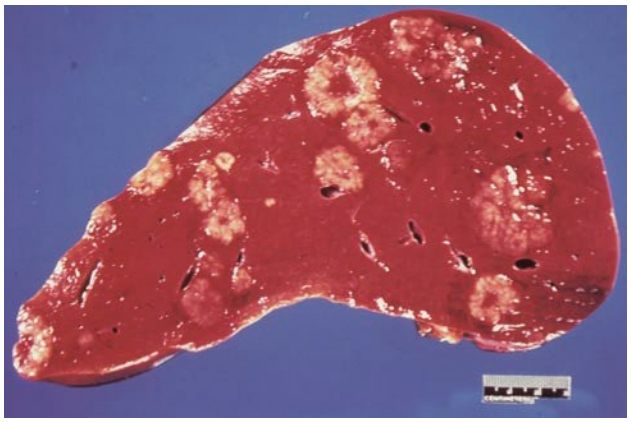


FIGURE 51–23 Fluorodeoxyglucose (FDG) positron emission tomography (PET) scan (coronal view) of a patient with adrenocortical carcinoma (ACC) showing FDG-avid left adrenal mass (*white arrow*) with bone metastases (*arrowhead*).



XFIGURE 51–24 Liver metastases from adrenocortical carcinoma.

should be part of the routine pathologic assessment of ACC; cases with Ki67 higher than 10% tend to have a worse prognosis, with a shortened time to recurrence after surgical resection and shorter survival compared with ACC cases with a lower Ki67 percentage.[85]

In general, FNA of suspected ACC is not recommended because of the risk of seeding the needle track with tumor. However, FNA may be considered after pheochromocytoma has been ruled out in the context of hormonally silent tumor with metastases before embarking on definitive therapy.

Table 51–11 Staging for Adrenocortical Carcinoma

Stage	ENSAT/AJCC 8th Edition
I	Primary tumor ≤5 cm with no nodal or distant metastasis
II	Primary tumor >5 cm with no extra-adrenal spread
III	Primary tumor not invasive but lymph node metastasis present *or* Primary tumor locally invasive or invading adjacent organs but without distant metastasis (lymph node metastasis may be present)
IV	Distant metastasis present (no other requirements)

AJCC, American Joint Committee on Cancer; ENSAT, European Network for the Study of Adrenal Tumors.

Genetics

An association has been observed between ACC and Li-Fraumeni syndrome, Lynch syndrome, and Beckwith-Wiedemann syndrome. Very rarely has ACC been seen in association with MEN1, familial adenomatous polyposis, neurofibromatosis type 1, and Carney complex.[86] As a result, it is important to review family history and to consider referral to genetic counseling in young patients diagnosed with ACC (Table 51–12).

Prognosis

ACC carries high rates of morbidity and mortality. A review of the National Cancer Institute's SEER database found a 1-year cause-specific mortality rate of 58% and a 5-year rate of 88%.[81] However, long-term survival is possible in these patients if complete resection with tumor-free margins can be achieved. At our institution, the 5-year survival rate has been found to be 38%, with a median overall survival of 3.21 years for all patients. As is seen in many other cancers, survival is inversely correlated with disease stage at diagnosis. For example, those with stage I disease had a mean survival of 24.1 years compared with 0.89 years for those with stage IV disease.[81]

Therapy

Surgical

Complete surgical resection is the most important treatment for ACC and offers the best chance for

Table 51–12 Genetic Syndromes Associated with Adrenocortical Carcinoma

Syndrome	Gene(s)	Inheritance	Common Clinical Findings
Li-Fraumeni syndrome	*TP53*	Autosomal dominant	Sarcoma, breast cancer, leukemia, brain tumors, radiation-induced cancers
Beckwith-Wiedemann syndrome	Multiple	Majority of cases are sporadic	Macrosomia, macroglossia, cleft palate, omphalocele, advanced bone age, Wilms tumor, hepatoblastoma
MEN1	*MENIN*	Autosomal dominant	Parathyroid adenoma, pituitary adenoma, pancreatic islet cell tumors, carcinoid, angiofibromas, collagenomas
Familial adenomatous polyposis	*APC*	Autosomal dominant	Colon polyps/cancer, pancreatic cancer, thyroid cancer, medulloblastomas, osteomas
Lynch syndrome	*MLH1, MLH2, MSH6, PMS2*	Autosomal dominant	Colorectal cancer, endometrial cancer, ovarian cancer, glioma, gastric cancer
Carney complex	*PRKAR1A*	Autosomal dominant	Primary pigmented nodular adrenocortical disease, lentigines, testicular cancer (Sertoli cell), thyroid cancer, pancreatic cancer, atrial myxoma
Congenital adrenal hyperplasia	*CYP21A2*	Autosomal recessive	Ambiguous genitalia, precocious puberty, infertility, hirsutism, electrolyte abnormalities

Data from Else T, Kim AC, Sabolch A, et al. Adrenocortical carcinoma. *Endocr Rev*. 2014;35(2):282-326; Libe R, Arlt W, Louiset E, et al. A feminizing adrenocortical carcinoma in the context of a late onset 21-hydroxylase deficiency. *J Clin Endocrinol Metab*. 2014;99(6):1951-1944; and Varma T, Panchani R, Goyal A, Maskey R. A case of androgen-secreting adrenal carcinoma with non-classical congenital adrenal hyperplasia. *Indian J Endocrinol Metab*. 2013;17(suppl 1):S243-S245.

prolonged disease-free survival. If ACC is suspected, laparoscopic adrenalectomy is not recommended because it can result in early locoregional recurrence and peritoneal carcinomatosis. Furthermore, it may decrease the ability to achieve tumor-free margins (R0) or adequate lymph node dissection.[87] Tumor encasement of the celiac axis, aorta, or proximal superior mesenteric artery may make the tumor unresectable. In contrast, the presence of tumor thrombus in the inferior vena cava or renal vein, or tumor invasion of the pancreas, spleen, or kidney, is not a contraindication for complete resection in selected patients. Although there is limited evidence of benefit from resection of the primary tumor in the presence of metastatic disease, there may still be a role for resection of the primary tumor and all visible metastases in an otherwise young, healthy patient, especially in cases of symptomatic, hormonally active tumors.

In corticosteroid-producing ACC, there is speculation that preoperative blockade of steroid production using agents such as ketoconazole or metyrapone may reduce postoperative morbidity. In these cases, the contralateral adrenal gland is usually atrophic, and patients may require peri- and postoperative corticosteroid replacement. In fact, relative adrenal insufficiency may last for months after successful resection.

Chemotherapy

In 1949, it was found that oral administration of the insecticide dichlorodiphenyltrichloroethane (DDT) to dogs caused selective necrosis of zona fasciculata and zona reticularis of the adrenal cortex. Since 1960, a DDT analog known as mitotane has been used to treat ACC. Mitotane is fat soluble and requires on average 3 to 4 months to achieve therapeutic serum levels (target 14–20 mg/L).[88] Mitotane is approved to treat metastatic/unresectable ACC but is often used in adjuvant setting based on retrospective data and expert guidelines.[89,90] In addition to adrenal toxicity, mitotane also increases corticosteroid-binding globulin and enhances steroid clearance. As a result, there are increased glucocorticoid requirements during mitotane therapy, and failure to adequately replace glucocorticoids can result in adrenal crisis. Other potential side effects include hypothyroidism, male hypogonadism, ovarian cysts, dyslipidemia, elevated liver enzymes, and, rarely, hematuria. Our starting mitotane dose is 1.5 g/day and the dose increases within 1 week to 4.5 g/day. Subsequently, mitotane use requires periodic measurement of mitotane serum levels (every 3–4 weeks initially, then every 2–3 months after achieving therapeutic levels). When the mitotane level reaches 20 mg/L or higher, or in patients with adverse events, we often reduce the dose by 25% to 50% and occasionally hold therapy temporarily. After achieving therapeutic level, most patients require much lower maintenance dose (1–2 g/day) to remain within therapeutic range. In addition to monitoring mitotane level, mitotane therapy requires careful clinical and biochemical assessment to manage unwanted adverse side effects (Fig. 51–25).[91]

In terms of other chemotherapeutic agents, an international phase 3 study (FIRM-ACT) compared mitotane plus EDP (etoposide, doxorubicin, cisplatin)



FIGURE 51–25 Chest radiographs of a patient with metastatic ACC. These images demonstrate the multiple bilateral lung metastases before mitotane (*left*) and remarkable improvement after mitotane use (*right*).

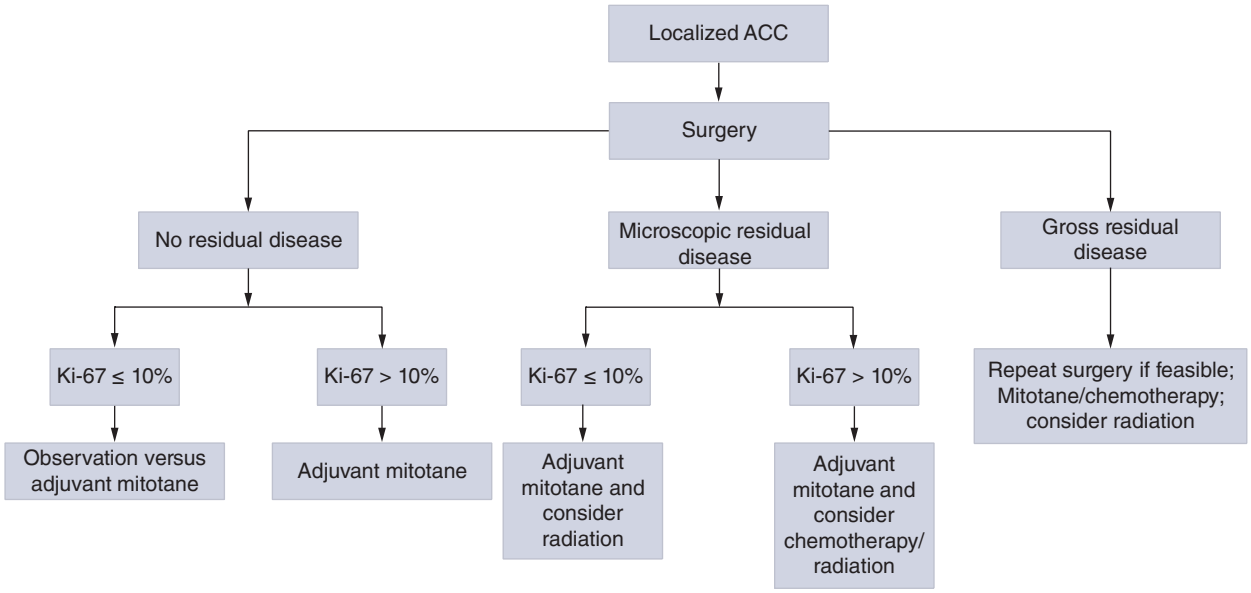


FIGURE 51–26 Management of localized adrenocortical carcinoma (ACC).

with mitotane plus streptozotocin. In this study, it was found that mitotane-EDP showed better tumor response compared with mitotane-streptozocin (23% vs 9%) and better PFS (5.3 vs 2.1 months).[92] Our current practice in managing ACC is summarized in Figs. 51–26 and 51–27. Beyond mitotane-EDP, there is no proven second-line chemotherapy regimen, and multiple treatments such as gemcitabine-capecitabine, temozolomine, and others did not prove to be reasonably effective.

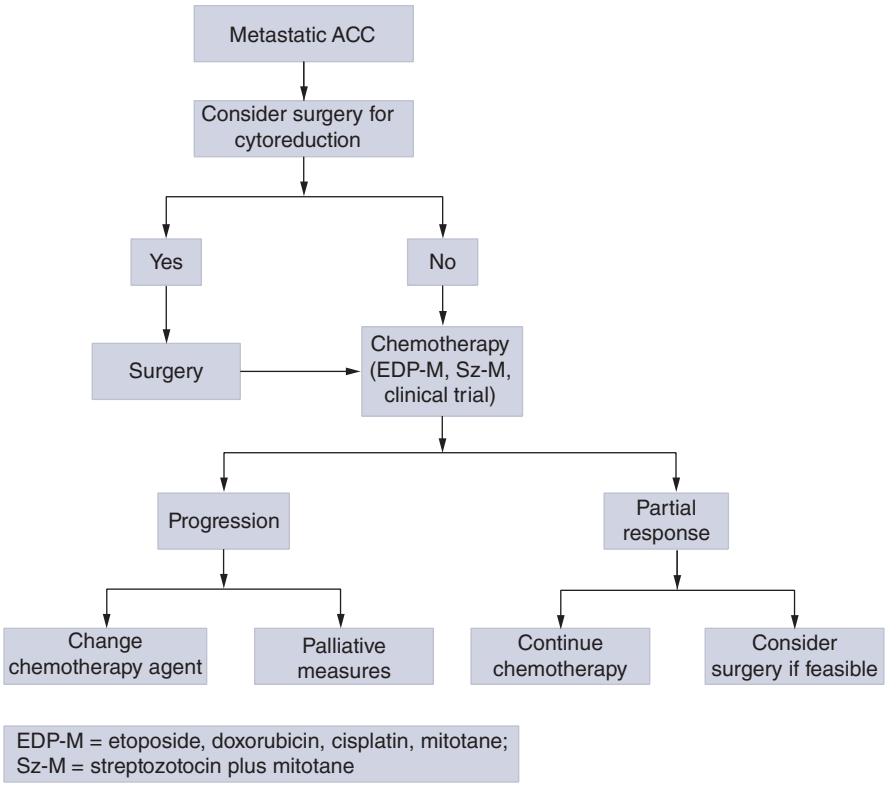


FIGURE 51–27 **Management of metastatic adrenocortical carcinoma (ACC).**

Targeted therapies are also a fertile area for clinical investigation. Potential candidates include insulin-like growth factor-1R inhibitors, epidermal growth factor receptor inhibitors, multitarget TKIs, mammalian target of rapamycin inhibitors, and Wnt signaling pathway inhibitors.[93] Enrollment in clinical trials for the use of investigational agents is favored to help answer important clinical questions regarding safety and efficacy.

Immunotherapy

The role of immunotherapy in ACC is evolving. Multiple studies reported the early experience with immune checkpoint inhibitors in advanced ACC. Avelumab (programmed cell death ligand 1 inhibitor), nivolumab (programmed cell death protein 1 inhibitor), and pembrolizumab (programmed cell death protein 1 inhibitor) were studied in patients with ACC.

Although few participants had prolonged disease control, the efficacy rates were generally low and ranged from 6% to 23%.[94] The combined use of TKIs (lenvatinib) with immunotherapy (pembrolizumab) has been reported in a small group of patients, and some patients had sustained response to therapy after failing to respond to multiple lines of therapy including prior use of immunotherapy alone.[95] It is very important to explore the combined use of immune checkpoint inhibitors with other available treatments (mitotane, cytotoxic chemotherapy, multikinase inhibitors) to improve the current status of ACC therapy.

Radiation and Radiofrequency Ablation

ACC is generally considered a radioresistant tumor, and adjuvant radiation may not reduce the risk of recurrence or increase overall survival, although recent retrospective data suggested survival benefit of adjuvant radiation therapy in patients who had positive resection margins after surgery.[96] More commonly, radiation treatment is used in selected patients with metastatic ACC for palliation of symptomatic metastasis. Percutaneous image-guided RFA has also been attempted in the setting of unresectable primary or metastatic ACC. This procedure may be useful for short-term, local control of small adrenal tumors, but further data are needed to elucidate the long-term efficacy and potential impact on survival.

MD ANDERSON PRACTICE TIPS

- Tumor profiling has transformed the management of patients with differentiated thyroid carcinoma. Patients with actionable mutation can be enrolled in clinical trials or use approved targeted therapy. The role of immunotherapy is evolving and often used in combination with targeted therapy
- The use of targeted therapy in patients with metastatic thyroid carcinoma must be guided by objective evidence of disease progression and not by circulating tumor markers alone.
- A multimodality approach in ATC has transformed the management and improved the outcomes of this disease. Tumor profiling to identify actionable mutations (mainly BRAF) can open the door to using BRAF/MEK inhibitors in combination with other therapies such as surgery, radiation, and immunotherapy.
- Aggressive control of hypertension is critical in patients with metastatic pheochromocytoma/paraganglioma before the use of radiopharmaceutical therapy. It is also very important to control blood pressure before the use of anti-angiogenic therapy.
- A laparoscopic approach is discouraged when managing disease in patients with suspected ACC. Open resection is associated with a higher chance to achieve complete resection with pathologically negative margins compared with the laparoscopic approach. The risk of peritoneal carcinomatosis is also higher with laparoscopic resection compared with open resection
- In patients with borderline resectable ACC, the use of neoadjuvant chemotherapy (mitotane + platinum-based chemotherapy) can facilitate surgical resection and is associated with improved outcome.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin.* 2020;70(1):7-30.
2. Yassa L, Cibas ES, Benson CB, et al. Long-term assessment of a multidisciplinary approach to thyroid nodule diagnostic evaluation. *Cancer.* 2007;111(6):508-516.
3. Guth S, Theune U, Aberle J, Galach A, Bamberger CM. Very high prevalence of thyroid nodules detected by high frequency (13 MHz) ultrasound examination. *Eur J Clin Invest.* 2009;39(8):699-706.
4. Nikiforov YE, Ohori NP, Hodak SP, et al. Impact of mutational testing on the diagnosis and management of patients with cytologically indeterminate thyroid nodules: a prospective analysis of 1056 FNA samples. *J Clin Endocrinol Metab.* 2011;96(11):3390-3397.
5. Alexander EK, Schorr M, Klopper J, et al. Multicenter clinical experience with the Afirma gene expression classifier. *J Clin Endocrinol Metab.* 2014;99(1):119-125.
6. Ivanov VK, Kashcheev VV, Chekin SY, et al. Radiation-epidemiological studies of thyroid cancer incidence in Russia after the Chernobyl accident (estimation of radiation risks, 1991-2008 follow-up period). *Radiat Prot Dosimetry.* 2012;151(3):489-499.
7. Ma J, Huang M, Wang L, Ye W, Tong Y, Wang H. Obesity and risk of thyroid cancer: evidence from a meta-analysis of 21 observational studies. *Med Sci Monit.* 2015;21:283-291.
8. Carhill AA, Litofsky DR, Sherman SI. Unique characteristics and outcomes of patients diagnosed with both primary thyroid and primary renal cell carcinoma. *Endocr Pract.* 2015;21(5):461-467.
9. Haugen BR, Sherman SI. Evolving approaches to patients with advanced differentiated thyroid cancer. *Endocr Rev.* 2013;34(3):439-455.
10. Bounacer A, Wicker R, Caillou B, et al. High prevalence of activating ret proto-oncogene rearrangements, in thyroid tumors from patients who had received external radiation. *Oncogene.* 1997;15(11):1263-1273.
11. Xing M, Alzahrani AS, Carson KA, et al. Association between BRAF V600E mutation and recurrence of papillary thyroid cancer. *J Clin Oncol.* 2015;33(1):42-50.
12. Xing M, Liu R, Liu X, et al. BRAF V600E and TERT promoter mutations cooperatively identify the most aggressive papillary thyroid cancer with highest recurrence. *J Clin Oncol.* 2014;32(25):2718-2726.
13. Carmeliet P, Jain RK. Molecular mechanisms and clinical applications of angiogenesis. *Nature.* 2011;473(7347):298-307.
14. Haugen BR. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: what is new and what has changed? *Cancer.* 2017;123(3):372-381.
15. Nixon IJ, Ganly I, Patel SG, et al. Thyroid lobectomy for treatment of well differentiated intrathyroid malignancy. *Surgery.* 2012;151(4):571-579.
16. Matsuzu K, Sugino K, Masudo K, et al. Thyroid lobectomy for papillary thyroid cancer: long-term follow-up study of 1,088 cases. *World J Surg.* 2014;38(1):68-79.
17. Vaisman F, Shaha A, Fish S, Tuttle RM. Initial therapy with either thyroid lobectomy or total thyroidectomy without radioactive iodine remnant ablation is associated with very low rates of structural disease recurrence in properly selected patients with differentiated thyroid cancer. *Clin Endocrinol (Oxf).* 2011;75(1):112-119.
18. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med.* 1994;97(5):418-428.
19. Sawka AM, Thabane L, Parlea L, et al. Second primary malignancy risk after radioactive iodine treatment for thyroid cancer: a systematic review and meta-analysis. *Thyroid.* 2009;19(5):451-457.
20. Schwartz DL, Lobo MJ, Ang KK, et al. Postoperative external beam radiotherapy for differentiated thyroid cancer: outcomes and morbidity with conformal treatment. *Int J Radiat Oncol Biol Phys.* 2009;74(4):1083-1091.
21. Chiovato L, Latrofa F, Braverman LE, et al. Disappearance of humoral thyroid autoimmunity after complete removal of thyroid antigens. *Ann Intern Med.* 2003;139(5 Pt 1):346-351.
22. Spencer C, Fatemi S, Singer P, Nicoloff J, Lopresti J. Serum Basal thyroglobulin measured by a second-generation assay correlates with the recombinant human thyrotropin-stimulated thyroglobulin response in patients treated for differentiated thyroid cancer. *Thyroid.* 2010;20(6):587-595.
23. Wexler JA. Approach to the thyroid cancer patient with bone metastases. *J Clin Endocrinol Metab.* 2011;96(8):2296-2307.
24. Brose MS, Nutting CM, Jarzab B, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. *Lancet.* 2014;384(9940):319-328.
25. Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N Engl J Med.* 2015;372(7):621-630.
26. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N Engl J Med.* 2018;378(8):731-739.
27. Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib and trametinib treatment in patients with locally advanced or metastatic BRAF V600-mutant anaplastic thyroid cancer. *J Clin Oncol.* 2018;36(1):7-13.
28. Wirth LJ, Sherman E, Robinson B, et al. Efficacy of selpercatinib in RET-altered thyroid cancers. *N Engl J Med.* 2020;383(9):825-835.
29. Carhill AA, Cabanillas ME, Jimenez C, et al. The noninvestigational use of tyrosine kinase inhibitors in thyroid cancer: establishing a standard for patient safety and monitoring. *J Clin Endocrinol Metab.* 2013;98(1):31-42.
30. Waguespack SG, Francis G. Initial management and follow-up of differentiated thyroid cancer in children. *J Natl Compr Canc Netw.* 2010;8(11):1289-1300.
31. American Thyroid Association Guidelines Task Force; Kloos RT, Eng C, Evans DB, Francis GL, Gagel RF, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. *Thyroid.* 2009;19(6):565-612.
32. Wohllk N, Cote GJ, Bugalho MM, et al. Relevance of RET proto-oncogene mutations in sporadic medullary thyroid carcinoma. *J Clin Endocrinol Metab.* 1996;81(10):3740-3745.
33. Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. *J Clin Endocrinol Metab.* 2001;86(12):5658-5671.
34. Wells SA Jr, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. *Thyroid.* 2015;25(6):567-610.
35. Tuttle RM, Ball DW, Byrd D, et al. Medullary carcinoma. *J Natl Compr Canc Netw.* 2010;8(5):512-530.
36. Brierley J, Tsang R, Simpson WJ, Gospodarowicz M, Sutcliffe S, Panzarella T. Medullary thyroid cancer: analyses of survival and prognostic factors and the role of radiation therapy in local control. *Thyroid.* 1996;6(4):305-310.
37. Tran K, Khan S, Taghizadehasl M, et al. Gallium-68 Dotatate PET/CT is superior to other imaging modalities in the detection of medullary carcinoma of the thyroid in the presence of high serum calcitonin. *Hell J Nucl Med.* 2015;18(1):19-24.
38. Smallridge RC, Ain KB, Asa SL, et al. American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. *Thyroid.* 2012;22(11):1104-1139.

39. Kebebew E, Greenspan FS, Clark OH, Woeber KA, McMillan A. Anaplastic thyroid carcinoma. Treatment outcome and prognostic factors. *Cancer.* 2005;103(7):1330-1335.
40. Smallridge RC, Copland JA. Anaplastic thyroid carcinoma: pathogenesis and emerging therapies. *Clin Oncol (R Coll Radiol).* 2010;22(6):486-497.
41. Maniakas A, Dadu R, Busaidy NL, et al. Evaluation of overall survival in patients with anaplastic thyroid carcinoma, 2000-2019. *JAMA Oncol.* 2020.
42. Iyer PC, Dadu R, Gule-Monroe M, et al. Salvage pembrolizumab added to kinase inhibitor therapy for the treatment of anaplastic thyroid carcinoma. *J Immunother Cancer.* 2018;6(1):68.
43. Hundahl SA, Fleming ID, Fremgen AM, Menck HR. Two hundred eighty-six cases of parathyroid carcinoma treated in the U.S. between 1985-1995: a National Cancer Data Base Report. The American College of Surgeons Commission on Cancer and the American Cancer Society. *Cancer.* 1999;86(3):538-544.
44. Schulte KM, Talat N. Diagnosis and management of parathyroid cancer. *Nat Rev Endocrinol.* 2012;8(10):612-622.
45. Talat N, Schulte KM. Clinical presentation, staging and long-term evolution of parathyroid cancer. *Ann Surg Oncol.* 2010;17(8):2156-2174.
46. Kutahyalioglu M, Nguyen HT, Kwatampora L, et al. Genetic profiling as a clinical tool in advanced parathyroid carcinoma. *J Cancer Res Clin Oncol.* 2019;145(8):1977-1986.
47. Kang H, Pettinga D, Schubert AD, et al. Genomic profiling of parathyroid carcinoma reveals genomic alterations suggesting benefit from therapy. *Oncologist.* 2019;24(6):791-797.
48. Schantz A, Castleman B. Parathyroid carcinoma. A study of 70 cases. *Cancer.* 1973;31(3):600-605.
49. Cetani F, Pardi E, Borsari S, et al. Genetic analyses of the HRPT2 gene in primary hyperparathyroidism: germline and somatic mutations in familial and sporadic parathyroid tumors. *J Clin Endocrinol Metab.* 2004;89(11):5583-5591.
50. Newey PJ, Bowl MR, Cranston T, Thakker RV. Cell division cycle protein 73 homolog (CDC73) mutations in the hyperparathyroidism-jaw tumor syndrome (HPT-JT) and parathyroid tumors. *Hum Mutat.* 2010;31(3):295-307.
51. DeLellis RA. Parathyroid tumors and related disorders. *Mod Pathol.* 2011;24(suppl 2):S78-S93.
52. Rodgers SE, Perrier ND. Parathyroid carcinoma. *Curr Opin Oncol.* 2006;18(1):16-22.
53. Busaidy NL, Jimenez C, Habra MA, et al. Parathyroid carcinoma: a 22-year experience. *Head Neck.* 2004;26(8):716-726.
54. Perrier ND, Arnold A, Costa-Guda J, et al. Hereditary endocrine tumours: current state-of-the-art and research opportunities: new and future perspectives for parathyroid carcinoma. *Endocr Relat Cancer.* 2020;27(8):T53-T63.
55. Beard CM, Sheps SG, Kurland LT, Carney JA, Lie JT. Occurrence of pheochromocytoma in Rochester, Minnesota, 1950 through 1979. *Mayo Clin Proc.* 1983;58(12):802-804.
56. Mannelli M, Ianni L, Cilotti A, Conti A. Pheochromocytoma in Italy: a multicentric retrospective study. *Eur J Endocrinol.* 1999;141(6):619-624.
57. Neumann HP, Bausch B, McWhinney SR, et al. Germ-line mutations in nonsyndromic pheochromocytoma. *N Engl J Med.* 2002;346(19):1459-1466.
58. Tsirlin A, Oo Y, Sharma R, Kansara A, Gliwa A, Banerji MA. Pheochromocytoma: a review. *Maturitas.* 2014;77(3):229-238.
59. Eisenhofer G, Peitzsch M. Laboratory evaluation of pheochromocytoma and paraganglioma. *Clin Chem.* 2014;60(12):1486-1499.
60. Baez JC, Jagannathan JP, Krajewski K, et al. Pheochromocytoma and paraganglioma: imaging characteristics. *Cancer Imaging.* 2012;12:153-162.
61. Dahia PLM, Clifton-Bligh R, Gimenez-Roqueplo AP, Robledo M, Jimenez C. Hereditary endocrine tumours: current state-of-the-art and research opportunities: metastatic pheochromocytomas and paragangliomas: proceedings of the MEN2019 workshop. *Endocr Relat Cancer.* 2020;27(8):T41-T52.
62. Brunaud L, Boutami M, Nguyen-Thi PL, et al. Both preoperative alpha and calcium channel blockade impact intraoperative hemodynamic stability similarly in the management of pheochromocytoma. *Surgery.* 2014;156(6):1410-7; discussion7-8.
63. Grubbs EG, Rich TA, Ng C, et al. Long-term outcomes of surgical treatment for hereditary pheochromocytoma. *J Am Coll Surg.* 2013;216(2):280-289.
64. Ayala-Ramirez M, Palmer JL, Hofmann MC, et al. Bone metastases and skeletal-related events in patients with malignant pheochromocytoma and sympathetic paraganglioma. *J Clin Endocrinol Metab.* 2013;98(4):1492-1497.
65. Ilanchezhian M, Jha A, Pacak K, Del Rivero J. Emerging treatments for advanced/metastatic pheochromocytoma and paraganglioma. *Curr Treat Options Oncol.* 2020;21(11):85.
66. Ayala-Ramirez M, Feng L, Johnson MM, et al. Clinical risk factors for malignancy and overall survival in patients with pheochromocytomas and sympathetic paragangliomas: primary tumor size and primary tumor location as prognostic indicators. *J Clin Endocrinol Metab.* 2011;96(3):717-725.
67. Timmers HJ, Kozupa A, Chen CC, et al. Superiority of fluorodeoxyglucose positron emission tomography to other functional imaging techniques in the evaluation of metastatic SDHB-associated pheochromocytoma and paraganglioma. *J Clin Oncol.* 2007;25(16):2262-2269.
68. Janssen I, Blanchet EM, Adams K, et al. Superiority of [68Ga]-DOTATATE PET/CT to other functional imaging modalities in the localization of SDHB-associated metastatic pheochromocytoma and paraganglioma. *Clin Cancer Res.* 2015;21(17):3888-3895.
69. Hamidi O, Young WF Jr, Gruber L, et al. Outcomes of patients with metastatic phaeochromocytoma and paraganglioma: a systematic review and meta-analysis. *Clin Endocrinol (Oxf).* 2017;87(5):440-450.
70. Jimenez C, Libutti SK, Landry C, et al. Adrenal neuroendocrine tumors. In: Amin MB, Edge S, Greene F, et al: *AJCC Cancer Staging Manual*. 8th ed. Springer; 2017:919-927.
71. Roman-Gonzalez A, Zhou S, Ayala-Ramirez M, et al. Impact of surgical resection of the primary tumor on overall survival in patients with metastatic pheochromocytoma or sympathetic paraganglioma. *Ann Surg.* 2018;268(1):172-178.
72. van Hulsteijn LT, Niemeijer ND, Dekkers OM, Corssmit EP. (131)I-MIBG therapy for malignant paraganglioma and phaeochromocytoma: systematic review and meta-analysis. *Clin Endocrinol (Oxf).* 2014;80(4):487-501.
73. Pryma DA, Chin BB, Noto RB, et al. Efficacy and safety of high-specific-activity (131)I-MIBG therapy in patients with advanced pheochromocytoma or paraganglioma. *J Nucl Med.* 2019;60(5):623-630.
74. Kong G, Grozinsky-Glasberg S, Hofman MS, et al. Highly favourable outcomes with peptide receptor radionuclide therapy (PRRT) for metastatic rectal neuroendocrine neoplasia (NEN). *Eur J Nucl Med Mol Imaging.* 2019;46(3):718-727.
75. Vogel J, Atanacio AS, Prodanov T, et al. External beam radiation therapy in treatment of malignant pheochromocytoma and paraganglioma. *Front Oncol.* 2014;4:166.
76. Venkatesan AM, Locklin J, Lai EW, et al. Radiofrequency ablation of metastatic pheochromocytoma. *J Vasc Interv Radiol.* 2009;20(11):1483-1490.
77. Niemeijer ND, Alblas G, van Hulsteijn LT, Dekkers OM, Corssmit EP. Chemotherapy with cyclophosphamide, vincristine and dacarbazine for malignant paraganglioma and pheochromocytoma: systematic review and meta-analysis. *Clin Endocrinol (Oxf).* 2014;81(5):642-651.
78. Ayala-Ramirez M, Chougnet CN, Habra MA, et al. Treatment with sunitinib for patients with progressive metastatic

pheochromocytomas and sympathetic paragangliomas. *J Clin Endocrinol Metab.* 2012;97(11):4040-4050.
79. Jasim S, Suman VJ, Jimenez C, et al. Phase II trial of pazopanib in advanced/progressive malignant pheochromocytoma and paraganglioma. *Endocrine.* 2017;57(2):220-225.
80. Jimenez C, Subbiah V, Stephen B, et al. Phase II clinical trial of pembrolizumab in patients with progressive metastatic pheochromocytomas and paragangliomas. *Cancers (Basel).* 2020;12(8).
81. Kebebew E, Reiff E, Duh QY, Clark OH, McMillan A. Extent of disease at presentation and outcome for adrenocortical carcinoma: have we made progress? *World J Surg.* 2006;30(5):872-878.
82. Ayala-Ramirez M, Jasim S, Feng L, et al. Adrenocortical carcinoma: clinical outcomes and prognosis of 330 patients at a tertiary care center. *Eur J Endocrinol.* 2013;169(6):891-899.
83. Takeuchi S, Balachandran A, Habra MA, et al. Impact of (1)(8)F-FDG PET/CT on the management of adrenocortical carcinoma: analysis of 106 patients. *Eur J Nucl Med Mol Imaging.* 2014;41(11):2066-2073.
84. Lau SK, Weiss LM. The Weiss system for evaluating adrenocortical neoplasms: 25 years later. *Hum Pathol.* 2009;40(6):757-768.
85. Beuschlein F, Weigel J, Saeger W, et al. Major prognostic role of Ki67 in localized adrenocortical carcinoma after complete resection. *J Clin Endocrinol Metab.* 2015;100(3):841-849.
86. Petr EJ, Else T. Genetic predisposition to endocrine tumors: diagnosis, surveillance and challenges in care. *Semin Oncol.* 2016;43(5):582-590.
87. Cooper AB, Habra MA, Grubbs EG, et al. Does laparoscopic adrenalectomy jeopardize oncologic outcomes for patients with adrenocortical carcinoma? *Surg Endosc.* 2013;27(11):4026-4032.
88. Kerkhofs TM, Baudin E, Terzolo M, et al. Comparison of two mitotane starting dose regimens in patients with advanced adrenocortical carcinoma. *J Clin Endocrinol Metab.* 2013;98(12):4759-4767.
89. Terzolo M, Angeli A, Fassnacht M, et al. Adjuvant mitotane treatment for adrenocortical carcinoma. *N Engl J Med.* 2007;356(23):2372-2380.
90. Fassnacht M, Dekkers OM, Else T, et al. European Society of Endocrinology Clinical Practice Guidelines on the management of adrenocortical carcinoma in adults, in collaboration with the European Network for the Study of Adrenal Tumors. *Eur J Endocrinol.* 2018;179(4):G1-G46.
91. Basile V, Puglisi S, Calabrese A, et al. Unwanted hormonal and metabolic effects of postoperative adjuvant mitotane treatment for adrenocortical cancer. *Cancers (Basel).* 2020;12(9).
92. Fassnacht M, Terzolo M, Allolio B, et al. Combination chemotherapy in advanced adrenocortical carcinoma. *N Engl J Med.* 2012;366(23):2189-2197.
93. Jasim S, Habra MA. Management of adrenocortical carcinoma. *Curr Oncol Rep.* 2019;21(3):20.
94. Altieri B, Ronchi CL, Kroiss M, Fassnacht M. Next-generation therapies for adrenocortical carcinoma. *Best Pract Res Clin Endocrinol Metab.* 2020;34(3):101434.
95. Bedrose S, Miller KC, Altameemi L, et al. Combined lenvatinib and pembrolizumab as salvage therapy in advanced adrenal cortical carcinoma. *J Immunother Cancer.* 2020;8(2).
96. Nelson DW, Chang SC, Bandera BC, Fischer TD, Wollman R, Goldfarb M. Adjuvant radiation is associated with improved survival for select patients with non-metastatic adrenocortical carcinoma. *Ann Surg Oncol.* 2018;25(7):2060-2066.

This page intentionally left blank

52 The Acquired Immunodeficiency Syndrome–Related Cancers

Adan Rios
Fredrick B. Hagemeister

KEY CONCEPTS

- One million, two-hundred thousand people in the United States (0.3%) were living with HIV in 2018; however, more than 36,000 new infections occurred, and an estimated 1 in 7 (14%) of those with the diagnosis were not aware of it. Forty-five percent of those with new diagnoses identified as Black or Latino. According to World Health Organization (WHO) statistics from 2018, the prevalence globally has not statistically changed among adults 15 to 49 years of age since 2014, and the prevalence is as high as 21% in sub-Saharan Africa (Botswana).
- Classically, Burkitt and aggressive B-cell lymphomas have been AIDS-defining malignancies. Although not originally described as HIV-related, other categories of lymphomas are now identified in the WHO classification as occurring in patients with HIV seropositivity include peripheral T-cell, marginal zone, and Hodgkin lymphoma (HL) subtypes, as well as primary effusion and plasmablastic lymphomas, and others. Cervical carcinoma is the only AIDS-defining cancer; however, other cancers increased in patients with HIV seropositivity include lung cancers and anal carcinomas in men.
- In the post–highly active antiretroviral therapy (HAART) era, there has been a reduction in the incidence of various lymphoma subtypes, including primary central nervous system (CNS) and systemic high-grade B-cell lymphomas, and Kaposi sarcoma (KS), but other lymphoma subtypes have not decreased, including Hodgkin and Burkitt lymphomas.
- Human herpesvirus 8 is responsible for KS, and, as in patients without HIV seropositivity, Epstein-Barr virus (EBV) in some patients with aggressive B-cell and Burkitt lymphomas and human papillomavirus in cervical carcinoma. Other agents associated with these cancers are unknown.
- Patients with advanced HL (stages III–IV) and known HIV disease should receive brentuximab vedotin plus adriamycin/vinblastine/dacarbazine chemotherapy. Limited-stage disease may be treated with therapy as for patients who are seronegative.
- Without the availability of randomized studies, EPOCH-R, tailored to disease extent with number of cycles of therapy adjusted to early positron emission tomography (PET) results, is the preferred regimen for treatment of patients with high-grade lymphomas; this combination is also recommended for those with Burkitt lymphomas, and those with other aggressive lymphoproliferative disorders.

THE CHANGING INCIDENCE OF MALIGNANCIES IN PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS DISEASE

The relationship between malignancies and AIDS changed in 1996 when highly active antiretroviral therapy (HAART) was introduced in industrial nations. Thanks to the United Nations and other philanthropy programs, HAART has also been successfully introduced into a number of developing nations.[1] Africa, the pandemic epicenter, is the exception, because of the epidemic magnitude on that continent and its significant political and social turmoil. Before 1996, epidemiologists noted specific malignancies afflicting patients with AIDS, with a risk proportional to host immune status. Before HAART, patients with AIDS could be separated into two groups: patients with an opportunistic infection as their first manifestation of AIDS (60%) and those with a malignancy as its mode of presentation (40%).[2]

Of those with an AIDS-related malignancy, up to 90% would have Kaposi sarcoma (KS) and the rest non-Hodgkin lymphomas (NHLs), including primary central nervous system lymphoma (PCNSL) and systemic diffuse large B-cell lymphoma (DLBCL). Despite an increase in human papilloma virus (HPV)–related invasive cervical cancers in women with high-grade uterine cervical dysplasia, recent findings of a lack of clear association between cervical cancer and HIV-related immunosuppression question the validity of including cervical cancer among AIDS-defining or associated malignancies.[3] After HAART, previously obvious relationships between AIDS and some malignancies have been challenged. An example is HIV-related Burkitt lymphoma, initially associated with AIDS-induced immunosuppression. Investigators have found that HAART improvement of immunity is associated with significant reductions in KS, PCNSL, and systemic DLBCL, but this is not the case with Burkitt lymphoma. Together with invasive cervical cancer, the incidence of Burkitt lymphoma has remained stable across the pre- and post-HAART eras, increasing its proportional frequency. Epithelial dysplasia and squamous cell carcinomas of the anal canal, rectum, and oral cavity are also observed in men infected by HIV. There has been a post-HAART era increase in HL (Epstein-Barr virus [EBV] related), lung cancer, nonmelanoma skin cancer, cancer of the anus, and cancer of the liver, which has remained similar during the early and late HAART periods and which are known as non–AIDS-defining cancer (NADCs). This category carries implications related to the complex relationship between immunity, aging, chronic antigenic stimulation, and viral oncogenesis. This increase of NADCs has changed malignancies as a cause of death in HIV-infected patients from fewer than 10% of all deaths to as high as 28% post-HAART.[4] Overall, the excess risk of a malignancy in HIV disease is observed mostly in cancers with an established or suspected infectious cause.[5]

In this chapter, we first discuss HIV and its effect on the immune system. We then concentrate on malignancies associated with AIDS immunosuppression. We include a discussion of malignancies (Burkitt lymphoma and HPV-related cancers) not directly associated with HIV immunosuppression occurring with a high enough incidence in HIV-infected patients to merit study.

HIV DISEASE

Historical Significance of the Virus

The AIDS pandemic came into the medical world in 1980 with the publication in the Centers for Disease Control and Prevention's (CDC) journal *Morbidity and Mortality Weekly Report* of a series of patients afflicted by de novo opportunistic infections, mostly *Pneumocystis jiroveci* (formerly known as *Pneumocystis carinii*) pneumonia and cytomegalovirus infections.[6] At about that time, these conditions were known to occur in immunodeficient patients. It was followed by a report of KS in 26 homosexual men thought to be immunologically healthy. The number of similar cases increased exponentially throughout the United States and Europe, with reports from other parts of the world confirming a new pandemic with an epicenter in sub-Saharan Africa. The high number of cases with similar clinical presentations gave way to a new syndrome, the acquired immunodeficiency syndrome, or AIDS. Twenty-five years later, much is known and much is to be learned about the cause of the syndrome, HIV, and its complications, including opportunistic infections and malignancies.[7]

HIV disease is caused by infection of a human subject with a retrovirus, human immunodeficiency virus. The virus is only transmitted through blood or unprotected sexual contact, causing a progressive destruction of the immune system with occurrence of opportunistic infections and malignancies. When an opportunistic infection or a malignancy occurs, it signals a significant degree of immunodeficiency. The association of opportunistic infections and immune suppression is well established in the medical literature and clinical practice. The relationship between immune surveillance dysfunction and development of malignancies has also been described in the medical literature. In the early 1970s, kidney transplantation programs in Canada reported an increased incidence of malignancies in patients treated with the immunosuppressant azathioprine.[8] Similar reports indicated that pharmacologically immune-suppressed patients had increases of several folds of magnitude of certain types of cancers and opportunistic infections.

Typically, they had KS or lymphoproliferative malignancies, although other types of malignancies were also reported. In a sense, these patients had chemically-induced AIDS, whereas HIV patients have biologically-induced AIDS.

Origin of the Disease

Human immunodeficiency virus was discovered in 1983,[9] dispelling much of the mystery surrounding AIDS. The syndrome in humans is caused by a retrovirus, HIV, a lentivirus (Latin *lentus*, meaning "slow," + virus), endemic in African primates, which entered the human population as a result of a cross-species transmission, or zoonosis. Two types of HIV have infected humans: HIV-1 and HIV-2. The HIV-1 virus originated from chimpanzees infected by a retrovirus, the SIVcpz

(the chimpanzee simian immunodeficiency virus), and HIV-2 originated from sooty mangabey monkeys endemically infected by another retrovirus, SIVsm. SIVcpz is the product of recombination in chimpanzees of two monkey retroviruses preyed upon by chimpanzees: the SIVrcm and the SIVgsn (the red capped mangabeys, *Cerocebus torquatus*, and the great spot-nosed monkeys, *Cercopithecus nictitans*, respectively). These viruses do not cause disease in their natural hosts and were named simian immunodeficiency viruses, or SIV, after their genetic and structural similarities with HIV. Both HIV types (1 and 2) are phylogenetically classified in groups and clades; HIV-1 has three groups: M (major), N (non-M, non-O), and O (outlier), with a possible group P ("pending" the identification of further human cases). The predominant group M comprises 12 clades A–L, and HIV-2 has eight clades, A–H. The HIV-1 and HIV-2 clades can recombine giving origin to genetically complex viral quasispecies. Transmission from animals to humans occurs when infected animals enter in contact with humans as a result of hunting and butchering (SIVcpz from chimpanzees) or through contact with infected animals used as domestic pets (sooty mangabey monkeys).[10]

The HIV-2 virus is endemic and contained in coastal West Africa. The HIV-1 virus is endemic in west equatorial Africa, with several clades from the group M responsible for the majority of worldwide infections. In the Western world, HIV-1B is responsible for more than 90% of infections, whereas in Africa, subtypes A, C, D, and G, and in Asia, subtype C and the circulating recombinant forms (CRFs) 01 and 02 can be found. The disease is diagnosed by detecting serum anti-HIV antibodies using an enzyme-linked immunosorbent assay (ELISA) test. The initial result can be corroborated by a repeated ELISA test (saying "with another ELISA test" implies a different type of ELISA) or by a Western blot blood test. The amount of replicating virus can be measured by quantitative polymerase chain reaction (PCR) or via signal amplification such as branch-DNA HIV viral load test.[11]

Status of the Pandemic and Its Effects on the Immune System

HIV and AIDS are responsible for a human tragedy of incalculable proportions. Since the pandemic's beginnings, there have been more than 30 million deaths and more than 70 million persons infected, including those who have died. The estimated rate of new infections is 5000 new infections per day. Most of these new infections occur in developing nations, affecting many women and children. The most frequent modes of transmission are unprotected sex and intravenous (IV) drug use. The main epicenter of the pandemic continues to be sub-Saharan Africa, with new epicenters in the former Soviet Union, China, India, and Latin America. In the United States, minority groups such as Hispanics and Blacks, as well as younger generations of gay men, are disproportionately affected by HIV.[12]

HIV is an enveloped diploid RNA virus (two RNA ribbons per particle), each with an armamentarium of enzymes essential for the virus life cycle. The viral particle membrane is composed of human leukocyte antigen (HLA) groups, other cell surface membrane proteins, and the viral protein gp120 in a trimer form. Among the enzymes within the viral particle are reverse transcriptase, integrase, and proteases. Eighty percent of transmitted mucosal HIV infections are established by a single transmitted/founder (T/F) variant, or T/F virus. The other 20% are transmitted by two to five variants (ie, IV drug users). These T/F viruses have specific phenotypic characteristics, including enhanced infectivity, higher envelope content, more efficient binding of dendritic cells, and relative resistance to interferon (IFN)-α.[13] Once HIV enters a susceptible host, the viral envelope spikes (gp120 trimers) bind to receptors (CD4) and coreceptors (CCR-5) of cells of the immune system, entering through a membrane fusion. The particle content is released into the cytoplasm, and viral RNA is transcribed into DNA. This viral DNA is then randomly integrated into the genome of the infected cell. Through a complex process of transcription activators and as a result of the frequent replication cycles of the immune system's cells, new viral particles are generated. These new particles are released through budding and lysis, continuing to infect new susceptible cells with this process, occurring at an unusually fast pace. Infection with HIV is characterized in simian models of AIDS and in man by a rapid destruction of memory cells of the gut-associated lymphoid tissue (GALT). This process occurs in days to a few weeks in animal models and in weeks in man. GALT harbors the majority of body lymphocytes compared with the 2% to 5% of lymphocytes located in the peripheral circulation.

The result of GALT's destruction, together with the activation of B cells and inhibition of the immune system function by HIV viral gene products such as the vif protein, which inhibits the APOBEC3 gene family, implicated in the control of HIV infection including the production of neutralizing antibodies, induces a severe immune dysfunction and depletion. (This is an important piece of information that addresses the mechanistic question of why we have such a difficult time developing neutralizing antibody against HIV).[14] Once HIV is integrated into the genome of the susceptible cells, there is a gradual destruction of the immune system, leading to a progressive status of immunodeficiency, with development of opportunistic infections and tumors. This early senescence of the immune system is implicated in changes at a molecular

level, resulting in loss of control of oncogenic viruses, and is associated with the malignant transformations observed in AIDS.

AIDS-DEFINING MALIGNANCIES

Kaposi Sarcoma

Epidemiology

KS was described by Dr Moritz Kaposi in 1872 as an indolent dermatologic disease characterized by the appearance of purplish nodules or plaques, particularly in the lower extremities of older men of Eastern European, Mediterranean, or Jewish descent (classical KS). Canadian investigators were one of the first to note in the 1970s that KS occurred in renal transplant patients exposed to immunosuppressant regimens (ie, azathioprine; transplant or iatrogenic KS). Their observations included reports of remissions when immunosuppressant regimens were temporarily discontinued, suggesting a relationship between immunodeficiency and the malignancies. They also noted a high incidence of NHL. In the 1960s, British investigators reported an aggressive lymphadenopathic form of KS confined to equatorial Africa (African KS). This form occurred in younger patients with aggressive involvement of lymph nodes and appearance of nodules and plaques of the lower extremities that rapidly became ulcerated. With the CDC's *Morbidity and Mortality Weekly Report* of 26 gay men with KS, the disease became one of the hallmarks of the AIDS epidemic (epidemic or AIDS-related KS).

In contrast to the classical form, the AIDS-related KS lesions appear with an aggressive pattern of distribution that includes the trunk, arms, and face in addition to the lower extremities.[15] Before antiretroviral therapies, patients died of a combination of tumor progression and opportunistic infections. Despite HAART, KS continues to be a prevalent cancer among HIV-infected patients, although HAART has significantly changed the incidence of the disease.

From 1990 to 1995, the incidence of KS in the United States was 1838.9 cases per 100,000 person-years in contrast to 334.6 cases per 100,000 person-years from 1996 to 2002. It is currently considered to have an incidence in the United States of six cases per 1 million people. In the United States and Europe, AIDS-related KS has been almost exclusively diagnosed in homosexual men, suggesting that its prevalence may vary among different categories of AIDS patients. In Africa, where human herpesvirus 8 (HHV-8), or KS herpesvirus (KSHV), is endemic, the male-to-female ratio of AIDS-related KS in some countries is 2:1, almost the same ratio observed in transplant- or iatrogenic-related KS. Thus, in the presence of profound immune suppression, factors that made the disease more prevalent in males than in females before the AIDS pandemic appear to be of little relevance. What is clear is that the incidence of AIDS-related KS is related to the degree of the immune suppression of the infected hosts, with most afflicted patients having CD4+ cell counts of 200 CD4+ cells/μL or less.

The Viral Etiology of Kaposi Sarcoma

The etiologic agent of all forms of KS is HHV-8, also called KSHV.[16] Early in the pandemic, other viruses or agents were implicated as the cause of AIDS-related KS, including cytomegalovirus. In 1994, sequences of a new herpeslike virus were isolated from the lesions of an AIDS-related KS patient. Using a subtractive PCR technique called representative differential analysis, investigators found sequences isolated from KS lesions homologous but not identical to other known herpesviruses, and thus it was named HHV-8, because it became the eighth known herpesvirus. Not all patients infected with HHV-8 develop KS; however, viral DNA and seroconversion can be detected in patients before the development of KS, confirming the role of HHV-8 as the cause of all forms of KS and the relationship of its pathogenesis to immunosuppression, in addition to other cofactors.

HHV-8 belongs to the γ-herpesvirus subfamily and the subgroup γ-2 or rhadinovirus (from the Latin term *rhadino*, referring to the tendency of the viral genome to break apart when it is isolated) and is the first human virus of this subfamily to be identified. The detection of the infection relies on the presence of antibodies against viral antigens using immunofluorescence assays based on the use of B lymphocytes as the antigen source or ELISA with recombinant immunogenic proteins or peptides of HHV-8. The infection seroprevalence mirrors the geographic distribution of AIDS-related KS, with the highest infection rates in central African countries (80%), rates of 25% to 50% among homosexual men in the Western world, and an intermediate level in the Mediterranean regions. The adult general population of blood donors in North America and Europe has an HHV-8 seroprevalence ranging from 0% to 8%. In addition to being the etiologic agent of AIDS-related KS, HHV-8 has been associated with two other lymphoproliferative disorders: primary effusion lymphoma (PEL, a subset of body cavity–based lymphomas [Fig. 52–1], subsequently called PELs) and multicentric Castleman disease (MCD).[16]

Pathogenesis of Kaposi Sarcoma

Human herpesvirus 8 incorporates a significant number of host genes such as cyclin D and growth factor interleukin (IL)-6.[17] These genes participate in

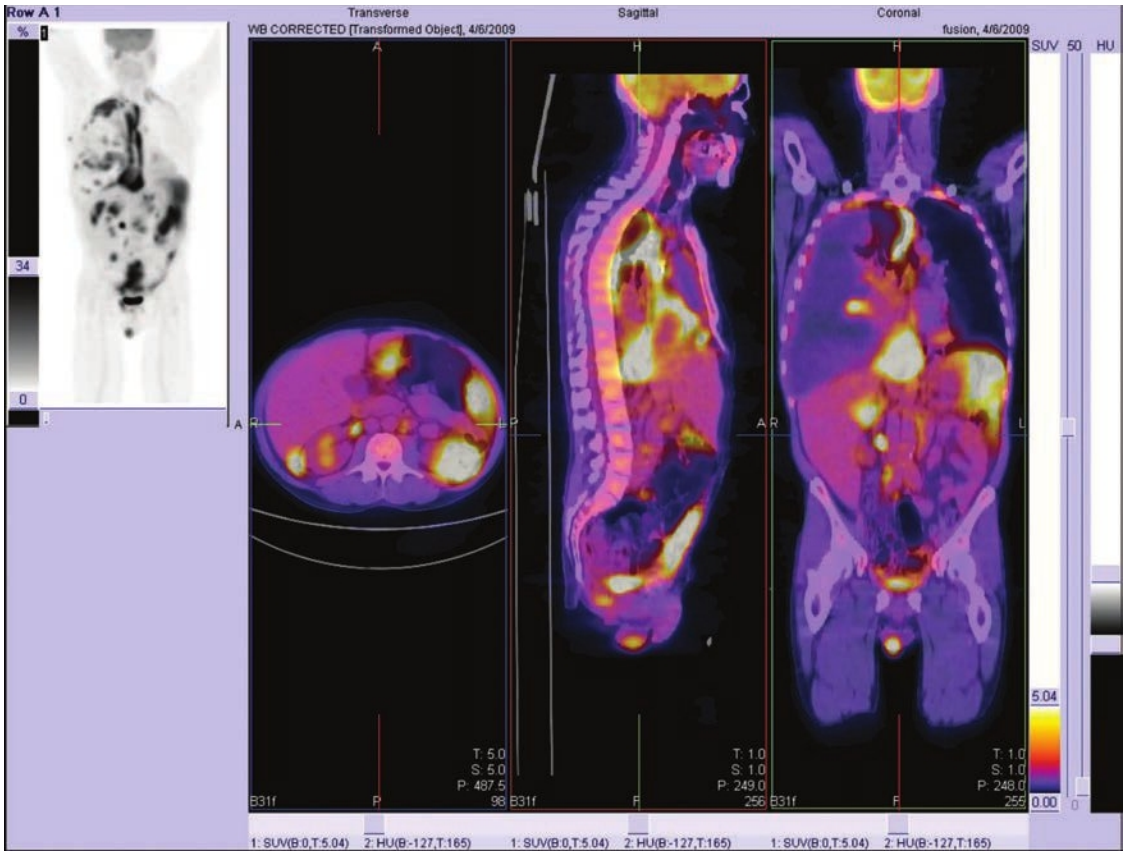


FIGURE 52–1 **Scan in a patient with primary effusion lymphoma (PEL) showing multiple sites of increased fluorodeoxyglucose activity and a large right pleural effusion.**

the replication, survival, and transformation of the infected tumor cells. The viral K1 gene kaposin and viral G protein-coupled receptor (vGPCR) have transformation potential. The viral K1 gene kaposin and viral G protein-coupled receptor (vGPCR0) have transformation potential. Others deregulate cell growth and lead to transformation including viral IL-6, viral IL-10, viral cc-class chemokines, and viral FLICE-inhibitory protein (vFLIP). The expression of the different key genes is related to the latency and lytic cycles of HHV-8. During the latency phase, genes such as *LANA-1* (latency-associated nuclear antigen 1), in addition to the maintenance of latency, inactivate p53, inhibiting apoptosis. In addition, a viral cyclin prevents cell cycle arrest by cyclin-dependent kinases, pRB and vFLIP, avoiding the activation of the Fas death receptor pathway. During the lytic phase, homologues of replication genes including the K1 kaposin gene, a Bcl-2 homologue, a viral G protein–coupled receptor gene (*vGPCRP*), a viral homologue of IL (IL-6), and viral macrophages and IFN regulatory factors become active. Some of these genes have immunosuppression functions, such as the inhibition by vFLIP including cytotoxicity of T-cells against HHV-8–infected cells and the inhibition of HHV-8 class 2 major histocompatibility complex (MHC)-mediated T-cell activation by K1.[18] Finally, other viral proteins such as K3 and K5 downregulate the presentation of MHC class 1 molecules on the cell surface.

Pathology of Kaposi Sarcoma

The histology of KS is characterized by the abundance of spindle cells in a matrix of neovascular formation and a rich background of mononuclear inflammatory cells and collagen. Vascular spaces are dilated and contain extravasated erythrocytes. Involvement of the reticular dermis, reflected by patchy lesions and the involvement of all the layers of the skin, clinically presents as nodular or plaque lesions that can coalesce, interfering with the lymphatic circulation, and are histologically and clinically associated with surrounding hemorrhage and subcutaneous edema. The spindle KS cells are rich in endothelial factor VIII. Recent microarray studies have demonstrated that the origin of the KS cell is from a virally transformed lymphatic endothelial cell. KS spindle cells express angiogenic/inflammatory cytokines and growth factors, including vascular endothelial growth factor, basic fibroblast growth factor, IL-1, and IL-6, among others. Kaposi sarcoma cells

also overexpress receptors for cytokines, suggesting growth through autocrine or paracrine mechanisms. They also proliferate in response to IL-1, IFN-γ, IL-6, and tumor necrosis factor, which are abundantly present in the serum of patients with poorly controlled HIV infection, and matrix metalloproteinases, enzymes involved in the destruction of extracellular matrix proteins required for angiogenesis and metastasis. In AIDS-related KS, Tat (the transactivator of transcription protein) stimulates KS spindle and endothelial cell replication, promoting an increase in the concentrations of basic fibroblast growth factor. This, in turn, upregulates the integrins α5β3 receptors for fibronectin and vitronectin, which are highly expressed in AIDS-related KS.

Clinical Features of Kaposi Sarcoma

Most patients with AIDS-related KS have CD4+ cell counts of 200 CD4+ cells/μL of blood, with an increased number and aggressiveness of lesions in those who are more severely immunosuppressed. There are periods of exacerbation alternated with quiescence related to oscillations of the patient's immunity. KS rarely invades the central nervous system (CNS). This is of biological interest because many other human malignancies are characterized by the invasion of the CNS.[19] The distribution of skin lesions in patients with AIDS-related KS often follows the Langer's folds of the skin. The occurrence of lesions in acral regions of the body such as the tip of the nose is common. The evolution of the skin lesions correlates with the patient's immune system status. In the pre-HAART era, severe involvement of the skin of the face by raised purplish lesions was frequent. With KS progression, there is frequent involvement of the gastrointestinal tract. Lesions of the palate and gums are often the first ones to be noted, and diarrhea and occasional bleeding can suggest KS involvement of the gastrointestinal tract. In the case of involvement of the lower extremities, progressive edema with nodular and coalescing plaque lesions can cause significant discomfort and pain. Prior to HAART, this was a frequent and serious complication of KS, because "elephantiasis" secondary to the progression of KS was extremely difficult to treat. Advanced cases often involve ulceration of lesions, particularly when located in the lower extremities. Lymph node involvement is frequent, and when there is only generalized lymph node involvement, a biopsy is required for confirmation of diagnosis. In advanced cases, lung involvement is manifested by bilateral basilar infiltrates mixed with a nodular appearance; however, severe hemoptysis or gastrointestinal bleeding is infrequent. During the early years of the epidemic, a significant number of patients experienced involvement by large masses of KS in vital organs such as the liver and heart, and death was caused by progression of their KS tumors and associated opportunistic infections.

Staging and Prognostic Factors for Patients with Kaposi Sarcoma

The usual TNM system used in other solid tumors is not easily applicable to AIDS-related KS. A system based on the work of Chachoua and colleagues was proposed in 1989 by the AIDS Clinical Trial Group (Table 52–1). This staging system included the extent of tumor involvement, the immune status measured by the level of CD4+ cell count, and the presence or absence of any systemic illness (B symptoms). In addition to a complete physical examination, it also included a complete blood count, serum chemistries, HIV viral load, panendoscopy of the gastrointestinal tract, computed tomography (CT) of the abdomen and pelvis, and when indicated, the performance of bronchoscopy when pulmonary involvement by KS was suspected. Biopsies of skin or lymph nodes were

Table 52–1 TIS Staging System for AIDS-Related Kaposi Sarcoma and Risk Status

Characteristics	Good Risk (0) All of the Following	Poor Risk (1) Any of the Following
Tumor (T)	Tumor confined to skin and lymph nodes and/or minimal oral disease[a]	Tumor-associated edema or ulceration; extensive oral KS; gastrointestinal KS; KS in other non-nodal viscera
Immune system (I)[b]	CD4 cells ≥150/mm^3	CD4 cells <150/mm^3
Systemic illness (S)	No history of opportunistic infection or thrush; no B symptoms[c]; performance status ≥70 (Karnofsky)	History of opportunistic infection and/or thrush; B symptoms; performance status <70 (Karnofsky); other HIV-related illness (eg, neurologic disease, lymphoma)

[a]Minimal oral disease defined as non-nodular KS confined to the palate.
[b]I stage has less prognostic value than T or S stages in the presence of HAART.
[c]B symptoms: fever, drenching night sweats, and/or >10% involuntary weight loss.
KS, Kaposi sarcoma.
Reproduced with permission from Levine AM, Tulpule A. Clinical aspects and management of AIDS-related Kaposi's sarcoma. *Eur J Cancer* 2001 Jul;37(10):1288-1295.

also suggested when indicated to rule out entities that could be similar in presentation, such as bacillary angiomatosis or pyoderma gangrenosum. After HAART, the extent of disease and the presence of HIV systemic symptoms became the most important prognostic factors; however, pulmonary involvement by KS still carries a particularly poor prognosis. Correlations with levels of HIV viral load and the status of HHV-8 infection are under study in relationship to their impact on survival.[20]

Therapy of Kaposi Sarcoma

HAART brought a dramatic decrease in the incidence of AIDS-KS. HAART consists of the administration of a combination of agents with anti-HIV activity, including integrase strand transference inhibitors, which inhibit HIV reverse transcriptase and protease inhibitors. The consensus of experts in the field about frontline components of HAART is periodically published in *Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents* by the Department of Human and Health Services (available online: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf). For patients in whom KS is part of the initial diagnosis of AIDS, HAART therapy should be started irrespective of the extent of the disease. For patients with minimal tumor burden, HAART initiation constitutes frontline therapy of their AIDS-related KS. This approach can control these lesions for long periods of time, often more than 1 year and, in many instances, results in complete disappearance of KS lesions.[21] Patients with extensive disease or visceral involvement can receive specific systemic KS therapies in addition to HAART.

Radiation Therapy for Kaposi Sarcoma

Radiotherapy is useful for the treatment of minimal local disease and when the use of systemic treatment other than HAART is not indicated. It can also be used as an adjunct treatment modality for patients in whom the administration of chemotherapy leads to incomplete results, enhancing the beneficial effects of the systemic treatment. Depending on the general condition of the patient and the size of the lesions to be treated, doses range from the administration of a single fraction to fractionated doses over periods of 2 to 4 weeks. For single lesions and frail patients, the administration of a single 800-cGy dose can be used. Radiotherapy can be used for cosmetic reasons, although this should be done carefully to avoid secondary side effects such as post-radiation cataracts in the case of periorbital lesions. For larger lesions or when the therapeutic intent is cosmetic, fractionated doses between 200 and 4000 cGy are effective and carry less risk. For patients receiving systemic therapy, radiotherapy can be an adjuvant for the treatment of complicated single lesions, particularly when they are bleeding, ulcerated, or painful, or when they affect the well-being of the patient. Such is the case in patients with disseminated disease receiving systemic treatment and in whom oral lesions may affect eating because of local pain or lesion size.

Local Therapy Other Than Radiotherapy for Kaposi Sarcoma

In the modern era, the use of local therapies such as cryotherapy and laser therapy may have a role for patients with few and small lesions. The use of surgery may be appropriate in selected cases such as large skin lesions or when there are complications (bleeding OR obstruction of a hollow viscus). Other treatments, such as intralesional injection of chemotherapeutic agents, particularly of the oral cavity, and application of alitretinoin gel, have been abandoned and replaced by a more sophisticated use of radiotherapy techniques, HAART, and systemic chemotherapy.

Immunomodulators in the Therapy of Kaposi Sarcoma

After the demonstration of the activity of IFN-α in hairy cell leukemia and renal cell cancer in 1984,[22] there was an impetus to use the same doses of IFN in patients with AIDS-related KS. Low doses of IFN-α effective against hairy cell leukemia and renal cell carcinoma were ineffective against AIDS-related KS (Rios A, personal observation). A dose-response study unequivocally demonstrated the therapeutic effect of IFN-α in KS when used at doses of 20–30 MU/m.[23,24] A different situation was observed with IFN-γ. Under the angiogenic stimuli of IFN-γ, KS has the capacity to replicate, resulting in a deleterious impact on patients treated with this agent in pilot studies. As a result of these trials, recombinant IFNs α-2a (Roferon-A, Roche Laboratories) and α-2b (Intron-A, Schering-Plough) were approved for the systemic treatment of patients with AIDS-related KS. Expanded use of these agents has revealed their true activity to be in the range of 15% to 20%.

Interferon can block the synthesis of viral proteins and the budding of viral particles from infected cells in addition to other complex pleiotropic effects. Interferon actions are accompanied by significant systemic side effects including tiredness, fatigue, anorexia, hepatotoxicity, and severe myelosuppression. With the development of HAART and the use of more effective systemic chemotherapy regimens in the treatment of AIDS-related KS, the interest in the use of IFN-α in the treatment of AIDS-related KS has declined.

Other Immunomodulatory Agents

Thalidomide, a known immunomodulatory agent, has been studied in KS, with partial responses seen in 47% of patients and stable disease seen in 12%. However, its use has been limited by adverse constitutional effects. More recently, pomalidomide, a derivative of thalidomide with antiangiogenic and antiproliferative activities has shown significant activity against AIDS-related KS, with an overall response rate of 60%. The median time to response was 4 weeks and a median progression-free survival of 16.6 months.[25]

Chemotherapy for Kaposi Sarcoma

Indications for the use of systemic chemotherapy in AIDS-related KS includes extensive skin, mucocutaneous, and visceral involvement by tumor. In patients who require systemic chemotherapy, local radiotherapy is used to treat local complications in addition to systemic disease. The introduction of HAART has resulted in better and more durable responses with increased tolerability and durability than those observed before the use of HAART. Before the discovery of antiretrovirals, a variety of chemotherapeutic agents had modest to significant activity as monotherapy for KS. These agents included etoposide, vinblastine, vincristine, bleomycin, doxorubicin, vinorelbine, and epirubicin, which induced responses in 40% to 69% of patients. After HAART, ABV (doxorubicin 20 mg/m^2, bleomycin 10 U/m^2, and vincristine at maximum doses of 1–2 mg) became the first standard treatment of AIDS-related KS. It produced a response rate of 60%, with complications depending on the performance status and general condition of the patient.[26] Antiretroviral and other supportive therapies with growth factors (granulocyte-macrophage colony-stimulating factor [CSF] and granulocyte CSF [G-CSF]) paired with vigorous prophylaxis of opportunistic infections reduced the risks of treatment. Complications of ABV were the expected ones with systemic chemotherapy including the potential for cardiac toxicity induced by doxorubicin. The ABV regimen was followed by the introduction of agents considered today to be the standard of care for AIDS-related KS, including liposomal-encapsulated anthracyclines (doxorubicin and daunorubicin) and taxanes (paclitaxel). The last of these promotes apoptosis and downregulates Bcl-2 protein expression in KS cells in vitro and in KS-like lesions in mice. In addition, it has an important antimitotic effect associated with its capacity for the disruption of tubulin activity during mitosis.

The current treatment of AIDS-related KS is based on the combination of an anthracycline (liposomal doxorubicin 20 mg/m^2 or liposomal daunorubicin 40 mg/m^2 *but not both together*) with paclitaxel 25 mg/m^2 with or without bleomycin or vincristine. Escalation of the dose of liposomal doxorubicin is not recommended because of a syndrome of desquamation of the skin of the palms and soles of the feet, known as palmar-plantar erythrodysesthesia. In contrast, the dose of liposomal-encapsulated daunorubicin can be increased to up to 60 mg/m^2 or even higher for patients who tolerate lower doses. This is of particular relevance in patients with advanced disease or significant pulmonary involvement and for whom prompt control and achievement of a quick therapeutic response is of great importance (Fig. 52–2).

Future Therapies for Kaposi Sarcoma

Only patients with early disease and relatively good performance status consistently achieve durable remissions with current therapies for KS. For the remaining patients, only palliation and stabilization of disease is achieved with current treatments. For these reasons, efforts are under way to develop new therapies based on the knowledge of the pathophysiology of the disease. For example, because angiogenesis is an important component of AIDS-related KS, agents such as thalidomide and anti-VEGF agents such as bevacizumab are of great interest in the therapy of this disease, although they continue to be recommended under certain circumstances. Metalloprotease inhibitors are also of great interest, and active clinical trials are in progress. Viruses associated with the production of malignancies tend to constitutively activate the nuclear factor–κB (NF-κB) pathway, and agents that can inhibit this pathway such as bortezomib may be of some value. Inhibition of signaling cell receptors implicated in the stimulation of angiogenesis such as platelet-derived growth factor receptor and C-kit receptor by agents such as imatinib, an orally administered tyrosine kinase inhibitor, approved by the Food and Drug Administration (FDA) for treatment of chronic myeloid leukemia and gastrointestinal stromal tumor, is being investigated.

There is significant interest in the development of therapies against the latent phase of HHV-8, the most common form of HHV-8 in KS cells, which does not respond to standard antiherpetic drugs such as foscarnet and cidofovir. This area of research has led to potential development of a vaccine against HHV-8. More recently it has been demonstrated in a small number of AIDS-KS patients the upregulation of PDL-1 with weak cytoplasmic expression in 50% of the studied patients. After this finding, another group treated a heterogeneous group of nine AIDS-KS patients with checkpoint immune inhibitors and observed one complete remission and five partial responses. There were no serious adverse toxicities above grade 2. This has triggered significant interest in the potential use of PD-1 checkpoint blockade in AIDS-KS.[27,28] Despite all these new potential therapeutic developments, the impact of HAART in the incidence of

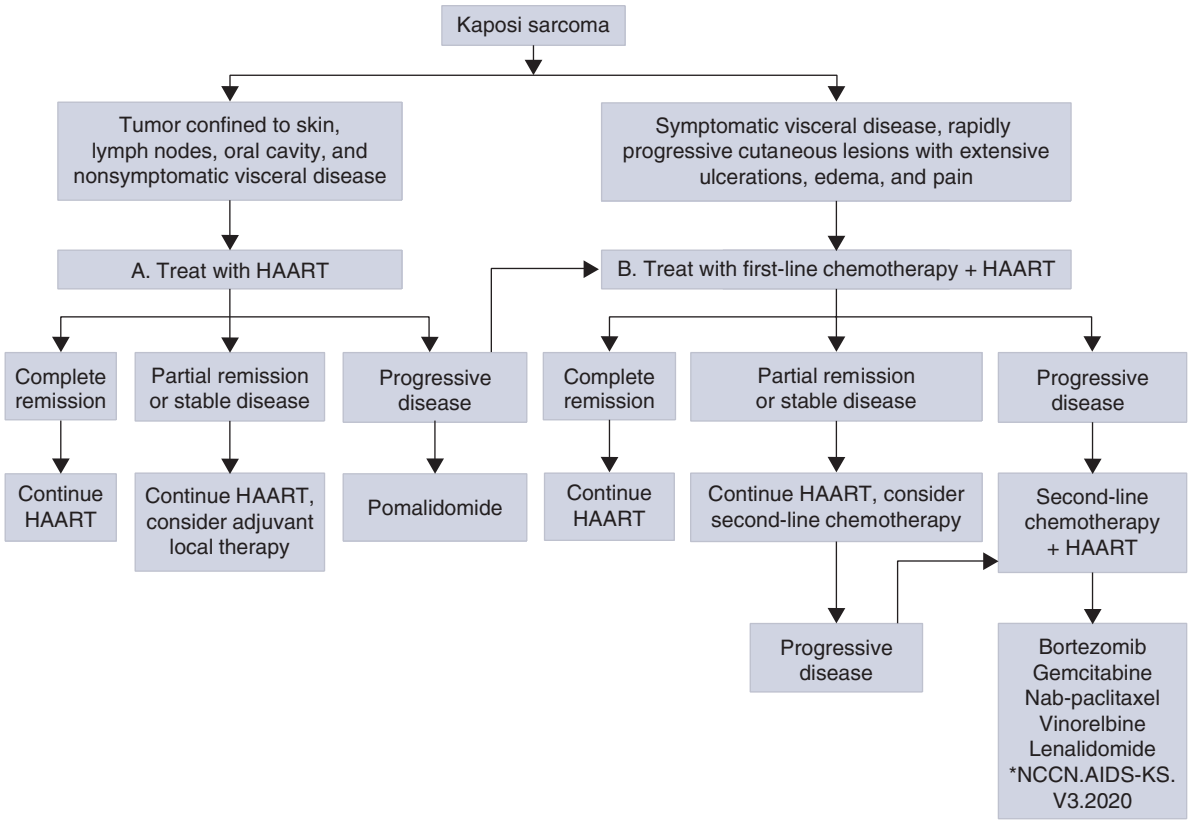


FIGURE 52–2 Algorithm for the management of AIDS-related Kaposi sarcoma. A. Monthly evaluation of Kaposi sarcoma clinical response and estimation of CD4+ cell count and HIV-RNA levels. B. Highly active antiretroviral therapy (HAART) regimen should be changed in the case of immunovirologic failure. (Reproduced with permission from Catellan AM, Trevenzoli M, Aversa SM: Recent advances in the treatment of AIDS-related Kaposi sarcoma, *Am J Clin Dermatol* 2002;3(7):451-462.)

AIDS-related KS cannot be overemphasized. The development of more potent and less toxic HAART regimens and the acceptance of earlier therapeutic intervention against HIV seem to be the main paths to controlling the epidemic of AIDS-related KS.

Other Diseases Associated with Kaposi Sarcoma Herpesvirus

KSHV is the etiologic agent of PEL (discussed in the Lymphomas section), KSHV-associated MCD, and a KSHV inflammatory cytokine syndrome.[29–31] KSHV-associated multicentric disease is a B-cell lymphoproliferative disease involving multiple regions of lymphadenopathy. The spectrum of histopathologic features includes hypervascular changes and *LANA*-expressing plasmablasts. Patients with KSHV-associated MCD have systemic inflammatory symptoms with generalized lymphadenopathy, hepatosplenomegaly, cytopenias, and organ dysfunction with excessive proinflammatory hypercytokinemia, including IL-6. Treatment consists of the administration of antivirals (valganciclovir, foscarnet), rituximab, and IL-6 inhibitors. When associated with AIDS-KS, specific therapy for KS is added. KSHV inflammatory cytokine syndrome is an inflammatory syndrome clinically similar to MCD but without MCD, which tends to occur in patients with high-KS burden and portends a poor prognosis. In contrast to MCD there is no splenomegaly, and the widespread lymphadenopathy typical of MCD.

AIDS-RELATED NON-HODGKIN LYMPHOMA

Systemic Non-Hodgkin Lymphoma

Epidemiology

NHL is the second most frequent AIDS-associated malignancy. Both KS and NHL were occurring with an incidence almost linear in its relationship to the patient's immunodeficiency status.[32] In 1985, high- or intermediate-grade B-1 l NHLs were considered part of the spectrum of AIDS-related malignancies. Eighty percent of AIDS-related NHLs were systemic (peripheral) lymphomas, involving nodal or extranodal sites, with 15% to 20% originating in the PCNSL. A small

proportion (<3%) of patients with systemic AIDS-related NHL had PELs, known as body cavity lymphomas. In general, the risk of AIDS-related NHL in patients with HIV appears to be higher in those who have poor immune function with an average CD4+ cell counts of 150 CD4+ cells/μL of blood. A viral relationship is implicated in the development of AIDS-associated lymphomas. EBV contributes to the development of most of these tumors, although HHV-8 is associated with the development of PEL.[29] There is no relationship between the risk of development of AIDS-related NHL and modes of HIV transmission. The incidence of pre-HAART AIDS-related NHL was 60 to 200 times higher than in a matched HIV-seronegative population; the relative risk was higher for PCNSL. Age, nadir of CD4+ cell count, and absence of anti-HIV therapy were critical factors that predicted the development of AIDS-related NHL. In the pre-HAART era, 80% of these NHLs, including systemic and PCNSL cases, were immunoblastic variants associated with CD4+ cell count depletion and EBV infection. In the post-HAART era, there has been a 30% reduction in peripheral cases and a 70% reduction in PCNSL, indicating the impact of immune reconstitution in the incidence of immunosuppression-related lymphomas. In contrast, the incidence of Burkitt lymphoma and of centroblastic DLBCL has remained stable without significant change from the pre- to the post-HAART eras.[33] When comparing the AIDS-related lymphomas with non–AIDS-related NHL, the former tend to be of higher histologic grade, with increased frequency of B symptoms, extranodal presentations, and an increased incidence of leptomeningeal and primary CNS involvement.[34] In the post-HAART era, the WHO has expanded the categories of lymphomas that can occur in patients with HIV to include extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type, peripheral T-cell lymphoma, and classical Hodgkin lymphoma (HL), as well as lymphomas that more specifically occur in patients with AIDS, including plasmablastic lymphomas of the oral cavity, polymorphic B-cell lymphomas (posttransplant lymphoproliferative disorder–like), and PEL.[35] Finally, the demographics of patients with AIDS-related NHL have changed in the last decade, reflecting changes in the demographics of the AIDS epidemic, with increasing incidence in Hispanic and Black patients and patients who have acquired HIV through heterosexual contact (Table 52–2).

Pathogenesis of AIDS-Related Non-Hodgkin Lymphomas

The development of NHLs in patients with HIV is similar to that of malignancies associated with other congenital or posttransplant immunodeficiency disorders.[36,37] In such conditions, most of the malignancies consist of NHL and KS. In the case of HIV, immunodeficiency and cofactors, including oncogenic viruses, chronic antigenic stimulation, and cytokine overproduction, are responsible for the development of AIDS-related NHL malignancies. In contrast to AIDS-associated KS, no one has yet found HIV sequences in tumor cells of AIDS-related NHLs,[38] although PCR analysis has revealed the presence of HIV in infiltrating T-cells. For patients with severe HIV immunodeficiency, the oncogenic nature of both EBV and HHV-8 is responsible for the development of the immunoblastic subtype of DLBCL, PCNSL, plasmablastic lymphoma of the oral cavity, and PEL. The last of these often results from coinfection with HHV-8 and EBV. These lymphomas are the result of active oncogenic viruses released from control by an effective immune surveillance.

EBV is central to the pathogenesis of AIDS-related NHLs, including those that are related to immunodeficiency and those that occur with a reconstituted immune system, such as centroblastic DLBCL and Burkitt lymphoma. The EBV genome presence is very high in immunodeficiency-associated AIDS-related NHLs (100%),[39] although it can only be detected in approximately 60% of centroblastic DLB- CLs and 30% of Burkitt lymphomas. This suggests that other factors, including other common latent or chronic viral infections, may be involved in the development of these tumors. In EBV-infected cells, the EBV virus is, for the most part, in a state of latency with brief periods of lytic activity. The malignant transformation of B cells occurs in the latent phase, requiring multiple molecular events.[40] EBV contributes to the cellular transformation process through expression of genes with oncogenic activity such as *LMP-1*, *LMP-2*, *EBNA-1*, and *EBNA-2*. There is also expression of small EBV-encoded nonpolyadenylated nuclear RNAs (EBERS), all of which participate in the oncogenic transformation phenomenon. These proteins can rescue cells from apoptosis by mimicking cell receptors such as CD40 and B-cell receptor. For example, LMP-1 (latent membrane protein-1) is capable of replacing the function of CD40 in germinal B cells, which otherwise would follow an apoptotic fate. The latency patterns of EBV gene expression have been classified as I, II, and III. Latency I is characterized by expression of EBV nuclear antigen 1 and is associated with Burkitt and PEL; latency III involves the expression of all nine EBV latent genes. The proteins expressed are highly immunogenic and thus this latency occurs in severely immunodeficient individuals and typically is associated with AIDS-DLBCL. Type II latency is an intermediate type of pattern of protein expression and is associated with HL and NK-T cell lymphomas.[41]

Table 52–2 Demographic Profile of 369 Patients with AIDS-Related Lymphoma Over Different Time Intervals

	1982–1986 (%)	1987–1990 (%)	1991–1994 (%)	1995–1998 (%)	Total (%)	*P* Value
No. of patients	44	88	132	105	369	
Median age (y)	40	36	38	39	38	.18
Sex						.25
Female	0 (0)	2 (2)	6 (5)	7 (7)	15 (4)	
Male	44 (100)	86 (98)	126 (95)	98 (93)	354 (96)	
Race						.001
Caucasian	33 (75)	50 (57)	64 (48)	42 (40)	189 (51)	[a]
Hispanic	7 (16)	26 (33)	51 (39)	58 (55)	145 (39)	[b]
Black	4 (9)	4 (5)	17 (13)	5 (5)	30 (8)	
Asian	0 (0)	5 (6)	0 (0)	0 (0)	5 (1)	
Risk						.039
MSM	37 (84)	67 (76)	105 (80)	69 (66)	278 (75)	[c]
IDU ± MSM	3 (7)	7 (8)	4 (3)	3 (3)	17 (5)	
Hetero	2 (5)	4 (5)	13 (10)	19 (18)	38 (10)	[d]
Transfusion	0	3 (3)	1 (0.5)	4 (4)	8 (2)	
Unknown	2 (5)	7 (8)	9 (7)	10 (10)	28 (8)	
KPS						.0008
>80%	14 (32)	28 (32)	75 (57)	45 (43)	162 (44)	
<80%	30 (68)	60 (68)	57 (43)	60 (57)	207 (56)	
Prior OI[e]	14 (32)	40 (45)	58 (44)	53 (50)	165 (45)	.22
Prior KS[e]	2 (5)	13 (15)	11 (8)	14 (13)	40 (11)	.20
Median CD4[f]	177	113	54	53	66	.0006
Range	0–1703	2–1927	0–710	0–700	0–1927	

Hetero, heterosexual risk factor for HIV; IDU, injection drug use; KPS, Karnofsky performance status; KS, Kaposi sarcoma; MSM, men who have sex with men; OI, opportunistic infection.
[a]*P* = .0007, comparing White versus all other races.
[b]*P* < . 0001, comparing Hispanics versus all other races.
[c]*P* = .045, comparing MSM with all other HIV risk groups.
[d]*P* = .011, comparing heterosexual transmission with all other HIV risk groups.
[e]Patients without a diagnosis of OI or KS before development of lymphoma presented with lymphoma as the first AIDS-defining condition.
[f]CD4 cell count at time of diagnosis of AIDS-related lymphoma.
Reproduced with permission from Levine AM, Seneviratne L, Espina BM, et al: Evolving characteristics of AIDS-related lymphoma, *Blood* 2000 Dec 15;96(13):4084-4090.

The Impact of Highly Active Antiretroviral Therapy on Distribution of Acquired Immunodeficiency Syndrome–Related Non-Hodgkin Lymphoma

In the post-HAART era, there has been a decline in the incidence of NHLs associated with immunodeficiency caused by AIDS. In contrast, the incidence of centroblastic DLBCL and Burkitt lymphoma appears to be similar before and after introduction of HAART. Factors influencing the pathogenesis of these diseases include an increase in regulatory cells of the immune system, associated with recovery of the immune status of the host, and effects of chronic antigenic stimulation by HIV with a resultant overproduction of cytokines. The existence of more than one pathogenic mechanism for the occurrence of AIDS-related NHLs can be inferred from the variety of genetic abnormalities displayed by the malignant cells.[42] The number and type of these genetic abnormalities vary according to the anatomic site and tumor histology. They include c-*myc* rearrangement, *bcl-6* gene rearrangement, *ras* gene mutations, and *p53* mutations/deletions.[43]

Pathology of Systemic Non-Hodgkin Lymphomas

The hallmark of AIDS-related NHL is a high-grade histology, regardless of the histologic subtype, including diffuse large cell, immunoblastic, and small noncleaved cell lymphomas and Burkitt and Burkitt-like lymphomas. The cells of PEL express CD45 and activation-associated antigens such as HLA-DR, CD30, CD38, CD71, epithelial membrane antigen, and CD 138/syndecan-1. PEL cells often lack B-cell antigens and c-*myc*

gene rearrangements and mutations and uniformly contain HHV-8 and frequently also contain EBV[42,43]). Other hematologic neoplasms, including low-grade B-cell lymphomas and lymphocytic leukemia, multiple myeloma/plasmacytomas, T-cell neoplasms, and various acute myeloid leukemias and myeloproliferative disorders, have been reported in patients with HIV infection. However, there is no evidence that the incidence of these neoplasms has increased in parallel with the AIDS epidemic.[42–48]

Clinical Features of Systemic Non-Hodgkin Lymphomas

Patients with AIDS-related NHLs usually present with advanced stages of the disease and B symptoms, including fever, weight loss, night sweats, and enlarged lymph nodes or masses. More than 60% of the patients will present with stage III or IV disease. Frequent extra nodal sites of involvement are bone marrow, CNS parenchyma and meninges, lungs, and spleen. Patients with PEL present with ascites or a pleural effusion and, less frequently, with a pericardial effusion. Masses are typically absent in the presentation of PEL, although sometimes a mass may accompany the development of the effusion (see Fig. 52–1).[49]

The staging of patients with AIDS-related NHL is similar to non–HIV-infected patients with NHL and should be reported according to the Ann Arbor system (Table 52–3). The International Prognostic Index (IPI) has been validated in pre-HAART studies, and significant changes in treatment outcomes have occurred since the initiation of HAART.[50] Complete blood count, β2-microglobulin, lactic dehydrogenase, and complete blood chemistry laboratory tests should be performed, and a radiologic staging should include magnetic resonance imaging (MRI) of the brain and positron emission tomography (PET)/CT scan. Patients in remission after two courses of treatment tend to remain in remission for the duration of induction therapy. Patients with Burkitt types of lymphoma should have a bone marrow aspiration and biopsy and a diagnostic lumbar puncture. All patients should be screened for hepatitis B, because the exacerbation of this virus by the use of rituximab or chemotherapy can be prevented by screening patients for hepatitis B surface antigen, hepatitis B core antibody, and hepatitis C. Hepatitis B surface antigen–positive patients or patients with a positive hepatitis B core antibody should have evaluation of e antigen, hepatitis B viral load by PCR, and surface antibody if one of the screening tests is positive because the rate of reactivation of hepatitis B virus with the risk of fulminant hepatitis is approximately 20% to 50%.These patients should be treated prophylactically and if there is active disease (PCR+) the treatment is not considered prophylactic but therapeutic.

Table 52–3 Ann Arbor Staging Classification for Hodgkin Lymphoma

Stage	Characteristics
I	Involvement of a single lymph node region (I) or a single extralymphatic organ or site (IE).
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site (IIE).
III	Involvement of lymph node regions on both sides of diaphragm (III) or localized involvement of an extralymphatic organ or site (IIIE) or spleen (IIIS) or both (IIISE).
IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymph node involvement. The organ(s) involved should be identified by a symbol: A, asymptomatic; B, fever, sweats, weight loss >10% of body weight.

Data from Carbone PP, Kaplan HS, Musshoff K, et al: Report of the Committee on Hodgkin's Disease Staging Classification, *Cancer Res* 1971 Nov;31(11):1860-1861.

A HAART regimen containing nucleoside reverse transcriptase inhibitors, active against HIV and hepatitis B, are recommended. For those infected with hepatitis C, the situation is different because hepatitis C–related liver failure is relatively rare with chemotherapy and thus antiviral treatment can wait until the completion of the chemotherapy.[51] Before HAART, the presence of an opportunistic infection, less than 100 CD4+ cells/μL of blood, bone marrow involvement, and increased age predicted poor survival, with patients often suboptimally treated because of poor tolerance to standard doses of chemotherapy. After HAART, two factors have become predictors of poor survival: a CD4+ cell count of less than 100 cells/μL and high-intermediate IPI scores.[52]

Therapy for AIDS-Related Systemic Non-Hodgkin Lymphoma

Prior to HAART, all regimens had in common reduced doses of chemotherapy. After 1996, it became clear that patients on HAART can receive standard doses of chemotherapy. The outcomes of treatment in the presence of HAART are related to the subtype of lymphoma and the specific treatment rather than the immunodeficiency status of the patient (Table 52–4). It is important that the use of HAART not contain ritonavir or cobicistat to avoid drug interactions because of the inhibition of cytochrome P-450 enzyme CYP3A4. Vigorous prevention of infections with prophylactic antibiotics, aggressive use of growth factors (G-CSF and pegylated G-CSF), and anti-CD20 antibodies

Table 52–4 Summary of Selected HIV-Related Lymphoma Trials

Chemotherapy Regimen	No. of Patients	Median CD4 Cell Count at Enrollment (/λL)	CR (%)	ORR (%)	HAART	OI (%)	OS	Year (ref.)
Modified m-BACOD vs	98	100	41	69	NR	22	35 weeks	1997[81]
m-BACOD+GM-CSF	94	107	52	78	NR	23		
MTX/LV	29	132	46	77	AZT	NR	12 months	1997[82]
CHOP-HAART Vs	24	190	50	NR	Yes	18	62% at 8.5 months	2001[44]
CHOP	80	146	36					
G-CSF+CHOP-R vs	95	133 total	58	NR	NR	NR	Median follow-up	2003[45]
G-CSF+CHOP	47		50				26 weeks	
Infusional CDE	62	NR	48	74	NR	NR	2.7 years	2002[46]
G-CSF+CDE-R	30	132	86	90	Yes	7	80% at 2 years	2002[47]
EPOCH	39	198	74	87	Held during chemotherapy	[a]	60% at 53 months	2003[48]

[a]0% during chemotherapy, 9% after.
AZT, azidothymidine; CDE, cyclophosphamide, doxorubicin, and etoposide; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin hydrochloride; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating hormone; HAART, highly active antiretroviral therapy; m-BACOD, methotrexate with leucovorin, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone; MTX/LV, methotrexate and leucovorin; NR, not reported; OI, opportunistic infection; ORR, overall response rate; OS, overall survival; R, rituximab.

(rituximab) where indicated have improved the outcomes for these patients (Table 52–5). Although investigators were originally concerned that rituximab might compromise the immune status of patients with CD20+ B-cell lymphomas, studies have demonstrated that rituximab can safely be used for patients with 50 or more CD4+ cells/all of blood.

Regimens commonly used to treat patients with AIDS-related DLBCL include CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or rituximab plus CHOP (R-CHOP), R-CDE (rituximab, cyclophosphamide, doxorubicin, and etoposide). Progression-free survival rates at 2 years for these different treatment regimens are 70% for R-CHOP and R-CDE.[53–58] A phase 2 study of dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin hydrochloride) plus rituximab (DA-EPOCH-R) showed a progression-free survival rate at 2 years of approximately 90% for dose-adjusted EPOCH-R.[59] A prospective trial in immunocompetent patients with DLBCL did not show an advantage of R-DA-EPOCH over R-CHOP.[60] However, in a recent large prospective study of EPOCH-R for patients with HIV seropositivity, six cycles of rituximab plus infusional EPOCH produced good results for first-line treatment of HIV-associated DLBCL, HHV8-positive DLBCL, and PELs, especially for those who achieved a complete response (CR).[61] Results from this study also suggested that, after two cycles of EPOCH plus rituximab, patients with HIV-associated lymphomas have excellent outcomes when therapy is limited to four cycles, reducing the risk of toxicity.

In the case of Burkitt lymphoma, CHOP and similar regimens are not recommended because the response is poor. Burkitt lymphoma was historically treated with R-HyperCVAD (rituximab plus cyclophosphamide, vincristine, doxorubicin, and dexamethasone)[62,63] or R-CODOX-M/IVAC (rituximab plus cyclophosphamide, doxorubicin, vincristine, methotrexate/ifosfamide, etoposide, high-dose cytarabine).[64] Both regimens achieved remissions of more than 92% and a 2-year overall survival rate of 49% (Figs. 52–3 and 52–4). However, EPOCH-R is now listed with other regimens and is a preferred therapy for HIV-associated Burkitt lymphoma, according to 2019 NCCN guidelines.[65] Such recommendations are supported by R-EPOCH results reported from phase 2 trials for HIV-associated DLBCL and high-grade lymphomas such as Burkitt lymphoma.[66,67] In a large meta-analysis, investigators have also found that DA-R-EPOCH has greater efficacy than that reported for R-CHOP for these patients.[68] In another analysis, a

Table 52–5 Suggested Supportive Care for the Patient with HIV Infection and Lymphoma or Other Malignancies

Indication	Drug(s)
Primary infection prophylaxis	
Pneumocystis carinii, Toxoplasma gondii	Trimethoprim-sulfamethoxazole 1 DS daily. Alternatives for patients with allergy to Bactrim-DS are dapsone 100 mg PO once a day or atovaquone 1500 mg once a day with food.
Oral and/or esophageal candidiasis	Fluconazole 100 mg daily
MAI complex (CD4 <50 cells/μL)	Azithromycin 1200 mg weekly
Secondary infection prophylaxis	
Herpes simplex infections	Acyclovir 400 mg bid or 200 mg tid
Cytomegalovirus infection	Ganciclovir 1 g tid
Mycobacterium avium complex	Clarithromycin 500 mg bid plus ethambutol
	15 mg/kg daily, with or without rifabutin 300 mg daily
Toxoplasma gondii	Sulfadiazine 1–1.5 g q6h, pyrimethamine 25–75 mg daily
	Leucovorin 10–25 mg daily qid
Cryptococcus neoformans	Fluconazole 200 mg daily
Salmonella bacteremia	Ciprofloxacin 500 mg bid
Hematopoietic growth factors	
For selected patients in whom the risk of febrile neutropenia ≥40%	G-CSF 5 μg/kg or GM-CSF 250 μg/m^2 SC daily beginning after completion of chemotherapy and continuing until neutrophil recovery
Antiretroviral agents	
Selecting patients for therapy	[a]Follow NIH guidelines
Role of therapy in controlling malignancy	
Kaposi sarcoma	Essential
Lymphoma	Unknown
Other tumors	Unknown
May be used with myelosuppressive drugs	General principles of HIV treatment: An INSTI, NNRTI, or PI combined with 2 NRTIs. Avoid regimens containing ritonavir or cobicistat (cytochrome P-450 enzyme CYP3A4 strong inhibitors). First Choice: NRTIs: emtricitabine/tenofovir alafenamide (Descovy) or abacavir/lamivudine (Epzicom); with an INSTIs: dolutegravir or raltegravir. Second choice: NNRTIs: rilpivirine (weak CYP3A4 inducer); efavirenz. Efavirenz can be combined with emtricitabine/tenofovir in a single capsule (Atripla). Strong inducer of CYP34A.
Avoid with myelosuppressive drugs/regimens	Zidovudine
Avoid with neurotoxic drugs/regimens	Didanosine, zalcitabine, stavudine
May alter the metabolism of cytotoxic drugs metabolized by cytochrome P-450 enzymes	All PIs and NNRTIs

bid, two times daily; DS, double strength; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; INSTI, integrase strand transfer inhibitor; MAI, *Mycobacterium avium-intracellulare*; NIH, National Institutes of Health; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTIs, nucleoside reverse transcriptase inhibitors; PI, protease inhibitor; qid, four times daily; SC, subcutaneous; tid, three times daily.

Reproduced with permission from Sparano JA. Clinical aspects and management of AIDS-related lymphoma. *Eur J Cancer.* 2001;37(10):1296-1305.

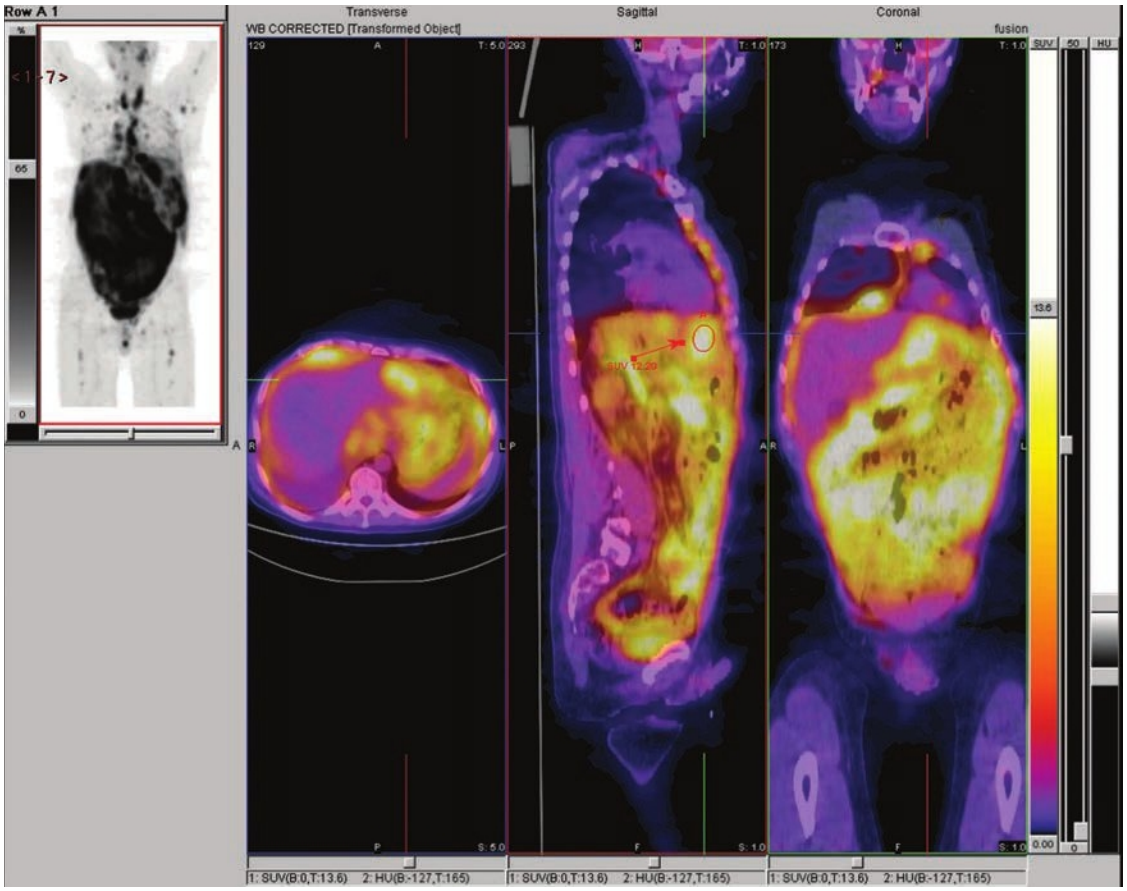


FIGURE 52–3 **Positron emission tomography/computed tomography (PET/CT) scan of a 51-year-old HIV-positive patient demonstrating extensive involvement of Burkitt lymphoma in the chest, abdomen, and pelvis.**

high proliferation rate predicted a better prognosis for such patients when they received R-EPOCH instead of R-CHOP.[69] A reported variation of the standard DA-EPOCH-R regimen, known as SC (for short)-R (rituximab days 1 and 5)-DA- EPOCH for HIV-related Burkitt lymphoma consists of a 4-day infusion of etoposide (50 mg/m^2/d), vincristine 0.4 mg/m^2/d, and doxorubicin (10 mg/m^2/d) admixed in the same solution, along with prednisone, at a dose of 60 mg/m^2/d orally on days 1 to 5. Cyclophosphamide is given at a dose of 750 mg/m^2 as a 2-hour infusion on day 5. Rituximab is given at a standard dose of 375 mg/m^2 on days 1 and 5.[60] Filgrastim is given subcutaneously starting on day 6 until the absolute neutrophil count (ANC) is 5000/μL (post nadir). Cyclophosphamide is increased or decreased from the previous course dose if the ANC nadir is more than 500/μL or less than 500/μL ANC, respectively. Importantly, only cyclophosphamide is dose-adjusted for hematologic toxicity. Patients receive one cycle after CR is established for a minimum of three cycles and a maximum of six cycles (Table 52–6). However, lower doses of cyclophosphamide in EPOCH-R for patients with HIV disease have also been described[59] and may provide similar results to standard-dose EPOCH-R. Patients with high-grade and Burkitt lymphomas should undergo PET and other CNS scans before therapy and should receive prophylactic intrathecal chemotherapy. For patients with relapsed or refractory lymphomas, R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) or R-ESHAP (rituximab, etoposide, methylprednisolone, cytarabine, and cisplatin) can be of value, although patients with relapsed disease usually have poor outcomes with most standard chemotherapy regimens. Patients with disease responsive to salvage therapy should be considered for high-dose chemotherapy and autologous stem cell transplantation as consolidative therapy.[70]

AIDS-Related Non-Hodgkin Lymphoma: Primary Central Nervous System Lymphoma

Epidemiology and Pathogenesis

Primary CNS lymphoma became an AIDS-defining malignancy in 1983. Primary CNS lymphoma accounted for up to 15% of NHLs in HIV-infected patients compared with only 1% of NHLs in the

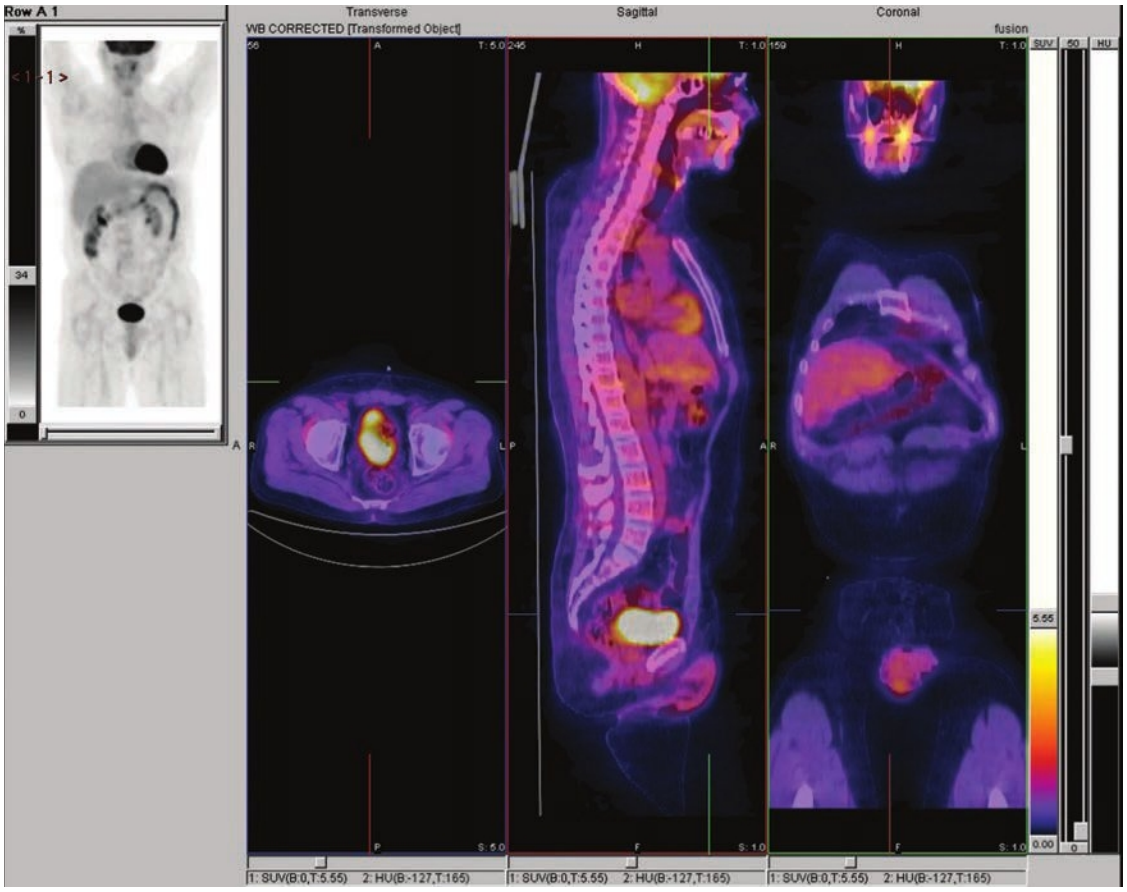


FIGURE 52–4 **The same patient as in Fig. 52–3. The PET/CT scan after four courses of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyperCVAD) alternated with high-dose methotrexate-ara-C and leucovorin rescue, reveals a dramatic improvement with no residual hypermetabolic activity. The patient went on to complete eight courses of treatment with hyperCVAD-HD methotrexate-Ara-C-leucovorin rescue. He remains in complete remission of the Burkitt lymphoma 4 years after treatment and on highly active antiretroviral therapy.**

general population. In the pre-HAART era, typical patients were men who were younger (median age, 40 years) than their immunocompetent counterparts, with CD4+ cell counts of less than 50 cells/μL of blood. The impact of HAART was evidenced by a significant decrease in the disease incidence after 1996 (from 313.2 per 100,000 person-years to 77.4 per 100,000 person-years).[3] The development of PCNSL is related to the effect of HIV immunodeficiency on the activity of EBV. The virus does not replicate in CNS tissue. Thus, infected B cells most likely reach the CNS in increased numbers as a result of the progression of the HIV infection. There is loss of capacity by specific T-cells for the production of IFN-γ in response to EBV peptides with increased expression of EBNA-2, LMPs, and EBERs. This pattern is seen when EBV transforms primary B cells in vitro. The expression of type III latency upregulates genes involved in transformation, including Bcl-*2* and *IRF-7*, and inactivation of *p53* and *Rb* tumor suppressor gene products.[71]

Clinical Presentation and Diagnosis

Patients with AIDS and PCNSL present with acute organic brain syndrome, in contrast to immunocompetent patients, in whom neurologic deterioration can be slow and progressive. Headaches, seizures, and focal neurologic signs and symptoms are common. Personality changes are frequent, and nausea and vomiting indicate an increased intracranial pressure. When the rare comatose state occurs, it indicates an acute intracranial catastrophe, such as intratumoral hemorrhage. Patients with a primary lesion in the brain and no history of systemic lymphoma usually have a brain lesion as the sole manifestation of the disease (Fig. 52–5). Radiologic diagnostic methods paired with analysis of the cerebrospinal fluid are the cornerstones of the diagnosis of PCNSL. Diagnostic MRI of the brain is preferred to CT scan because of the capacity of the former to detect small lesions. When MRI is not available, CT is acceptable because it allows detection of

Table 52–6 Short-Course Dose-Adjusted EPOCH[a]

Drug	Dose	Route	Treatment Days
Infused agents[b]			
Etoposide	50 mg/m²/d	CIV	1, 2, 3, 4 (96 h)
Doxorubicin	10 mg/m²/d	CIV	1, 2, 3, 4 (96 h)
Vincristine[c]	0.4 mg/m²/d	CIV	1, 2, 3, 4 (96 h)
Bolus agents			
Cyclophosphamide (cycle 1)	750 mg/m²/d	IV	5
Cyclophosphamide dose adjustment (after cycle 1)[d] nadir ANC <500/μL or platelets <25,000/μL for 2–4 days	↓ 187 mg/m²; route and treatment days remain unchanged below previous cycle	NA	NA
If the nadir ANC <500/μL or platelets <25,000/μL for more than 5 days, reduce cyclophosphamide by 50% of the initial full dose.	375 mg/m² below previous cycle; under Route and Treatment Days put NA		
Prednisone	60 mg/m²/d	PO	1, 2, 3, 4, 5
Rituximab	375 mg/m²	IVPB	1 and 5
Filgrastim	5 μg/kg/d	SC	6→ANC >5000/μL past nadir)
Next cycle[e]			Day 21

[a]Data are for cycle 1 except where noted in "cyclophosphamide dose adjustment."
[b]Etoposide, doxorubicin, and vincristine can be admixed in the same solution. Etoposide, doxorubicin, and vincristine are never dose-adjusted for hematologic toxicity.
[c]Vincristine dose should never be routinely capped.
[d]Dose based on previous cycle ANC nadir (complete blood count, twice-weekly) maximum cyclophosphamide dose, 750 mg/m².
[e]Begin day 21 if ANC ≥1000/μL and platelets ≥75,000/μL.
Intrathecal therapy: Intrathecal therapy with 12 mg of methotrexate or 100 mg of cytarabine is administered intrathecally on days 1 and 5 every 3 weeks beginning in cycle 3 for 8 doses for patients without central nervous system involvement. For patients with central nervous involvement please refer to original reference.
ANC, absolute neutrophil count; BSA, body surface area; CIV, continuous intravenous infusion; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin hydrochloride; IV, intravenous; IVPB, intravenous piggyback; NA, not applicable; PO, oral; SC, subcutaneous.
Data from Dunleavy K, Pittaluga S, Shovlin M, et al: Low-intensity therapy in adults with Burkitt's lymphoma, *N Engl J Med* 2013 Nov 14;369(20):1915-1925.

larger lesions (≥1 cm) and provides information about the safety of performing a lumbar puncture. Before and after HAART, the most important differential diagnosis of PCNSL has been cerebral toxoplasmosis, the most frequent cause of cerebral infection and masses in severely HIV-immunosuppressed patients.[72] In both PCNSL and cerebral toxoplasmosis, multiple lesions can occur, and both can also have enhancing ring lesions, so distinction between the two can be difficult. A positive serology for toxoplasmosis can be helpful if titers are greater than 1:256. If the toxoplasmosis serology is negative, the presence of EBV DNA found by PCR in the cerebral spinal fluid and a positive single-photon emission CT–thallium scan of the brain has high specificity for the diagnosis of PCNSL.[73,74] More recently, flow cytometry examination of the cerebrospinal fluid has been used to detect occult disease.[75]

During the early years of the AIDS pandemic, it was difficult to perform invasive procedures in patients afflicted by an infectious process of which little was known, and much was feared. These difficulties resulted in a series of practices borne out of necessity rather than rational approaches to the management and treatment of these patients such as the routine empirical treatment of brain lesions with antitoxoplasmosis therapy and gauging the diagnosis of the patient based on the clinical response to the antitoxoplasmosis treatment. Today, there is little room for continuation of such practices, and they should be avoided. They cause unnecessary delays in diagnosis and complicate the patient's management because there are potential side effects associated with treatment for an illness the patient may not have. Therefore, unless there is an absolute contraindication, the standard of care for a patient with a brain lesion and AIDS is the performance of a stereotactic biopsy of the brain, particularly in patients with a negative serology for toxoplasmosis.

Treatment of Primary Central Nervous System Lymphoma

HAART is the first step in the treatment of these patients. There is a clear correlation between the immune status of the patient and prognosis. The use of steroids and anticonvulsants is debated among some investigators concerned with the potential of steroids to confound the histologic diagnosis. However, a few days of steroids (4–5 days) can be of clinical benefit, particularly when there is an obvious mass effect. Anticonvulsive therapy administered for a few days

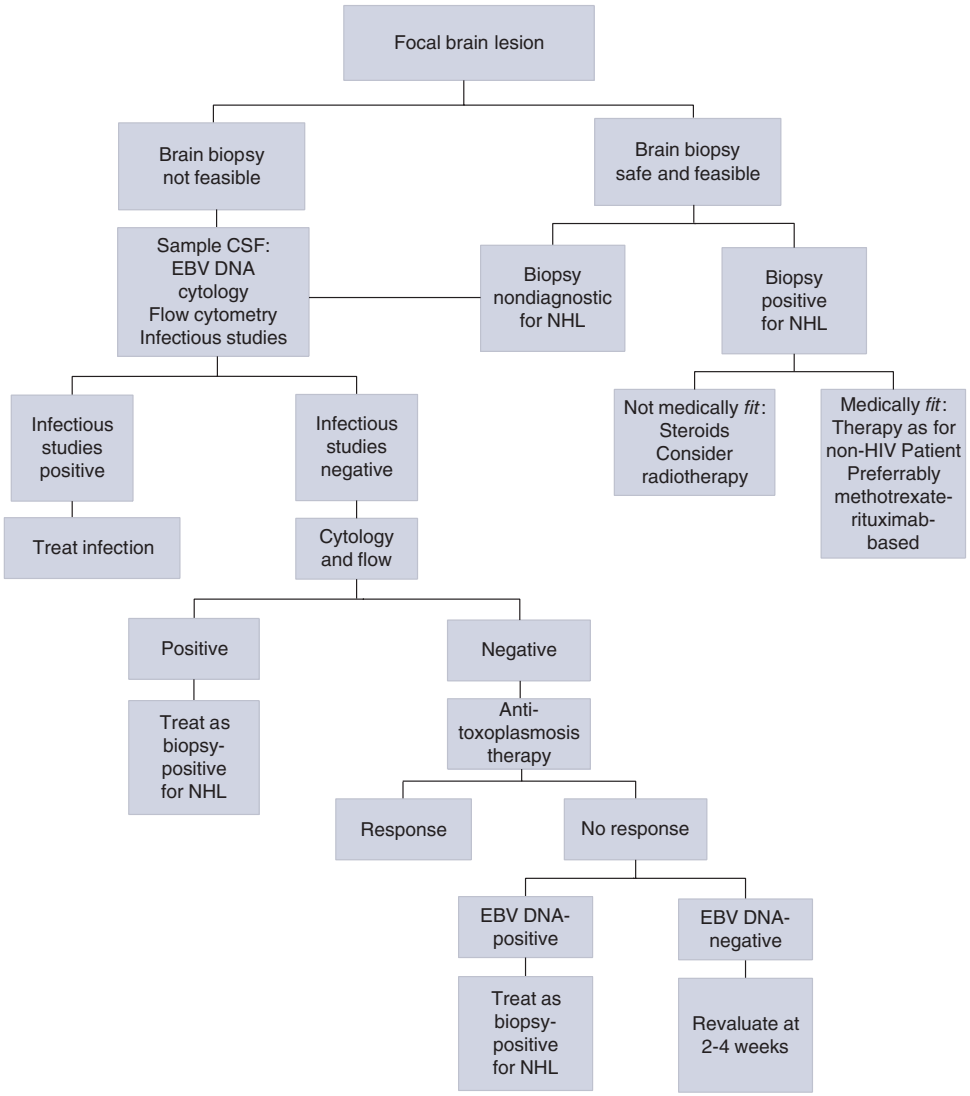


FIGURE 52–5 Evaluation of brain lesions in patients with HIV disease. CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; NHL, non-Hodgkin lymphoma. (Adapted with permission from Sparano JA. Clinical aspects and management of AIDS-related lymphoma, *Eur J Cancer* 2001 Jul;37(10):1296-1305.)

can allow the stabilization of the neurologic condition of the patient, controlling the risk of focal or grand mal seizures. Even solitary lesions of PCNSL tend to infiltrate surrounding tissues. Thus, there is no role for surgical resection in the treatment of this disease.

Before HAART, whole-brain radiotherapy was the standard of care for PCNSL, until it was replaced by best comfort measures, because the brains of severely immunocompromised patients tolerated the administration of radiotherapy poorly. Similar to immunocompetent patients with PCNSL, high-dose methotrexate and rituximab have replaced the administration of radiotherapy in patients with HIV and PCNSL. Investigators have suggested a modification of a standard regimen used for the treatment of patients without HIV, which includes rituximab 500 mg/m^2 on day 1 and methotrexate 3.5 g/m^2 and vincristine 1.4 mg/m^2 given only on day 2. Leucovorin rescue is given in standard fashion, and HAART treatment is initiated or continued. This modified regimen is administered for five to six cycles depending on the tolerance of the patient, followed by four courses of monthly maintenance with radiotherapy administered in a stereotactic manner at the discretion of the treating physician.[76] For patients not eligible to receive high-dose methotrexate, options include the use of temozolomide-rituximab and, in selected cases, focal radiotherapy followed by maintenance with an immunomodulatory agent such as lenalidomide or pomalidomide.[77–79]

New Therapies for Primary Central Nervous System Lymphoma

Activated Bruton tyrosine kinase signaling is common in PCNSL. For this reason, Bruton tyrosine kinases have been explored with evidence of activity in PCNSL although responses tend to be of short duration. This has prompted its exploration in combination regimens to achieve more durable responses. Another extremely promising new area is the potential use of immune checkpoint inhibitors. Based on the observation of alterations in the copy numbers of 9p24.1 and results of a small retrospective study, a multicenter clinical trial is in progress to investigate their activity in PCNSL and testicular cancer.[80]

HODGKIN LYMPHOMA: AN AIDS-DEFINING ILLNESS?

Epidemiology, Clinical Features, and Therapy

People infected with HIV have a 10-fold higher risk of developing HL than do HIV-seronegative persons. However, in contrast to KS and NHL, the risk is more pronounced in patients with HIV who only have moderate immunosuppression. In general, patients with HIV have a higher incidence of an unfavorable histology, including mixed cellularity and lymphocyte depletion subtypes of HL, when compared with that seen in patients without HIV infection. Instead of observing a decrease in HL in patients in the post-HAART era, as with certain NHL subtypes, investigators have noted an increase in the incidence of HL in patients with HIV.[81] This observation has made the relationship between immunodeficiency and HL uncertain. Despite the WHO inclusion as an AIDS-defining malignancy, HL is not considered by most experts as a true AIDS-associated disease. From the pathogenesis point of view, EBV is often associated with HIV-related HL, in the range of 80% to 100%. The Reed-Sternberg cells of HIV-related HL express the EBV-encoded LMP-1, known to have oncogenic properties.[82] However, despite this association, EBV virus biomarkers such as EBV DNA and antibodies have no prognostic value in patients with AIDS and HL treated with HAART.[83] Another recently described aspect of the pathogenesis of HL of great therapeutic importance is the 9p24.1 amplification in the Reed-Stenberg cell. The 9p24.1 amplicon is a recurrent genetic abnormality that increases PD-1 ligand expression. This amplicon also includes JAK-2 and Jak2/signal transducer and activator of transcription activity, which further increases PD-1 ligand transcription. Together with the known increased expression of PD-1 ligand as a result of the EBV infection, the PD-1 pathway is essential for HL survival and has become an important therapeutic target for immune checkpoint blockade in HL.[84] Also, in the post-HAART era, it has been postulated that an increase in CD4+ cells as a result of antiretroviral therapy fosters the development of the appropriate cellular milieu seen in HL in patients without HIV infection. These CD4+ cells, generated as a result of immune reconstitution by HAART, produce ligands for membrane receptors in the Reed-Sternberg cells that activate the classical NF-κB pathway.[81]

Clinically, patients with HIV and HL are young and usually have stage III or IV disease with B symptoms (fever, night sweats, and loss of >10% of body weight). Bone marrow involvement is frequent at the time of diagnosis.[85] In the pre-HAART era, the immunodeficiency of the patients limited the use of standard chemotherapeutic regimens in patients with HL. In the post-HAART era, the standards of care applicable to patients without HIV disease and HL have been applied successfully to patients with AIDS and HL once the HIV disease is controlled. Prior to HAART, Levine and colleagues in the AIDS Clinical Trial Group evaluated the efficacy of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) with G-CSF in 21 HIV-seropositive patients. There was an overall response rate of 62%, with 43% CR and 19% partial response. The median survival in this cohort was 1.5 years. Almost half the patients experienced grade 4 neutropenia, and 29% of patients developed opportunistic infections.[86] In this study, patients did not receive antiretroviral therapy while on treatment. After the introduction of HAART during treatment, investigators reported that ABVD induced a 91% complete remission rate and a median time to relapse of more than 36 months.[87] Other investigators used the Stanford V regimen, administering only short-term chemotherapy (12 weeks) with adjuvant radiotherapy. Of 59 patients who received this therapy, 69% completed the treatment without dose reduction or delays in the administration of the chemotherapy. Eighty-one percent of the patients achieved a complete remission, and with a median follow-up of 17 months, 33 (56%) of 59 patients were alive and free of disease.[88] After the introduction of HAART, the response rates for patients treated with ABVD or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) became essentially similar, irrespective of the patient's stage of the disease. However, more treatment-related mortality occurred in patients who received BEACOPP.[89] A more recent European study has confirmed that not only is ABVD as effective and less toxic, but that the overall survival is the same for both regimens.[90] Two new therapeutic interventions have significantly changed the landscape of the therapy of AIDS HL with ABVD. One is the addition of brentuximab vedotin, a chimeric

monoclonal antibody, conjugated to a toxin, monomethyl auristatin E, which selectively targets tumor cells expressing the CD30 antigen, typically expressed in HL and two, immune checkpoint blockade to which effects HL has exquisite sensitivity. It has now been demonstrated that both therapeutic interventions can be done in HIV patients with cancer without affecting the course of HIV infection and similar tolerance and effectivity as in non–HIV-infected patients with cancer.[91–93] The available data previously suggested that ABVD with HAART should be the initial treatment of choice for HIV-related HL. However, as demonstrated recently in the ECHELON-1 study, brentuximab vedotin combined with AVD (adriamycin, vinblastine, dacarbazine) is an option for patients with stage III–IV disease with no known neuropathy, if the IPI score is 4 or higher or bleomycin is contraindicated.[94] In a follow-up of 41 patients with HIV and stage II–IV HL, investigators reported 2-year progression-free survival and overall survival rates of 86% and 92%, respectively.[95] For patients with refractory disease, brentuximab vedotin alone or in combination with nivolumab[96] have become important choices in addition to usual regimens such as ICE or ESHAP. High-dose chemotherapy and autologous stem cell transplantation continue to be explored for patients who have disease progression while on treatment or relapse after remission induction. Thus, because of HAART, patients with HL and HIV disease can be treated with standard-of-care options that are similar to those used for non–HIV-infected patients with HL.

OTHER MALIGNANCIES AFFECTING HIV-INFECTED PATIENTS

Cervical Neoplasms

Epidemiology

In the early 1980s, reports appeared signaling an increased association between HIV infection and cervical intraepithelial neoplasia in HIV-infected women. It was not until 1993 that cervical cancer was officially added to WHO recommendations as an AIDS-related malignancy.[97] Women with HIV disease have a higher incidence of infection with multiple types of oncogenic HPV and a higher incidence of dysplastic changes of the cervix than women without HIV disease, events that can culminate in the development of cervical cancer (Table 52–7). There is no obvious association between the level of CD4+ cell count and cervical cancer, and the statistical correlations between the association of HIV and HPV-induced cervical cancer remains moderately strong at best. The decline observed for KS and PCNSL after HAART has not been seen in the incidence of HPV-related malignancies.

Table 52–7 Traditional Factors for Cervical Cancer Risk

History of more than six sexual partners
Cigarette smoking
Early age of first intercourse
History of sexually transmitted disease
Immunosuppression
Human papillomavirus

Data from Stier E. Cervical neoplasia and the HIV-infected patient, *Hematol Oncol Clin North Am* 2003 Jun;17(3):873-887.

Human papillomavirus infects the basal keratinocytes of the stratified epithelium, and its replication is coupled to the process of keratinocyte differentiation in the infected squamous epithelium. From an initial low-copy number in basal keratinocytes, there is a dramatic increase in the concentrations of proteins E1 and E2 by the time the keratinocytes differentiate and enter the stratum spinosum layer of the epithelium. In addition, for oncogenic strains of HPV such as 16, 18, and 31, there is also an increase in the expression of E6 and E7, which have a high oncogenic capacity manifested by the functional inactivation of p53 and R.[98,99] Regardless, this is a slow process, and it takes several years for an HPV-induced cervical lesion to transform into cancer. For these reasons, there is uncertainty regarding the relationship between HIV and cervical cancer as an AIDS-related malignancy.

Cervical Cytology and Screening

Papanicolaou tests in HIV-infected women have a high prevalence of cytologic abnormalities, ranging from 20% to 40%. Women with negative Pap smears will, over the course of 3 to 5 years, develop cytologic abnormalities at a higher rate than will HIV-negative women, and there is evidence of a higher rate of progression to cervical cancer after the longevity induced by HAART.[100] Therefore, it is imperative that patients with HIV infection be screened with Pap smears, colposcopy, and biopsy when needed for the early detection of cervical cancer. Pap smears interpreted as demonstrating "atypical squad-mouse cells" cannot exclude a high-grade squamous intraepithelial lesion (HGSIL) and must be evaluated with colposcopy (see Fig. 52–4). Current US Public Health Service and Infectious Diseases Society of America guidelines recommend Papanicolaou tests every 6 months during the first year after HIV diagnosis; if both tests are normal, annual screening is suggested (Fig. 52–6).[101]

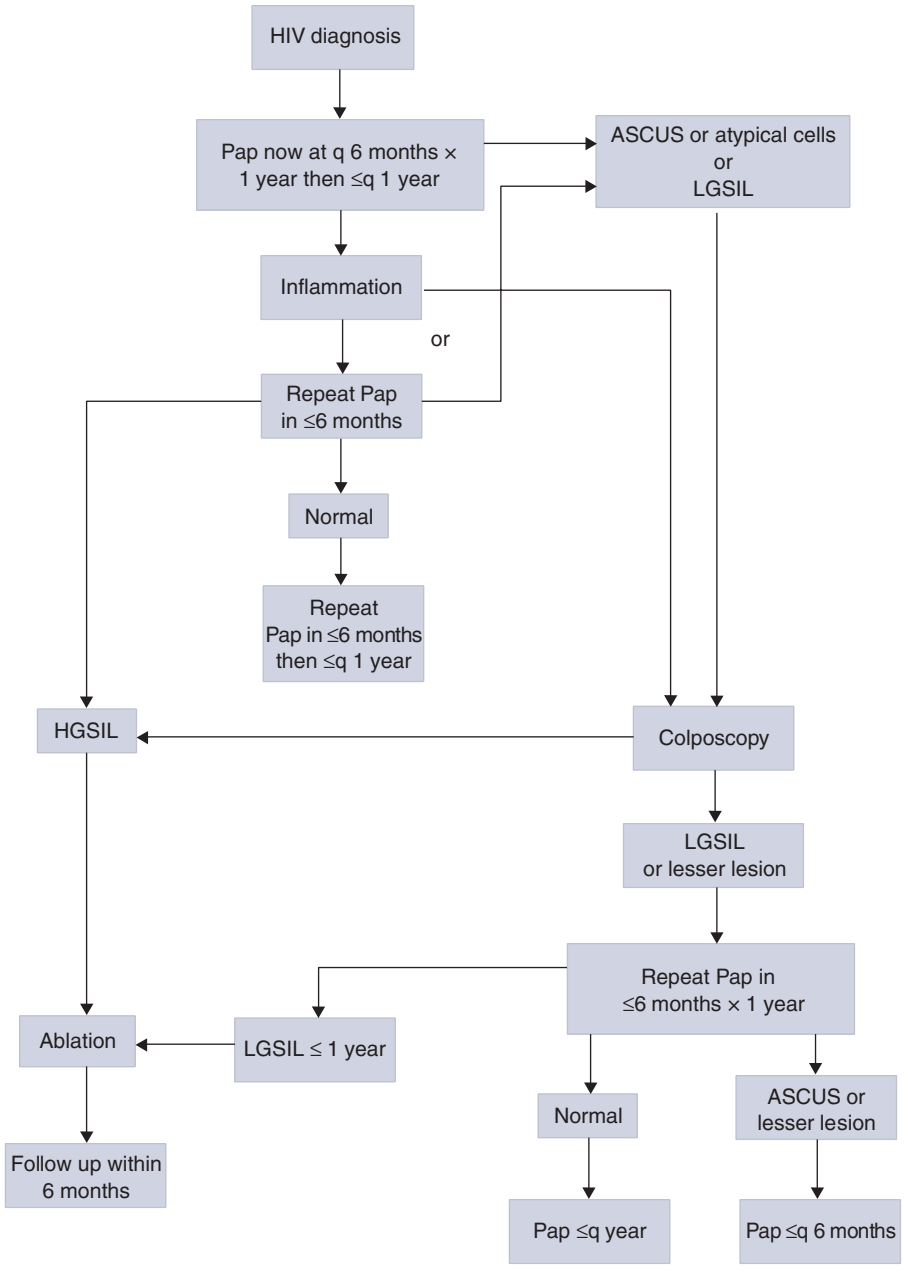


FIGURE 52–6 **Screening/treatment algorithm for cervical cancer. ASCUS, atypical squamous cells of undetermined significance; HGSIL, high-grade squamous intraepithelial lesion; LGSIL, low-grade squamous intraepithelial lesion; q, every.**

Despite controversies regarding the relationship between HIV, HPV, and cervical cancer, the increased incidence of infections by oncogenic HPV types in patients with HIV in contrast to non–HIV-infected women highlights the importance of mandatory cervical screening of HIV-infected women. However, recent studies have suggested that HIV-infected women are not being offered cervical screening, even though older women without HIV for whom the relevance of the screening may not be considered as important are routinely screened. Clearly, educational efforts are necessary as the number of HIV-infected women increases in the United States and elsewhere.

Treatment for Cervical Cancer

Because cervical intraepithelial neoplasia grade 1 lesions rarely progress and often go away on their own, the American Society for Colposcopy and Cervical Cytopathology recommends close observation

of them. However, treatment of invasive cervical cancer is the same as for HIV-seronegative women: surgery in early stages and a combination of surgery and chemoradiotherapy in intermediate stages. For cervical intraepithelial neoplasia grade 2, the preferred mode of treatment is the loop electrosurgical excision procedure. Cryotherapy and laser surgery can also be used, although these methods are usually reserved for larger lesions. Chemotherapy alone is used for more advanced cases, although the immune status of the patient can influence the response to treatment.[102]

One of the most important advances against HPV-induced cervical cancer has been the development of preventive HPV vaccines. The HPV vaccines made of viral-like particles display a remarkable structural and antigenic similitude to HPV virions and can induce the production of high titers of neutralizing antibodies.

Two versions of HPV viral-like particle vaccines are available for immunization of humans against HPV. Gardasil (Merck, Sharp, and Dohme) has viral-like particles of HPV subtypes 16 and 18 (oncogenic subtypes) and 6 and 11 (the causes of genital warts). Cervarix (GlaxoSmithKline) contains viral-like particles of HPV subtypes 16 and 18. They are both administered intramuscularly and have demonstrated almost 100% protection in clinical trials before their approval by the FDA. They should be used before the initiation of sexual activity, and neither have demonstrated therapeutic efficacy in the treatment of preexisting infections. Future work is aimed at increasing the immunogenicity of the viral-like particles and expanding the number of HPV oncogenic subtypes available for vaccination.[103]

Anorectal Carcinoma

Infection of the anogenital tract in men with oncogenic strains of HPV has the same consequence as it does in women. After HAART, the incidence of this disease has increased as patients live longer and the biological characteristics unique to the HPV oncogenic transformation are expressed over time (Table 52–8). The incidence of anal cancer has increased from 19.0 per 100,000 person-years in the pre-HAART era (1992–1995) to 48.3 persons per 100,000 person-years in the immediate post-HAART period (1996–1999) to 78.2 per 100,000 person-years more recently (2000–2003; $P < .001$).[104]

The same subtypes of HPV and pathogenic mechanisms involved in the oncogenic activity of HPV in women also apply to men. The screening and treatment of CIN 2 and 3 is of relevance in these patient populations. There has been a greater understanding of the need for anal screening of both men and women with HIV disease (Fig. 52–7).[99] The treatment of HGSILs includes the use of local therapies such as podophyllotoxin, liquid nitrogen, and laser surgery (Fig. 52–8). Investigators have recommended that men with HIV infection and anal HPV–related lesions undergo Papanicolaou tests every 6 months the first year after diagnosis and yearly thereafter. Invasive lesions are treated as in the general population, with the use of chemoradiotherapy followed by salvage surgery when there is no response or relapse after initial treatment.[105,106]

Table 52–8 Risk Factors for AIDS-Associated Anal Carcinoma

HIV seropositivity
Low CD4 cell count
Persistent HPV infection
High-risk HPV genotypes
Multiple HPV genotypes
History of anal intercourse
Cigarette smoking
Immunosuppression

HPV, human papillomavirus.
Data from Martin F, Bower M. Anal intraepithelial neoplasia in HIV positive people, *Sex Transm Infect* 2001 Oct;77(5):327-331.

Other Malignancies

Patients with HIV can develop other malignancies not necessarily associated with HIV. For example, the incidence of lung cancer continues to increase in this population. In general, smoking is one of the most important negative factors predicting poor survival in patients with HIV, even in the presence of HAART. Patients with HIV often see malignant tumors develop at an earlier age and tend to have atypical presentations, and frequently their tumors follow a very aggressive course.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

In patients with advanced HIV disease (<100 CD4+ cells/μL of blood), the initiation of HAART can be accompanied by a paradoxical worsening of established infections or the appearance of new ones. This phenomenon is most frequent in patients who have tuberculosis or cryptococcal disease as their opportunistic infection but can happen with any other type of infection. This syndrome is known as immune reconstitution inflammatory syndrome (IRIS). The management of IRIS consists of the administration of specifically indicated therapies and a short course of steroids for 1 to 2 weeks with a rapid taper. The recommended dose of prednisone is 1 to 2 mg/kg per day. Antiretroviral therapy should only be interrupted

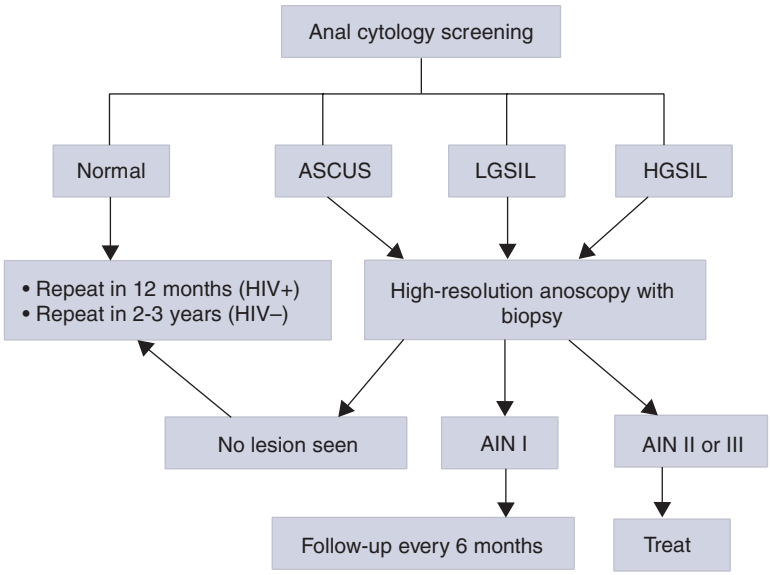


FIGURE 52–7 Protocol for screening anal intraepithelial neoplasia (AIN). ASCUS, atypical squamous cells of indeterminate significance; HGSIL, high-grade squamous intraepithelial lesion; HIV, human immunodeficiency virus; LGSIL, low-grade squamous intraepithelial lesion. (Reproduced with permission from Chin-Hong PV, Palefsky JM. Natural history and clinical management of anal human papillomavirus disease in men and women infected with human immunodeficiency virus, *Clin Infect Dis* 2002 Nov 1;35(9):1127-1134.)

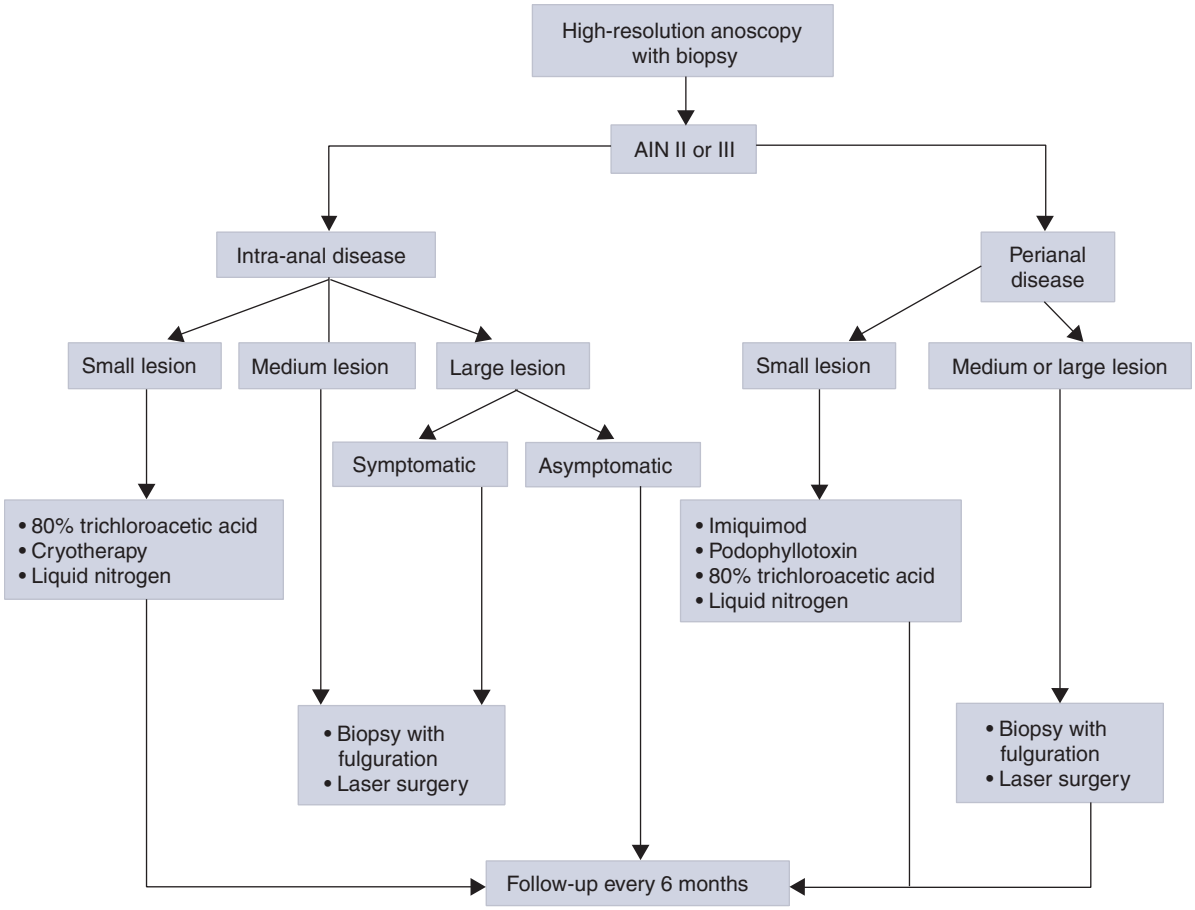


FIGURE 52–8 Treatment of anal intraepithelial neoplasia (AIN) II and III. Imiquimod and podophyllotoxin have not been approved by the FDA for this indication. (Reproduced with permission from Chin-Hong PV, Palefsky JM. Natural history and clinical management of anal human papillomavirus disease in men and women infected with human immunodeficiency virus, *Clin Infect Dis* 2002 Nov 1;35(9):1127-1134)

in severe cases because most patients respond to the use of steroid or antiinflammatory agents depending on the severity of the IRIS. Because the management of patients with AIDS-related malignancies involves a multidisciplinary team and, given the importance of the use of HAART in the management of patients with AIDS and malignancies, treating oncologists must be familiar with this condition to avoid unnecessary delays or interruptions in the HAART of their patients.[107]

MD ANDERSON CANCER CENTER AND THE AIDS PANDEMIC

When the AIDS pandemic began, Houston quickly became an AIDS epicenter, occupying the fourth place among cities with the highest number of AIDS cases in the United States for several years. The Department of Epidemiology, under the leadership of Peter W. Mansell and its Director, Guy Newell, took a leading role in studying methods for the prevention of AIDS and organizing public education efforts. Their work, together with the collaboration of R. Palmer Beasley, Dean of the University of Texas Health Science Center School of Public Health, the Department of Immunology and Biological Therapy, under the direction of Evan Hersh, and the collaboration of immunologists and virologists including James M. Reuben and Blaine F. Hollinger, was recognized with one of the first AIDS Treatment Evaluation Units Grants awarded for basic science and clinical research in AIDS. This work led to the creation of the Institute for Immunological Disorders under the direction of Peter W. Mansell and Adan Rios. Although the institute was ahead of its time, it opened doors for a humane treatment of patients with AIDS and the development of new therapies and strategies for research of the disease. This base of knowledge was instrumental in development of community strategies subsequently applied in the management and treatment of AIDS in the state of Texas. This effort extends to current times with the pioneering work done at the institution in the treatment of Burkitt lymphoma in patients with HIV by Drs Jorge Cortes, Debbie Thomas, and Houston AIDS community physicians using what is considered today a standard strategy for treatment of AIDS-related malignancies: the use of HAART in combination with the best-known strategy for the treatment of the malignancy.

CONCLUSIONS

The complexities of the AIDS pandemic are captured in the history of the AIDS-related malignancies (Table 52–9). The introduction of effective anti-HIV therapy or HAART in 1996 brought a profound change in the overall management of cancer in patients with HIV. One important predictor of good outcomes in the therapy of cancer and HIV is the administration of HAART.[108] The common goals for treatment of patients with AIDS and cancer are to treat HIV with HAART and the cancer with the same standards of care that exists for patients without HIV disease, along with vigorous prophylaxis of opportunistic infections, supportive therapy including growth factors, and appropriate nutritional and emotional support.

Table 52–9 AIDS-Associated Cancers[a]

Cancer Type	Observed Cases	Expected Cases	Relative Risk	Etiologic or Contributing Factors
Kaposi sarcoma				KSHV
Men	5583	57.3	97.5[b]	
Women	200	1.0	202.7[b]	
Non-Hodgkin lymphoma				EBV and KSHV
Men	2434	65	37.4	
Women	342	6.3	54.6	
Cervical, invasive				HPV
Women	133	14.7	9.1	
Hodgkin lymphoma				EBV

Table 52–9 AIDS-Associated Cancers[a] (*Cont.*)

Cancer Type	Observed Cases	Expected Cases	Relative Risk	Etiologic or Contributing Factors
Men	160	20	8	
Women	20	3.1	6.4	
Tongue				HPV and EBV
Men	17	9.3	1.8	
Women	5	0.7	7.1	
Rectal, rectosigmoidal, and anal				HPV (anal carcinoma)
Men	75	22.7	3.3	
Women	9	3.0	3.0	
Liver (primary only)				HCV,[c] HBV, alcohol
Men	36	7.1	5.1	
Tracheal, bronchial, and lung				Smoking[d]
Men	217	66.1	3.3	
Women	50	6.7	7.5	
Brain and CNS				EBV for CNS lymphoma
Men	42	13.4	3.1	
Women	7	2.0	3.4	
Skin, excluding Kaposi sarcoma				HPV[e] and ultraviolet light exposure
Men	133	6.4	20.8	
Women	8	1.1	7.5	
Melanoma, skin				
Men	24	17.3	1.4	
Testicular				
Men	38	25.6	1.5	
Colon				
Men	32	38.2	0.8	
Women	5	6.3	0.8	
Prostate				
Men	37	53.7	0.7	
Breast				
Women	47	59.9	0.8	
Ovarian				
Women	6	7.8	0.8	

[a]Data are based on the observed number of cases in HIV-positive individuals (men and women aged 15–69 years), expected cases based on the incidence in a nonimmunocompromised population in New York State (NYS), relative risk, and etiologic factors. Data from the AIDS/Cancer Matched Cohort NYS, 1981–1991.
[b]Relative risk for Kaposi sarcoma (KS) is lower than in other studies, probably because the background population in NYS is enriched with population groups (eg, Italian, Greek, and Jewish) that have an increased risk for classic KS.
[c]HCV contributes to increased incidence of liver cancer, particularly in HIV-infected men with hemophilia, and in intravenous drug users.
[d]The increase in lung cancer might be confounded by the fact that HIV-infected individuals have been reported to smoke more cigarettes per day than HIV-negative individuals.
[e]In Africa, HPV and ultraviolet light exposure have been implicated in the high incidence of conjunctival squamous carcinoma, and HPV is also implicated as the cause of skin cancers seen after an organ transplant. Misdiagnosis of KS might also contribute to increased risk of skin cancer.
CNS, central nervous system; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papillomavirus; KSHV, Kaposi sarcoma–associated herpesvirus.
Reproduced with permission from Boshoff C, Weiss R. AIDS-related malignancies. *Nat Rev Cancer*. 2002;2(5):373-382.

MD ANDERSON PRACTICE TIPS

- Every patient with newly diagnosed lymphoma should undergo a test for seropositivity for HIV 1/2. Patients also should undergo repeat testing at the time of relapse therapy. Viral loads and lymphocyte subset counts are tested before therapy if the antibody test is positive.
- If a patient with HIV seropositivity and newly diagnosed cancer is receiving HAART before initiation of therapy for the cancer, HAART should be continued throughout treatment. However, if liver function become abnormal during therapy, it may be necessary to temporarily discontinue HAART until the completion of treatment, at which time HAART may be restarted. For the patient who has not begun HAART at the time of therapy for the cancer, HAART may be delayed until the completion of therapy, depending on the type of treatment necessary and the lymphocyte counts.
- Most patients with advanced classical HL and HIV now have results with BV (A)-AVD that are as good as those reported for patients without HIV-seropositivity and is the recommended choice for those with advanced (stage III–IV) disease. Patients with limited disease (stage I–II) have positive results with therapy as do those without HIV disease.
- Patients with aggressive B-cell lymphomas should undergo EPOCH-R and CNS prophylaxis with methotrexate, with doses determined by the performance status of the patient and lymphocyte counts. Reduced doses may be necessary for those with low lymphocyte counts, with subsequent escalated dose adjustments determined by neutrophil and platelet nadirs. Patients achieving PET negativity after two cycles may only need two more cycles of therapy. Those with CNS disease or marrow disease require specialized therapy, as for patients without HIV disease.
- Patients with HIV seropositivity should undergo annual HPV cervical and anal testing for the virus by PCR. Other screening tests should be administered as for patients without HIV disease.
- For patients with AIDS-KS with minimal tumor burden, HAART initiation constitutes frontline therapy of their AIDS-related KS. This approach can control these lesions for long periods of time, often more than one year, and in many instances results in complete disappearance of KS lesions. Patients with extensive disease or visceral involvement can receive specific systemic KS therapies in addition to HAART.

REFERENCES

1. Hogg RS, Heath KV, Yip B, et al. Improved survival among HIV-infected individuals following initiation of anti-retroviral therapy. *JAMA*. 1998;279:450-454.
2. Sepkowitz KA. AIDS—the first 20 years. *N Engl J Med*. 2001;344:1764-1772.
3. Biggar RJ, Anil K, Chaturvedi AK, et al. AIDS-related cancer and severity of immunosuppression in persons with AIDS. *J Natl Cancer Inst*. 2007; 99:962-972.
4. Franceschi S, Lise M, Clifford GM, Rickenbach M, et al. Changing patterns of cancer incidence in the early- and late-HAART periods: the Swiss HIV Cohort Study. *Br J Cancer*. 2010;103:416.
5. Stebbing J, Duru O, Bower M. Non-AIDS-defining cancers. *Curr Opin Infect Dis*. 2009;22:7-10.
6. Centers for Disease Control and Prevention. Pneumocystis pneumonia—Los Angeles. *MMWR Morb Mortal Wkly Rep*.1981;30:250-252.
7. Gottlieb MS. AIDS—past and future. *N Engl J Med*. 2001;344:1788-1791.
8. Farge D, Lebbé C, Marjanovic Z, et al. Human herpes virus-8 and other risk factors for Kaposi's sarcoma in kidney transplant recipients. Groupe Cooperatif de Transplantation d'Ile de France (GCIF). *Transplantation*. 1999;67:1236-1242.
9. Barré-Sinoussi F, Chermann JC, Rey F, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science*. 1983;220:868-871.
10. Hahn BH, Shaw GM, De Cock KM, et al. AIDS as a zoonosis: scientific and public health implications. *Science*. 2000;287:607-614.
11. WHO/UNAIDS. The importance of simple/rapid assays in HIV testing. *Wkly Epidemiol Rec*. 1998;73:321-328.
12. WHO/UNAIDS. AIDS epidemic update. Accessed August 23, 2020. https://www.unaids.org/sites/default/files/media_asset/2020_aids-data-book_en.pdf.
13. Parrish NF, Gao F, Li H, et al. Phenotypic properties of transmitted founder HIV-1. *Proc Natl Acad Sci U S A*. 2013;110:6626-6633.
14. Santiago ML, Montano M., Benitez R, et al. Apobec3 encodes Rfv3, a gene influencing neutralizing antibody control of retrovirus infection. *Science*. 2008;321:1343-1346.
15. Centers for Disease Control and Prevention. Kaposi's sarcoma and pneumocystis pneumonia among homosexual men—New York City and California. *MMWR Morb Mortal Wkly Rep*. 1981;30:305.
16. Chang Y, Cesarman E, Pessin MS, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. *Science*. 1994;266:1865-1869.
17. Moore PS, Boshoff C, Weiss RA, et al. Molecular mimicry of human cytokine and cytokine response pathways genes by KSHV. *Science*. 1996;274:1739-1744.
18. Nicholas J. Human herpesvirus 8-encoded proteins with potential roles in virus-associated neoplasia. *Front Biosci*. 2007;12:265-281.
19. Dezube BJ. Clinical presentation and natural history of AIDS-related Kaposi's sarcoma. *Hematol Oncol Clin North Am*. 1996;5:1023-1029.
20. Cattelan AM, Calabró ML, Gasperini P, et al. Acquired immunodeficiency syndrome-related Kaposi's sarcoma regression after highly active antiretroviral therapy: biologic correlates of clinical outcome. *J Natl Cancer Inst Monogr*. 2001;28:44-49.
21. Cattelan AM, Calabró ML, De Rossia A, et al. Long-term clinical outcome of AIDS-related Kaposi's sarcoma during highly active antiretroviral therapy. *Int J Oncol*. 2005;3:779-785.
22. Quesada JR, Reuben J, Manning JT, et al. Alpha interferon for induction of remission in hairy-cell leukemia. *N Engl J Med*. 1984;310:15-18.
23. Krown SE. The role of interferon in the therapy of epidemic Kaposi's sarcoma. *Semin Oncol*. 1987;14(2 suppl 3):27-33.
24. Rios A, Mansell PW, Newell GR, et al. Treatment of acquired immunodeficiency syndrome-related Kaposi's sarcoma with lymphoblastoid interferon. *J Clin Oncol*. 1985;4:506-512.
25. Polizzotto MN, Uldrick TS, Wyvill KM, et al. Pomalidomide for symptomatic Kaposi's sarcoma in people with and without HIV infection: a phase I/II study. *J Clin Oncol*. 2016;34:4125-4131.
26. World Health Organization. Guidelines on the Treatment of Skin and Oral HIV-Associated Conditions in Children and Adults. World Health Organization; 2014.
27. Mletzko S, Pinato D, Robey R, et al. Programmed death ligand 1 (PD-L1) expression influences the immunetolerogenic microenvironment in antiretroviral therapy-refractory Kaposi's sarcoma: a pilot study. *Oncoimmunology*. 2017;6:e1304337.
28. Galanina N, Goodman AM, Cohen PR, Frampton GM, Kurzrock R. Successful treatment of HIV-associated Kaposi's sarcoma with immune checkpoint blockade. *Cancer Immunol Res*. 2018;6:1129-1135.
29. Cesarman E, Chang Y, Moore P, at al. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body cavity-based lymphomas. *N Engl J Med.* 1995;332:1186-1191.
30. Souller J, Grollet L, Oksendhendler E, at al. Kaposi's sarcoma-associated herpes-virus-like DNA sequences in multicentric Castleman's disease. *Blood.* 1995;86:1276-1280.
31. Polizzotto M, Uldrick T, WyvIII K, et al. Clinical features and outcomes of patients with symptomatic Kaposi sarcoma herpesvirus (KSHV)-associated inflammation: prospective characterization of KSHV inflammatory cytokine syndrome (KICS). *Clin Infect Dis*. 2016;62:730-738.
32. Carbone A, Cesarman E, Spina M, et al. HIV-associated lymphomas and gamma herpesviruses. *Blood*. 2009;113:1213-1224.
33. National Cancer Institute-sponsored study of classifications of non-Hodgkin's lymphomas: summary and description of a working formulation for clinical usage. The Non-Hodgkin's Lymphoma Pathologic Classification Project. *Cancer*. 1982;49:2112-2135.
34. Barclay LR, Buskin SE, Kahle EM, et al. Clinical and immunologic profile of AIDS-related lymphoma in the era of highly active antiretroviral therapy. *Clin Lymphoma Myeloma*. 2007;4:272-279.
35. Swerdlow HS, Campo E, Harris NL, et al. *World Health Organization Classification of Tumors of Haematopoietic and Lymphoid Tissues*. IARC Press; 2017.
36. Levine AM. Acquired immunodeficiency syndrome-related lymphoma. *Blood*. 1992;80:8-20.
37. Vajdic CM, van Leeuwen MT. What types of cancers are associated with immune suppression in HIV? Lessons from solid organ transplant recipients. *Curr Opin HIV/AIDS*. 2009;1:35-41.
38. Pelicci P, Knowles DM, Arlin ZA, et al. Multiple monoclonal B cell expansions and c-myc oncogene rearrangements in acquired immune deficiency syndrome-related lymphoproliferative disorders. *J Exp Med*. 1986;164:2049-2076.
39. Carbone A, Gloghini A. AIDS-related lymphomas: from pathogenesis to pathology. *Br J Haematol*. 2005;130:662-670.
40. Angeletti PC, Luwen Z, Wood C. The viral etiology of AIDS-associated malignancies. *Adv Pharmacol*. 2008;56:509-557.
41. Cesarman E. Gamma herpesviruses and lymphoproliferative disorders. *Ann Rev Pathol Mech Dis*. 2014.9:349-372.
42. Vaghefi P, Martin A, Prévot S, et al. Genomic imbalances in AIDS-related lymphomas: relation with tumoral Epstein-Barr virus status. *AIDS*. 2006;20:2285-2291.
43. Gaidano G, Pastore C, Lanza C, et al. Molecular pathology of AIDS-related lymphomas. Biologic aspects and clinicopathologic heterogeneity. *Ann Hematol*. 1994;69:281-290.
44. Knowles DM. Molecular pathology of acquired immunodeficiency syndrome-related non-Hodgkin's lymphoma. *Semin Diagn Pathol*. 1997;1:67-82.

45. Voelkerding KV, Sandhaus LM, Kim HC, et al. Plasma cell malignancy in the acquired immune deficiency syndrome. *Am J Clin Pathol*. 1989;92:222-228.
46. Levine AM, Sadeghi S, Espina B, et al. Characteristics of indolent non-Hodgkin lymphoma in patients with type 1 human immunodeficiency virus infection. *Cancer*. 2002;94:1500-1506.
47. Goldstein J, Becker N, Delrowe J, et al. Cutaneous T-cell lymphoma in a patient infected with human immunodeficiency virus type 1. Use of radiation therapy. *Cancer*. 1990;66:1130-1132.
48. Tsimberidou AM, Medina J, Cortes J, et al. Chronic myeloid leukemia in a patient with acquired immune deficiency syndrome: complete cytogenetic response with imatinib mesylate: report of a case and review of the literature. *Leuk Res*. 2004;6:657-660.
49. Ziegler JL, Beckstead JA, Volberding PA, et al. Non-Hodgkin's lymphoma in 90 homosexual men. Relation to generalized lymphadenopathy and the acquired immunodeficiency syndrome. *N Engl J Med*. 1984;311:565-570.
50. Rossi G, Donisi A, Casari S, et al. The International Prognostic Index can be used as a guide to treatment decisions regarding patients with human immunodeficiency virus-related systemic non-Hodgkin lymphoma. *Cancer*. 1999;86:2391-2397.
51. Sanherr M, Hentrich M, von Lilienfeld-Toal M, et al. Antiviral prophylaxis in patients with solid tumors and haematological malignancies—update of the Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO). *Ann Hematol*. 2015;94:1441-1450.
52. Bower M, Gazzard B, Mandallia S, et al. A prognostic index for systemic AIDS-related non-Hodgkin lymphoma treated in the era of highly active antiretroviral therapy. *Ann Intern Med*. 2005;143(4):265-273.
53. Vaccher E, Spina M, di Gennaro G, et al. Concomitant cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy plus highly active antiretroviral therapy in patients with human immunodeficiency virus-related, non-Hodgkin lymphoma. *Cancer*. 2001;91:155-163.
54. Kaplan LD, Scadden DT. No benefit from rituximab in a randomized phase III trial of CHOP with or without rituximab for patients with HIV-associated non-Hodgkin's lymphoma: AIDS Malignancies Consortium Trial 010. *Proc Am Soc Clin Oncol*. 2003;abstract 2268.
55. Sparano JA, Weller E, Nazeer T, et al. Phase II trial of infusional cyclophosphamide, doxorubicin, and etoposide in patients with poor-prognosis, intermediate-grade non-Hodgkin lymphoma: an Eastern Cooperative Oncology Group trial (E3493). *Blood*. 2002;100(5):1634-1640.
56. Tirelli U, Spina M, Jaeger U, et al. Infusional CDE with rituximab for the treatment of human immunodeficiency virus-associated non-Hodgkin's lymphoma: preliminary results of a phase 1/II study. *Recent Results Cancer Res*. 2002;159:149-153.
57. Sparano JA. Clinical aspects and management of AIDS-related lymphoma. *Eur J Cancer*. 2001;37(10):1296-1305.
58. Antinori A, Cingolani A, Alba L, et al. Better response to chemotherapy and prolonged survival in AIDS-related lymphomas responding to highly active antiretroviral therapy. *AIDS*. 2001;15:1483-1491.
59. Little RF, Pittaluga S, Grant N, et al. Highly effective treatment of acquired immunodeficiency syndrome-related lymphoma with dose-adjusted EPOCH: impact of antiretroviral therapy suspension and tumor biology. *Blood*. 2003;101(12):4653-4659.
60. Bartlett N, Wilson W, Sin-Ho J, et al. Dose-adjusted EPOCH-R compared with R-CHOP as frontline therapy for diffuse large B-cell lymphoma: clinical outcomes of the phase III Intergroup Trial Alliance/CALGB. *J Clin Oncol*. 2019;37:1790-1799.
61. Sparano J, Lee J, Kaplan L, et al. Response-adapted therapy with infusional EPOCH chemotherapy plus rituximab in HIV-associated B-cell non-Hodgkin lymphoma. *Haematologica*. 2020;105. doi.org/10.3324/haematol2019.243386.
62. Levine AM. Management of AIDS-related lymphoma. *Curr Opin Oncol*. 2008;20:522-528.
63. Cortes J, Thomas D, Rios A, et al. Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone and highly active antiretroviral therapy for patients with acquired immunodeficiency syndrome-related Burkitt lymphoma/leukemia. *Cancer*. 2002;94:1492-1499.
64. Wang ES, Straus DJ, Teruya-Feldstein J, et al. Intensive chemotherapy with cyclophosphamide, doxorubicin, high dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine (CODOX-M/IVAC) for human immunodeficiency virus-associated Burkitt lymphoma. *Cancer*. 2003;98:1196-1205.
65. Zelenetz A, Abramson J, Advani R, et al. NCCN clinical practice guidelines in oncology: non-Hodgkin's lymphomas. *J Natnl Compr Cancer Netw*. 2010;8:288-334.
66. Dunleavy K, Pittaluga S, Shovlin M, et al. Low intensity therapy in adults with Burkitt lymphoma. *N Engl J Med*. 2013;369:1915-1925.
67. Dunleavy K, Noy A, Abramson J. Risk-adapted therapy in adults with Burkitt lymphoma: preliminary report of a multicenter prospective phase II study of DA-EPOCH-R. *Blood*. 2015;126:342.
68. Barta S, Xue X, Wang D, et al. Treatment factors affecting outcomes in HIV-associated non-Hodgkin lymphomas: a pooled analysis of 1546 patients. *Blood*. 2013;122:3251-3262.
69. Chadburn A, Chiu A, Lee J, et al. Immunophenotypic analysis of AIDS-related diffuse large B-cell lymphoma and clinical implications in patients from AIDS Malignancies Consortium clinical trials 010 and 034. J Clin Oncol. 2009;27:5039-5048.
70. Krishnan A, Molina A, Zaia J, et al. Durable remissions with autologous stem cell transplantation for high risk HIV associated lymphomas. *Blood*. 2004;105:874-878.
71. Pagano JS. Epstein-Barr virus: the first human tumor virus and its role in cancer. *Proc Assoc Am Physicians*. 1999;111:573-580.
72. Wong SY, Israeli ski DM, Remington JS. AIDS-associated toxoplasmosis. In: Sande MA, Volberding PA, eds. *The Medical Management of AIDS*. 4th ed. WB Saunders; 1995:460.
73. Lorberboym M, Wallach F, Estok L, et al. Thallium-201 retention in focal intracranial lesions for differential diagnosis of primary lymphoma and nonmalignant lesions in AIDS patients. *J Nucl Med*. 1998;39:1366-1369.
74. Corcoran C, Rebe K, van de Plas H, Myer L, Hardie DR. The predictive value of cerebrospinal fluid Epstein-Barr viral load as a marker of primary central nervous system lymphoma in HIV-infected persons. *J Clin Virol*. 2008;42:433-436.
75. Broomberg JEC, Breems DA, Kran J, et al. CSF flow cytometry greatly improves diagnostic accuracy in CNS hematologic malignancies. *Neurology*. 2007;68:1674-1679.
76. Shah GD, Yahalom J, Correa DD, et al. Combined immunochemotherapy with reduced whole-brain radiotherapy for newly diagnosed primary CNS lymphoma. *J Clin Oncol*. 2007;25:4730-4735.
77. Wong ET, Tishler R, Barron L, et al. Immunochemotherapy with rituximab and temozolomide for central nervous system lymphomas. *Cancer*. 2004;101:139.
78. Rubinstein JL, Geng H, Fraser E, et al. Phase I investigation of lenalidomide/rituximab plus outcomes of lenalidomide maintenance in relapsed CNS lymphoma. *Blood Adv*. 2018;2:1595.
79. Rubnstein JL. Biology of CNS lymphoma and the potential of novel agents. *Am Soc Hematol Educ Program*. 2017;556-564.

80. Grommes C, Nayak L, Tun W, et al. Introduction of novel agents in the treatment of primary CNS lymphoma. *Neuro Oncol*. 2018;21:306-313.
81. Carbone A, Gloghini A, Serraino D, et al. HIV-associated Hodgkin lymphoma. *Curr Opin HIV/AIDS*. 2009;4:3-10.
82. Carbone A, Gloghini A, Dotti G: EBV-associated lymphoproliferative disorders: classification and treatment. *Oncologist*. 2008;13:577-585.
83. Lupo J, Germi R, Lancar R, et al. Epstein-Barr virus biomarkers have no prognostic value in HIV-related Hodgkin lymphoma in the modern combined antiretroviral therapy era. *AIDS*. 2019;233:993-1000.
84. Green M, Monti S, Rodig S, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. *Blood*. 2010;116:3268-3277.
85. Vaccher E, Spina M, Tirelli U. Clinical aspects and management of Hodgkin's disease and other tumors in HIV-infected individuals. *Eur J Cancer*. 2001;37:1306-1315.
86. Hessol NA, Katz MH, Liu JU, et al. Increased incidence of Hodgkin's disease in homosexual men with HIV infection. *Ann Intern Med*. 1992;117:309-311.
87. Levine AM, Li P, Cheung T, et al. Chemotherapy consisting of doxorubicin, bleomycin, vinblastine, and dacarbazine with granulocyte-colony-stimulating factor in HIV-infected patients with newly diagnosed Hodgkin's disease: a prospective, multiinstitutional AIDS clinical trials group study (ACTG 149). *J AIDS*. 2000;15:444-450.
88. Berenguer J, Miralles P, Ribera JM, et al. Characteristics and outcome of AIDS-related Hodgkin's lymphoma before and after the introduction of highly active antiretroviral therapy. *J Acquire Immune Defic Syndr*. 2008;47:422-428.
89. Spina M, GA barre J, Rossi G, et al. Stanford V regimen and concomitant HAART in 59 patients with Hodgkin's disease and HIV infection. *Blood*. 2002;100:1984-1991.
90. Mondello P, Mussolino C, Dogliotti I, et al. ABVD vs BEACOPP escalated in advanced-stage Hodgkin's lymphoma: results from a multicenter European study. *Am J Hematol*. 2020;95:1030-1037.
91. Rubinstein, Moore P, Rudek M, et al. Brentuximab vedotin with AVD shows safety, in the absence of strong CYP3A4 inhibitors, in newly diagnosed HIV-associated Hodgkin lymphoma. *AIDS*. 2018;32:605-611.
92. Spano J, Veyri M, Gobert A, et al. Immunotherapy for cancer in people living with HIV: safety with an efficacy signal from the series in real life experience. *AIDS*. 2019;33:F13-F19.
93. Chang E, Rivero G, Patel N. et al. HIV-related refractory Hodgkin lymphoma: a case report of complete response to nivolumab. *Clin Lymph Myel Leuk*. 2017;18:e143-e146.
94. Straus D, Duglosz-Danecka M, Alekseev S, et al. Brentuximab vedotin with chemotherapy for stage III/IV classical Hodgkin lymphoma: 3-year update of the ECHELON-1 study. *Blood*. 2020;135:735-742.
95. Rubinstein P, Moore P, Bimali M, et al. Safety and efficacy of brentuximab vedotin with AVD in stage II-IV classical Hodgkin lymphoma: results of the phase 2 study, AMC085. *Blood*. 2019;134:130.
96. Herrera A, Moskowitz A, Bartlett N, et al. Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. *Blood*. 2018;131:1183-1194.
97. Stier E. Cervical neoplasia and the HIV-infected patient. *Hematol Oncol Clin North Am*. 2003;17:873-887.
98. Chow LT, Brooker TR. Papillomavirus DNA replication. *Intervirology*. 1994;37:150-158.
99. Munger K, Phelps WC, Bubb V, et al. The E6 and E7 genes of the human papillomavirus type 16 together are necessary and sufficient for transformation of primary human keratinocytes. *J Virol*. 1989;63:4417-4421.
100. Ellerbrock TV, Chiasson MA, Bush TJ, et al. Incidence of cervical squamous intraepithelial lesions in HIV-infected women. *JAMA*. 2000;282:1031-1037.
101. US Preventive Services Task Force. Screening for cervical cancer. In: AHRQ Publication No. 03–515A, January 2003. Agency for Healthcare Research and Quality; 2003.
102. Koh W-J., Abu-Rustum N. R., Bean S. et al. Cervical Cancer, Version3.2019, NCCN Clinical Practice Guidelines in Oncology. *JNCCN*. 2019;17:64-84.
103. Zur Hausen H. Papillomaviruses and cancer: from basic studies to clinical application. *Nat Rev Cancer*. 2002;2:342-350.
104. Martin F, Bowers M. Anal intraepithelial neoplasia in HIV-positive people. *Sex Transm Inf*. 2001;77:327-331.
105. Chin-Hong PV, Palefsky JM. Natural history and clinical management of anal human papillomavirus disease in men and women infected with human immunodeficiency virus. *HIV/AIDS*. 2002;35:1127-1134.
106. Benson III A.B., Venook A.P., Al-Hawary M.M. et al. Anal Carcinoma, Version 2.2018, Clinical Practice Guidelines in Oncology. *JNCCN*. 2018;16: 852-871.
107. Manzardo C, Guardo AC, Letang E, et al. Opportunistic infections and immune reconstitution inflammatory syndrome in HIV-1-infected adults in the combined antiretroviral therapy era: a comprehensive review. *J M Expert Rev Anti Infect Ther*. 2015;13:751.
108. Valencia Ortega, ME. AIDS-related malignancies: a new approach. *AIDS Rev*. 2008;10:125-127.

This page intentionally left blank

53 Carcinoma of Unknown Primary

Gauri R. Varadhachary
Kanwal P. Raghav
Ryan W. Huey

KEY CONCEPTS

- Carcinoma of unknown primary (CUP) is defined as biopsy-proven metastatic cancer where a primary site is unidentifiable after adequate workup.
- CUP is a rare tumor with an incidence of less than 10 per 100,000 individuals and constitutes nearly 2% of all cancers diagnosed in the United States.
- Favorable and specific clinicopathologic subsets in CUP should be identified and treated with selective and aggressive treatments.
- Limited data support the use and therapeutic impact of molecular profiling assays for tissue of origin (ToO) determination in CUP.
- Chemotherapy for patients with CUP can be either empiric or site-specific (guided by putative primary site determined by clinicopathologic factors), and novel effective therapies for known primaries may impact the treatment decision.
- Overall prognosis in CUP is poor, but a great degree of heterogeneity based on patient and disease characteristics exists.

OVERVIEW

Carcinomas of unknown primary (CUPs), with their heterogeneous presentations, pose a challenge diagnostically and therapeutically. Depending on the extent of evaluation, CUP comprises about 2% of all malignancies.[1–3] A working definition for CUP is biopsy-proven metastatic cancer with no identifiable primary source by history; physical examination; chest radiography; complete blood cell count; chemistry; computed tomography (CT) of the chest, abdomen, and pelvis; prostate-specific antigen (PSA) in men; and mammography in women.[2] The natural history of disease for CUP is diverse and is dependent on multiple variables, such as, age, number of metastatic sites, dominant area of disease, and histology. This considerable heterogeneity presents a challenge to the systematic study of CUPs. In addition, the emergence of sophisticated imaging, robust immunohistochemistry (IHC), and genomic and proteomic tools have challenged the "unknown" designation. Depending on histologic features, sites of disease, and performance status, a small but significant minority of patients will be long-term survivors, and it is important to identify these groups of patients.[4,5]

This chapter discusses the evaluation of patients with CUP and optimal therapeutic strategies in the era of sophisticated diagnostics. The differing natural histories in CUP, depending on both the sites of disease and histology, are also discussed. Studies showed that in this population a search for the primary tumor beyond "routine" evaluation is unrewarding in the majority of patients.[5] This fact has caused much consternation for both patients and physicians. The foundation for cancer treatment traditionally relies on identification of the tumor origin, thereby allowing treatment to be chosen based on the known natural history, as well as specific therapies, that have proven to be effective for the cancer; this is becoming even more important with the rapid emergence of targeted therapies. Without knowledge of the primary site, the oncologist is often hesitant to recommend therapy, especially given the disease heterogeneity. Although most patients with metastatic CUP have tumors that respond poorly to current treatments and will consequently have a poor prognosis, it has become evident over the last two decades that subsets of patients with CUP have a favorable prognosis and respond to chemotherapy or can be treated successfully with regional

therapy alone. The current era of sophisticated diagnostics and introduction of targeted therapies has been particularly important in the CUP setting; this cancer entity is the epitome of personalized therapy.

EPIDEMIOLOGY

The incidence of CUP cancers as estimated from the cancer registries and databases of "unknown and unspecified cancers" is reported to be approximately 2% of all cancers.[6] This is probably an overestimation because this group includes a mix of patients: those with true CUP, those with primaries not yet diagnosed at the time of death, and those with difficult-to-diagnose tumors. Further, improved imaging allowing identification of small primary tumors suggests that the incidence of true CUP is decreasing.

A minority of patients (10%) with CUP have a history of an antecedent cancer. In autopsies performed before the advent of CT, the occult primary tumor was identified in 60% to 80% of cases. In one autopsy series, the two most commonly identified primary sites were the pancreas (20%) and lungs (18%).[7,8] Given the current high-quality CT imaging and positron emission tomographic (PET) scans, it is unclear whether these cancer profiles are still the majority.

The classification of CUP continues to evolve. The last four decades have seen a shift in our understanding of CUP. First, improved imaging increased our confidence for the entity termed *occult primary*. Later, "favorable" CUP subsets were determined, based primarily on histopathology, the pattern of spread of select types of CUP, and serum markers. Subsequently, with the advent of novel IHC markers and advances in diagnostic pathology, tissue of origin (ToO) profiles were described that assigned additional putative primary sites to CUP cancers based on IHC patterns. Current research involves the application of proteomic and genomic tools to CUP cancers.

BIOLOGY, CHROMOSOMAL ABERRATIONS, AND MUTATIONAL PROFILING

CUPs, despite their heterogeneity, are a clinically unique oncologic entity; as such, they share many common features that set them apart from other malignancies. The central unifying clinical feature of CUP is the absence of a detectable primary tumor. Previous studies have shown that, even after an autopsy, the primary site will not be identified in 20% to 40% of cases; that number is likely much lower with significant improvements in imaging. It is not known why primary carcinomas exhibit this unique biological behavior. One current hypothesis is that the acquisition of a "metastatic phenotype" is an early event in CUPs, soon after oncogenesis, thus enabling cells to metastasize early, before the development of a clinically detectable tumor.[9] It has also been hypothesized that the primary tumors may regress or involute before the metastases become clinically evident, attributed to a host immunologic response. A third hypothesis is that the primary tumor is exposed to antiangiogenic factors locally, whereas the metastases acquire the angiogenic phenotype after a period of dormancy.[10]

Several studies have demonstrated a specific nonrandom pattern of chromosomal aberrations that seems to be unique to CUPs. These data suggest that some of these genetic changes may be the underlying cause of the metastatic phenotype. CUP is characterized by greater genetic instability, with massive genomic alterations, when compared with other distant metastases. In a study by Pantou and colleagues,[11] cytogenetic profiling of tumors from 20 patients with CUP was performed, revealing an average of 11 chromosomal changes per case. Of the three histologic subtypes in this study, adenocarcinomas had not only the highest number of cytogenetic changes (16 vs 3) but also involvement of distinct sites (4q31, 6q15, 10q25, and 13q22) when compared with carcinomas or undifferentiated malignancies. The latter group was distinguished by the involvement of changes at 11q22. Overall, the most commonly rearranged chromosomal regions were 1q21, 3p13, 6q21–23, 7q22, 11p12–5, and 11q14–24. The number of cytogenetic alterations was found to be prognostically relevant. Median survival was significantly greater for patients with five or fewer cytogenetic changes compared with those with more than five changes (3 vs 18 months; $P = .003$). An older study of 12 CUP cell lines also demonstrated a preponderance of chromosome 1 abnormalities. These changes were observed on both the long arm (eg, 1p deletion, isochromosome 1p, and translocations with a 1p breakpoint) and on the short arm (1q21), suggesting the importance of chromosome 1 in the biology of CUPs.[12] Chromosome 1p aberrations are also commonly associated with advanced malignancies.

Chromosome 12 abnormalities have also been shown in CUP. This is of particular interest because one of the observed alterations, isochromosome 12p (i12p), is present in as many as 80% of germ cell tumors. Motzer and colleagues reported that 30% of patient tumors in their series had either i12p or 12q deletions. The presence of either of these two cytogenetic abnormalities was found to be predictive of a complete response to cisplatin-based chemotherapy (75% vs 17%; $P = .002$).[13,14] In the current era of

sophisticated IHC, we rarely miss a patient with an extragonadal presentation and seldom order cytogenetics to inform therapeutic plans.

The tumor suppressor gene *p53* is commonly mutated in human cancers, especially in advanced malignancies. Paradoxically, this does not seem to be true in CUP. Bar-Eli and colleagues found *p53* mutations to be less frequent than expected (26%) in CUP after evaluating 15 biopsy specimens and eight cell lines.[15] However, work by other researchers evaluating IHC studies of *p53* in CUP has found this protein to be highly expressed in 70% of the tumors examined.[16,17] Nevertheless, *p53* expression has not been found to have prognostic relevance. Molecular studies have also demonstrated the overexpression of other oncogenes, such as c-*myc*, *ras*, *bcl-2*, and *Her2/neu*, in CUPs, but none have been found to have any correlation with either survival or response to chemotherapy.[18]

NATURAL HISTORY AND CLINICAL PRESENTATION

The clinical course of patients with CUP varies widely. Median survival in large retrospective studies has ranged from 11 weeks to 11 months. In a study from the MDACC, the 5-year overall survival (OS) rate was only 11%. Although survival is poor as a whole, there are certain prognostic variables that correlate with longer survival, including disease limited to one organ site, involvement of lymph nodes only, and histologic diagnosis of squamous or neuroendocrine carcinoma. Variables suggestive of a poor prognosis include male sex, histologic diagnosis of adenocarcinoma, and metastatic involvement of the liver, lungs, bone, pleura, or brain (Table 53–1).[4]

Table 53–1 Favorable Versus Poor Prognosis Carcinoma of Unknown Primary

Favorable Prognosis	Poor Prognosis
Extragonadal germ cell syndrome	Liver metastases (non-neuroendocrine)
Isolated single small metastasis	Pleural or lung metastases
Papillary peritoneal adenocarcinoma (women)	Adrenal metastases
Isolated axillary adenocarcinoma (women)	Multiple brain metastases
Cervical adenopathy (squamous cell)	
Isolated inguinal adenopathy	
Neuroendocrine histology	

By performing multivariate analyses on a consecutive series of 1000 patients with CUP with classification and regression tree (CART) analysis, Hess and colleagues[4] were able to more closely study the interactions between different clinical variables and how this influenced survival.

Patients with CUP present with symptoms and signs similar to those of patients with advanced malignancies of known origin. In one review, the most common symptoms at presentation of CUP were general deterioration (73%), digestive symptoms (58%), liver enlargement (58%), abdominal pain (56%), respiratory symptoms (45%), ascites (26%), and node enlargement (16%).[19] Most patients with CUP present with multiple metastases, with three or more organs involved. In patients with a dominant (or single) site of metastasis, the most common reported sites were liver (25%), bone (22%), lungs (20%), lymph nodes (15%), pleural space (10%), and brain (5%).

DIAGNOSTIC EVALUATION

In the past, minimalist diagnostic strategies had been advocated, limiting the scope of initial evaluations to differentiate only between treatable and untreatable disease. Others have supported a more aggressive approach, wherein a complete assessment of the extent of the disease and detection of the primary tumor site are attempted. In our experience, a more pragmatic approach is better. Extensive evaluation of all patients presenting with metastases is an expensive and wasteful extreme that does not benefit patients. In one study, the average cost of evaluating a patient with CUP was $17,973 and much higher with recent testing.[20,21] In that study, mean survival was 8.1 months, representative of the natural history of CUP, with only 18% of patients surviving one year. However, a strictly minimalist approach may result in the oversight of treatable and potentially curable neoplasms.

An important determinant of the appropriate extent of evaluation for any patient with CUP is whether the data obtained by a diagnostic test will influence treatment decisions. If a treatable or potentially curable cancer is strongly suspected (eg, a germ cell tumor or lymphoma or oligometastatic disease treated with surgery or multimodality therapy), further investigation should proceed until a precise clinical diagnosis can be made, provided that therapy is not unreasonably delayed. The recommended general approach at the present time is thus one of a directed evaluation based on clinical presentation and pathologic findings; predictions of tumor origin or mutations from molecular profiling techniques may also play a role in streamlining the scope of evaluation.

Physical Examination and Laboratory Tests

A thorough medical history and physical examination, including a digital prostate examination in men and a breast and pelvic examination in women, should be performed. Determination of the patient's performance status, nutrition, and the presence or absence of concomitant medical illnesses and malignancy-related complications (eg, paraneoplastic syndromes or painful metastases) that may affect patient care is required.

Laboratory tests should include routine biochemical and hematologic surveys. The role of tumor markers in the evaluation of patients with CUP is often not diagnostic. Most tumor markers are nonspecific and are not useful for identifying a primary site or for prognostic purposes. Adenocarcinoma markers (eg, carcinoembryonic antigen, cancer antigen [CA] 125, CA 15-3, and CA 19-9) are often elevated in patients with CUP and cannot be reliably used to identify a specific primary site or to predict either OS or the exact burden of metastatic disease.[22–24] Serum tumor markers may play a role in helping to evaluate patients for responses to therapy, although levels are not always predictive of response to chemotherapy.

Their selective use in a directed approach is more helpful than ordering a large battery of tumor markers on all patients who present with CUP. Men who present with metastatic adenocarcinoma and CUP with osteoblastic bone metastases should have PSA and prostatic acid phosphatase levels measured. In all men with undifferentiated (or poorly differentiated) midline carcinomas, β-human chorionic gonadotropin and α-fetoprotein levels should be measured, especially if the clinical presentation suggests an extragonadal germ cell tumor. In patients with hepatic tumors, α-fetoprotein levels should also be measured if there are risk factors or pathologic characteristics that suggest the possibility of primary hepatocellular carcinoma.

Diagnostic Imaging and Invasive Studies

In the absence of contraindications, a baseline intravenous contrast CT scan of the chest, abdomen, and pelvis is the standard of care, as supported by the National Comprehensive Cancer Network and National Institute for Health and Clinical Excellence (NICE) CUP radiology guidelines.[25–27] Patients with CUP should then be approached in a "directed" fashion. Endoscopy of the upper and lower gastrointestinal (GI) tract is indicated for patients with abdominal complaints, ascites, liver metastases, or other findings in the initial workup and pathology that are indicative of a possible GI primary tumor.

All women with CUP and adenocarcinoma should undergo mammography. In cases of suspicious findings on a breast examination and negative mammography findings, patients should have breast sonography and a biopsy as indicated. Because both the sensitivity (23%–29%) and specificity (71%–73%) of mammography in detecting an occult carcinoma are low, breast magnetic resonance imaging (MRI) has been evaluated as an alternative in patients with a high suspicion for breast primary cancer. In the setting of isolated axillary adenopathy, MRI is sensitive in detecting occult primary breast cancers (>75%) and should be performed in women with isolated axillary adenopathy and negative mammography findings.[28–33] Women with adenocarcinoma presenting with metastatic sites other than cervical or axillary adenopathy that are compatible with breast cancer (ie, bone, liver, or lungs) may also undergo breast MRI if the mammography findings are negative.[32,33]

Patients with upper or midcervical adenopathy with a squamous cell carcinoma on pathology should undergo a thorough head and neck evaluation, including panendoscopy (ie, laryngoscopy, bronchoscopy, and esophagoscopy) with random biopsies. Ipsilateral or (more often) bilateral tonsillectomy has also been recommended as part of the staging process because this has been shown to identify an occult primary lesion deep in the tonsillar crypts in up to 30% of patients with this presentation of CUP.[34–36] CT of the head and neck region is routinely done as part of the initial workup. In addition, the utility of 18-fluorodeoxyglucose positron emission tomography (FDG-PET) has been well documented in patients with squamous carcinoma and cervical adenopathy; small prospective and retrospective studies suggest that a primary head and neck tumor is identified in 25% to 30% of these patients.[36–42] A retrospective review found that the primary tumor site was identified in 44% of these patients undergoing PET-CT fusion scans, and this modality appears to be emerging as a superior alternative to either PET or CT alone.[38,39]

Outside the indication given previously, the role of PET-CT is unclear. Several small studies have evaluated the utility of PET in patients with CUP.[43,44] Moller et al reviewed ^{18}FDG-PET as a diagnostic tool for patients with extracervical CUP.[44] They identified four publications (152 patients); these studies were retrospective and heterogeneous in their inclusion criteria, study design, and diagnostic workup before FDG PET–CT. The primary tumor was detected by FDG PET–CT in 39% of patients with extracervical CUP. Lung was the most commonly detected primary tumor site (≈50%). Pooled estimates of sensitivity, specificity, and accuracy of FDG PET–CT in the detection of the primary tumor site were 87%, 88%, and 87.5%, respectively. They concluded that FDG PET–CT may have a role in identification of the primary tumor in extracervical CUP; however, prospective studies with more uniform inclusion criteria are warranted. Although not studied

prospectively, PET-CT scans may be useful in selected patients with solitary metastases before definitive locoregional therapies and in follow-up of patients with predominant bone disease.[2]

Histopathologic Evaluation

All pathologic material obtained at biopsy from a patient with CUP should be evaluated by an experienced pathologist familiar with CUP workup. The pathologist should also be informed of the patient's pertinent history and clinical findings so that he or she can recommend further analysis on the basis of this information. In the realm of CUP, pathology trumps radiology. Collaboration between the pathologist and treating oncologist is critical. Adequate tissue sampling is essential.

The CUP cancers include adenocarcinoma, poorly differentiated adenocarcinoma (60%); poorly differentiated carcinoma (PDC), undifferentiated carcinoma, or undifferentiated neoplasm (30%); squamous cell carcinoma (5%); and neuroendocrine cancer (2%). Rarely (2%), CUP can present as mixed tumors, including sarcomatoid, basaloid, and adenosquamous carcinomas (Table 53–2).

Adequacy of tissue is essential, especially when the pathologist has to make a diagnosis from deep fine-needle aspirations and there is insufficient tissue for IHC staining. The diagnosis of a poorly differentiated neoplasm implies that the pathologist is unable to classify it into any of the general neoplastic categories (carcinoma, lymphoma, melanoma, or sarcoma).

Table 53–2 Major Histologic Findings in Carcinoma of Unknown Primary

Histology	Proportion (%)
Well to moderately differentiated adenocarcinoma	55
Poorly differentiated adenocarcinoma	30
Squamous	6
Neuroendocrine	4
Undifferentiated malignancy	5

Subsequent evaluation of this group of poorly differentiated lesions by means of special IHC techniques is warranted because some of these patients will have tumors that are potentially curable and very responsive to treatment. Many IHC reagents are at the disposal of the pathologist, making the histologic classification of the tumor easier (Table 53–3).

Especially useful are the antibodies to common leukocyte antigens present in lymphoma and the antibodies to PSA present in most prostate cancers. Other useful IHC markers include cytokeratin CK7, CK20, and thyroid transcription factor (TTF-1). Thyroid transcription factor is a nuclear transcription factor that is normally expressed in lung and thyroid tissues and in their neoplasms. Staining positive for TTF-1 is frequent in lung cancer, especially in adenocarcinomas

Table 53–3 Commonly Utilized Immunoperoxidase Stains to Assist in the Differential Diagnosis of Poorly Differentiated Neoplasms

Stain	Likely Primary Site
Estrogen/progesterone receptor, gross cystic disease fluid protein-15, low molecular weight cytokeratin	Breast cancer
Thyroid transcription factor, CK7, CK20, surfactant protein A precursor	Lung cancer
Prostate-specific antigen, epithelial membrane antigen, alpha-methylacyl coenzyme A racemase/P504S	Prostate cancer
Leukocyte common antigen, CD3, CD4, CD5, CD20, CD45	Lymphoma
Vimentin, desmin,[a] factor VIII[b]	Sarcoma
Chromogranin/synaptophysin, neuron-specific enolase, cytokeratin	Neuroendocrine tumor
Epithelial membrane antigen, β-human chorionic gonadotrophin, α-fetoprotein, placental alkaline phosphatase	Germ cell tumor
CK7, CK20,[c] uroplakin III	Urothelial malignancies
S100, vimentin, human melanomablack-45, neuron-specific enolase	Melanoma
CK7, CK20,[c] caudal type homeobox-2, carcinoembryonic antigen	Colorectal cancer

[a]Positive in desmoid tumors, rhabdomyosarcomas, and leiomyosarcomas.
[b]Positive in angiosarcomas.
[c]Whereas a $CK7^{+}/CK20^{-}$ staining pattern is typical of lung neoplasms, $CK7^{-}/CK20^{+}$ is suggestive of a colorectal primary. Dual $CK7^{+/}CK20^{+}$, however, is suggestive of urothelial primary.

(60%–75%) and small cell lung cancers (66%–87%); however, it is inconsistently expressed in squamous cell carcinoma. Among the various monoclonal antibodies against various cytokeratins, CK7 and CK20 can help differentiate between different solid tumors. (For instance, CK7 is more commonly associated with pulmonary or gynecologic malignancies, whereas CK20 is frequently seen in GI adenocarcinomas.) The $CK7^{+}/CK20^{-}$ immunophenotype, in conjunction with TTF-1 staining, is suggestive of a lung primary and is a highly sensitive and specific method for differentiating primary pulmonary adenocarcinomas from metastatic extrapulmonary adenocarcinomas (Fig. 53–1).[45–49] In contrast, the $CK7^{-}/CK20^{+}$ immunophenotype is suggestive of a colorectal primary site. $CK7^{+}$ and $CK20^{+}$ dual staining suggests a malignancy of urothelial or pancreaticobiliary origin. Using light microscopy and IHC, a putative primary tumor may be assigned in up to one-third of CUP cases. Immunohistochemistry can also suggest biomarker studies with potential therapeutic impact (eg, *Kras*, epidermal growth factor receptor, Her2, and anaplastic lymphoma kinase mutations).

Hep par 1 is an antigen whose expression is confined to benign and malignant hepatocytes and aids in the diagnosis of hepatocellular carcinoma in patients with CUP presenting with liver lesions. In women, depending on the pathology and pattern of metastasis, estrogen receptor and progesterone receptor staining is done to look for a breast primary. Another marker for a breast primary is gross cystic disease fluid protein 15, which is present in 62% to 72% of breast cancers.

Dennis and colleagues[50] have identified other novel molecular markers using a bioinformatics approach. All publicly available gene expression data from various adenocarcinomas were pooled together, and four novel proteins not previously recognized as tumor markers were found to be significantly upregulated. This was confirmed by reverse transcription–polymerase chain reaction. One example was lipophilin B, which was found to be restricted to breast, ovarian, and prostate cancers.

The use of cytogenetic analysis in the diagnosis of CUPs is limited. Specific chromosomal abnormalities have been identified in several types of lymphoma (8;14 translocation in small non–cleaved-cell non-Hodgkin lymphoma), germ cell tumors (i12p), and Ewing sarcoma (t11;22 or t21;22). In the cytogenetic study by Pantou et al,[11] lymphoma was diagnosed in four patients with CUP on the basis of the presence of immunoglobulin (Ig) H/Alk-1 rearrangement, which was identified by fluorescence in situ hybridization. In addition, one patient was diagnosed with Ewing sarcoma owing to detection of characteristic rearrangement of chromosomes 11 and 22. In the era of novel and sophisticated IHC, cytogenetics is rarely ordered to help with therapy decisions. Most useful are patterns and groups of IHC used in an effective algorithm that can prove to be clinically appropriate and cost-effective, although the approach to this is not uniform in the community.[51,52]

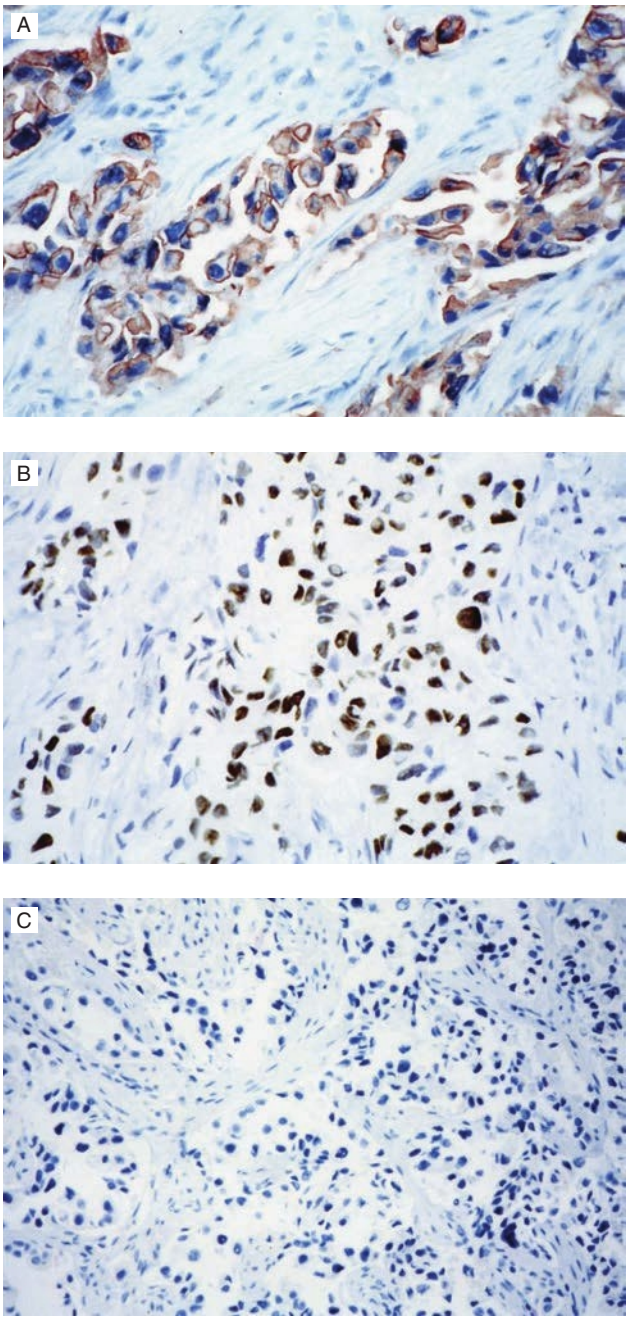


FIGURE 53–1 Immunohistochemical stains performed on the biopsy specimen from a patient with primary metastatic adenocarcinoma to a supraclavicular lymph node. Immunoperoxidase stains were positive for CK-7 (A) and TTF-1 (B) but negative for CK-20 (C), thus suggestive of metastatic non–small cell lung cancer. (Used with permission from Dr. Nelson Ordoñez, Department of Pathology, MDACC.)

Tissue of Origin Studies of Carcinomas of Unknown Primary

ToO molecular profiling using DNA microarray and reverse transcription–polymerase chain reaction is a promising technique to establish the putative primary diagnosis in patients with CUP.[53,54] The performance of these assays in known cancers has been validated using independent blinded sets of tumor samples, with an accuracy of approximately 90%.[55–57] The feasibility of using formalin-fixed small biopsy or fine-needle aspiration samples makes this practical for use in the clinic setting.

Messenger RNA- or microRNA-based ToO assays have been studied in prospective and retrospective CUP trials. Recently, a genome-derived algorithm has used artificial intelligence to predict ToO, taking into account multiple molecular features of a tumor. In CUP, these assays and algorithms suggest a specific primary tumor in about 70% of patients studied.[58–65] Because by definition the primary tumor site is not known in CUP, validation of site prediction in CUP remains a challenge. Results from multiple small studies suggest that ToO predictions are likely accurate. Indicators include (1) concordant results of ToO testing and the appearance of a latent primary during the course of the patient's illness (or many years later); (2) strong correlation between ToO assay results and diagnostic IHC (both suggesting a single putative primary); and (3) a prospective study demonstrating that patients treated with ToO-based site-directed therapy had survival similar to those with the corresponding known primary.[66]

In the United States, there are currently three commercially available Medicare-approved tests. They differ in the platform used, the number of potential cancers identified, the size and histologic samples of the training set, and the reporting format. All three assays report on identifying a putative primary in about 75% to 85% of patients with CUP. No comparative studies have been conducted, although in our personal experience, when IHC is diagnostic, all three tests usually produce similar results.

A prospective, single-arm study evaluated the role of the 92-gene assay to predict the ToO and assay-directed site-specific therapy in patients with CUP.[66] The authors concluded that the median OS of 12.5 months (95% CI 9.1–15.4) for patients who received assay-directed site-specific therapy compares favorably with previous studies using empiric therapy. Biliary and urothelial profiles were 33% of the predictions. Unfortunately, firm conclusions of therapeutic impact cannot be drawn from this study given the nonrandomized design, statistical biases, confounding variables such as use of subsequent lines of (empiric) therapy, and the heterogeneity of the CUP cancers.

Two prospectively defined blinded studies of difficult-to-diagnose primary cancers (several poorly differentiated) have reported on the diagnostic accuracy of ToO molecular profiling over IHC. Samples were evaluated by IHC/morphology analysis or the ToO molecular profiling test.[67] Accuracy was defined based on comparison with pathology of known primary. In one, the assay demonstrated overall accuracy of 79% for tumor classification versus 69% for IHC/morphology analysis ($P = .019$). Mean IHC use was 7.9 stains per case (range 2–15). The other study also confirmed similar findings[68]; the assay accurately identified 89% of specimens compared with 83% accuracy using IHC ($P = .013$). In the subset of poorly differentiated and undifferentiated carcinomas, assay accuracy exceeded that of IHC (91%–71%; $P = .023$). These results have important implications for management of CUP cancers and warrant a study of an integrated algorithm evaluating ToO molecular profiling complementing IHC in select patients.

Multiple clinical trials have been designed to evaluate the therapeutic impact of ToO molecular profiling assays, including one that has been reported, detailed below, and others that are ongoing. These data and other creative trial designs are urgently needed to study CUP subsets and the impact of these assays on survival and quality of life in patients with CUP.

Next-Generation Sequencing in Carcinomas of Unknown Primary

As our molecular understanding of cancer improves, more therapies are being used to target specific molecular features of a cancer rather than the ToO. Next-generation sequencing has emerged as a diagnostic tool to discover these molecular features, which likely have therapeutic implications for patients with CUP. Ross and colleagues retrospectively studied 200 consecutive CUP tumor specimens that underwent comprehensive genomic profiling using the hybrid-capture–based FoundationOne assay.[69] The DNA extracted from these CUP tumor specimens was analyzed after hybridization capture of 3769 exons from 236 cancer-related genes and 47 introns of 19 genes commonly rearranged in cancer. There were 125 adenocarcinomas of unknown primary site (ACUPs) and 75 non-adenocarcinomas (non-ACUPs). The authors reported that a large number of CUP samples (85%) harbored at least one clinically relevant genomic alteration with the potential to influence and personalize therapy. The mean number of genomic alterations was 4.2 per tumor. The ACUP tumors were more frequently driven by genomic alterations in the receptor tyrosine kinase/Ras/mitogen-activated protein kinase signaling pathway than non-ACUP tumors. The authors concluded that comprehensive genomic profiling can

identify novel treatment paradigms and suggested that early testing may have utility in CUP management.

As diagnostic approaches and the design of clinical trials evolve, molecular pathways have emerged as treatment targets regardless of the ToO. Both the mismatch repair pathway and TRK fusions have been studied across multiple tumor types.[70,71] Given the therapeutic implications, these should be considered for testing in patients with CUP as part of a broad molecular analysis.

Liquid Biopsies in Carcinomas of Unknown Primary

Since the discovery of fragments of tumor-derived DNA shed into the bloodstream, there has been considerable interest in liquid biopsies in the role of cancer diagnostics and treatment.[72] Advances in DNA analysis have allowed for the genotyping of circulating tumor DNA (ctDNA), which has been used for mutational detection in some cancers, such as epidermal growth factor receptor mutations in non–small cell lung cancer.[73] Liquid biopsies have the benefit of being less invasive than a tumor biopsy, making the collection of serial samples much easier for the patient. Another benefit is the potential to overcome tumor heterogeneity and molecular differences in primary versus metastatic tumors. In CUP, the role of liquid biopsies has been examined by a group studying up to 70 genes using next-generation sequencing of ctDNA.[74] Of 442 patients studied, 66% had one or more characterized alteration, most commonly TP53. This work highlights the feasibility for ctDNA and its potential for future utility. However, one limitation of liquid biopsies is determining the biological significance of each mutation, because many can be found in healthy individuals. Further work is needed to delineate these differences.

MANAGEMENT OF SPECIFIC CLINICOPATHOLOGIC SUBGROUPS

Carcinomas of Unknown Primary Presenting as Isolated Brain Metastases

In as much as 15% of patients presenting with brain metastases, the primary site remains unknown.[75,76] The important factor in treating patients with brain lesions is to distinguish patients with metastatic disease from those with primary brain tumors. Once this distinction has been made, patients with single metastatic lesions should be considered for surgery, and those with multiple lesions should receive radiotherapy. In a recent small prospective study, patients with CUP who had single brain metastases treated with gross total resection and subsequent whole-brain radiotherapy (WBRT) had a median survival of 13 months. Patients with CUP who had multiple brain metastases and who underwent either WBRT alone or gross resection of symptomatic lesions followed by adjuvant WBRT had a median survival of only 6 to 8 months.[76] Stereotactic brain radiation is often used in the CUP setting using the same principles as for brain metastases from known primary cancers.

Carcinomas of Unknown Primary Presenting as Metastatic Cervical Adenopathy

In this subgroup, patients present with high- to midcervical or -supraclavicular adenopathy; on histopathologic analysis, these tumors are squamous cell or PDCs. For squamous cell carcinoma, the primary site is eventually identified during follow-up in approximately 20% of patients, with the tonsil being the most common site, followed by the pyriform sinus and base of the tongue.

Adenocarcinoma is much less common and generally derives from either metastatic nonpapillary thyroid carcinoma or advanced malignant disease from a distant site (GI tract, lung, or breast carcinoma presenting as a metastatic supraclavicular node). Of all malignancies of the head and neck, only 5% to 10% are classified as unknown primary after imaging and panendoscopy. The prognosis for patients with cervical CUP overall is better than that for other CUP clinical subgroups, but even within this group, significant heterogeneity exists. Yalin et al,[77] in a retrospective study of 107 patients with cervical CUP (62% PDC, 24% squamous carcinoma, and 14% adenocarcinoma), reported a 5-year OS rate of 35.5%. In another retrospective study by Issing et al,[78] 5- and 10-year OS rates were 42.7% and 30.6%, respectively. The prognosis is significantly worse in the presence of any of the following: adenocarcinoma, level III/IV lymphadenopathy, multiple lymph nodes, and bulky disease.

Patients with supraclavicular adenopathy have a far worse prognosis than those with adenopathy in other lymph node–bearing areas. Carcinoma affecting supraclavicular lymph nodes on the right most commonly arises from occult primary tumors of the lungs and breast. When disease affects the lymph nodes on the left side, spread from intra-abdominal malignancies by way of the thoracic duct (Virchow node) is an additional possibility.

The management of cervical CUP in patients has become increasingly controversial, primarily because of the question of postoperative radiation therapy. The notion of adjuvant irradiation of all potential mucosal sites has been questioned because of the absence of any demonstrated survival benefit in randomized studies. To date, postoperative radiation therapy in cervical CUP significantly improves locoregional control, but

this does not translate into improved OS. This being said, combined-modality therapy (surgery and radiation therapy) is better than either modality alone.[79] Most patients with only cervical or supraclavicular involvement should have regional therapy consisting of surgery, postoperative radiation therapy, and close follow-up. Patients who undergo an excisional biopsy for diagnosis usually do not need additional surgery if no gross disease is left behind, only a single lymph node measuring less than 6 cm is involved, and no extracapsular extension is noted on pathologic review. If any of these features is present, a neck dissection is indicated. In addition, for patients with squamous cell carcinoma, unilateral tonsillectomy ipsilateral to the presenting neck mass is commonly advocated as part of the surgical treatment because occult tonsillar carcinomas are usually found in 18% to 39% of patients who undergo tonsillectomy.[78,79] Identification of the primary site would thereby reduce morbidity by limiting the field of radiation and would improve surveillance.

In patients with N1 or N2a disease (squamous cell), it is unclear whether postoperative radiation improves local control because studies have been contradictory. In this case, close surveillance would also be an acceptable option after surgery. All other patients should receive postoperative radiation to the bilateral neck covering all potential occult primary sites (ie, nasopharynx, oropharynx, and hypopharynx). The 3-year survival rate after radical neck dissection or radical neck irradiation ranges from 35% to 60%. Within this group, patients with N1 disease have a better prognosis; patients with N3 disease, regardless of the local treatment modality used (surgery, radiotherapy, or both), fail to achieve complete remission in 65% of cases.

Although the role of chemotherapy in patients with cervical CUP remains poorly defined, extrapolation of phase 2/3 data in head and neck cancer indicates a role in patients with advanced nodal disease (N3). A recent large meta-analysis of more than 10,000 patients in 63 trials with head and neck squamous cell carcinoma treated with chemotherapy demonstrated a small but significant absolute survival benefit of 4% at 5 years.[80] Intensive concurrent chemoradiotherapy in unresectable squamous cell head and neck cancers with cisplatin/5-fluorouracil–based and cetuximab-based regimens has resulted in improved complete response rates, locoregional control, and preservation of organ function, albeit at the cost of significant toxicities.

Women with Carcinomas of Unknown Primary and Isolated Axillary Adenopathy

Women who present with adenocarcinoma in the axillary lymph nodes compose another subset with a more favorable prognosis. Disease in these patients is often managed as that for women with stage II breast cancer. Isolated axillary adenopathy is an uncommon presentation of breast cancer, accounting for only 1 to 3 of every 1000 diagnosed breast cancers. Mammography and ultrasonography should be performed, and biopsies should be performed on any identified lesions. If mammography findings are normal, additional imaging of the breast with MRI is indicated because of its greater ability to detect small primary breast tumors (70%–95% sensitivity). MRI has a very low false-negative rate. Of approximately 40 women reported in the literature with isolated axillary adenocarcinoma and negative breast MRI findings, only four were found to have breast cancer at surgery or during follow-up.[81]

The present recommended management of disease in women with CUP of the axilla includes axillary dissection, axillary radiotherapy for those at high risk of local recurrence (eg, extracapsular invasion or >4 positive lymph nodes), and appropriate systemic therapy for breast cancer, depending on age, menopausal status, and biomarkers. If breast MRI findings are negative, neither mastectomy nor breast irradiation is recommended.[82–84] If the breast MRI is positive or suspicious, radiation to the breast is usually recommended. The prognosis is not as favorable in men who present with axillary adenopathy only.[82]

This management paradigm is changing as molecular profiling complements pathology as a diagnostic tool in this subset of patients. All women with axillary adenopathy do not have occult breast cancer. Profiling for ToO can help with treatment decisions especially if the IHC does not correlate with breast cancer and estrogen receptor, progesterone receptor, and Her-2 status is negative.

Carcinomas of Unknown Primary Presenting as Isolated Inguinal Adenopathy

A few patients with CUP present with inguinal adenopathy. Undifferentiated (anaplastic) carcinoma is identified in at least half of these cases. Some of these anaplastic "carcinomas" appear to be melanomas with no obvious primary skin lesion. The remaining patients have squamous cell carcinomas arising from the skin, genitourinary tract, anus, or pelvis. A detailed investigation for primary lesions in these areas is important because curative therapy is available for carcinomas of the anus, vulva, vagina, and cervix, even with spread to regional lymph nodes. In patients with carcinomas and PDCs confined to the groin nodes, where no primary site was identified, a superficial groin dissection should be performed with or without radiation therapy. Bimodality therapy with surgery and radiation may increase the risk of significant lymphedema and requires careful planning. Chemotherapy, before definitive therapy and

in the context of a clinical trial, may be offered to patients with bulky locoregional adenopathy and is not an uncommon practice in the clinic.

Carcinomas of Unknown Primary and Isolated Pleural Effusions

Most patients with isolated pleural effusions have adenocarcinomas, which may sometimes be difficult to differentiate from mesotheliomas. Newer IHC markers (eg, calretinin, CK 5/6, and WT1 [Wilms tumor-1]) that are more sensitive in differentiating epithelioid malignant mesothelioma from pulmonary adenocarcinoma can assist in the diagnosis.[85] Additional IHC markers, including TTF-1, CK 7/20, and breast markers, should routinely be done as first- and second-tier diagnostics to aid in treatment. If the effusion reaccumulates quickly, pleurodesis may be attempted to slow the rate of fluid re-accumulation, or as done more often (as of this writing), a pleural catheter with daily aspirations is preferred (this can be removed after chemotherapy response is noted and the flow decreases). Chemotherapy is initiated in most patients based on their IHC profile, and taxane plus carboplatin versus gemcitabine plus cisplatin are commonly used doublets.

Carcinomas of Unknown Primary Presenting as Malignant Ascites

Patients with malignant ascites usually belong to one of two subsets, each with a very different natural history of disease. The first group consists of patients with mucin-producing adenocarcinoma who may present with ascitic fluid that contains signet-ring cells. These patients often have multiple peritoneal implants, with the primary site most likely being the GI tract (ie, stomach, small bowel, appendix, colon, or pancreaticobiliary). Given the current armamentarium of drugs available for treatment of metastatic colon cancer and the improved survival rate, it is important to consider those combinations for patients with IHC suggestive of colon profile ($CK20^+$, $CK\ 7^-$, and $CDX\text{-}2^+$). The second patient subset is composed of women with primary serous papillary peritoneal carcinomatosis. This disease is often also associated with pelvic adenopathy or masses. These patients may have elevated CA 125 levels but do not have detectable ovarian cancer. Some investigators consider these patients to have true unknown primary ovarian tumors or primary serous carcinomas of the peritoneum.[86,87] Disease management should be the same as for women with ovarian carcinoma. A prolonged median survival of 13 months, with 25% of patients having a progression-free survival lasting more than 2 years, was reported for paclitaxel/carboplatin-based chemotherapy in patients with peritoneal carcinomatosis. In this study, a high overall response rate (ORR) and number of complete responses were reported for this subgroup of patients with CUP (68.4% and 20%, respectively).

Carcinomas of Unknown Primary Presenting as Isolated Bony Metastases

When bone metastases are detected, men should be evaluated for prostate cancer and women for breast cancer given that they may be candidates for hormonal therapy, which is relatively easier compared with cytotoxic therapies. Other cancer profiles include lung, cholangiocarcinoma, renal, and, rarely, melanoma. Patients with a single bony metastasis may be candidates for surgery or radiation and then monitored. Patients with disease at multiple sites and good performance status and whose tumors progress after radiation therapy should be offered a trial of chemotherapy. Many experimental agents are currently available in ongoing clinical trials. Therapy with bone-seeking radioisotopes (eg, strontium 89) may be useful in the treatment of disseminated painful bone metastases in a few patients. Bisphosphonates are routinely used as in other malignancies, such as multiple myeloma, breast cancer, and prostate cancer. Often, PET-CT is the imaging modality of choice to follow response to therapy for disseminated osseous metastatic disease.

Carcinomas of Unknown Primary Presenting as Hepatic Metastases

Patients with hepatic metastases constitute 30% to 40% of people with CUPs; they compose a clinical subgroup with a relatively poor prognosis, with reported median OS between 49 days and 7 months. The most important diagnostic considerations in this class are to distinguish primary liver and biliary tumors (hepatocellular carcinoma and cholangiocarcinoma) from cancers that have metastasized to the liver, and to identify patients with neoplasms of a more indolent nature (eg, neuroendocrine tumors). A careful pathologic review with IHC of liver biopsy specimens is therefore essential. The two most common histologic findings in primary CUP of the liver are adenocarcinoma (55%) and poorly differentiated/undifferentiated carcinoma (30%). The recommended initial therapy for unresectable disease is systemic chemotherapy, and surgery may be considered as an option for those with resectable disease.

Neuroendocrine Tumors of Unknown Primary Site

Neuroendocrine tumors compose about 4% of all CUPs and commonly present with diffuse liver or bone metastases. Histologically, neuroendocrine tumors can

be well differentiated or low grade, with features that are typical of carcinoid or islet cell tumors exhibiting a more indolent behavior. Management of these tumors should be similar to established guidelines for metastatic low-grade neuroendocrine tumors from a known primary site. In patients with limited disease, surgical resection or chemoembolization may be appropriate. If not amenable to local therapy, then targeted therapy is considered with (anti–vascular endothelial growth factor agents, including sunitinib, or mammalian target of rapamycin inhibitors, including everolimus).

A second group involves high-grade neuroendocrine tumors that may present as PDC by light microscopy but have strong neuroendocrine features revealed by IHC (ie, neuron-specific enolase, chromogranin A, and synaptophysin positive). These high-grade neuroendocrine tumors are treated like small cell lung carcinoma with etoposide plus platinum or irinotecan plus platinum combinations, with high reported response rates.

Carcinomas of Unknown Primary and Extragonadal Germ Cell Syndrome

As a group, patients who have undifferentiated carcinoma or PDC are younger than 50 years and present with rapidly growing midline tumors involving the lymph nodes, mediastinum, or retroperitoneum; their tumors have been found to be very responsive to chemotherapy, particularly to platinum-containing regimens. It is believed that these patients have poorly differentiated extragonadal germ cell tumors. They have response rates to chemotherapy of 35% to 50%, and those who achieve a complete response often enjoy a durable remission. In a prospective study by Hainsworth and colleagues of 220 patients with PDC or poorly differentiated adenocarcinoma (PDAC) treated between 1978 and 1989 with cisplatin-based chemotherapy regimens, approximately half of the patients had a predominant tumor location in the mediastinum, retroperitoneum, or peripheral lymph nodes. The ORR was 63%, with 26% complete responses and an actuarial 10-year disease-free survival rate of 16%.

However, this was not found to be true by Lenzi and colleagues,[4] who retrospectively reviewed the clinical outcomes of 337 patients with PDC/PDAC. No prolonged survival was observed in this cohort of patients, and no significant survival advantage resulted from cisplatin-based chemotherapy. Moreover, elevated serum levels of α-fetoprotein or β-human chorionic gonadotropin, contrary to other reports in the literature, were not found to be predictive of an improved median OS. This discrepancy may have resulted from several confounding factors.

First, older studies of extragonadal germ cell syndrome included patients with PDCs who in actuality did not have CUP but had other highly treatable malignancies.[4] In a study by Hainsworth et al,[88] of the 36 long-term survivors, 20% were subsequently found to have either lymphoma,[5] testicular cancer,[1] or leiomyosarcoma.[1] Conversely, in the study by Lenzi, patients in whom the primary site was identified were excluded from the analysis. Most of these patients were found to have highly treatable malignancies, such as lymphoma (6%), breast cancer (8%), ovarian cancer (3%), germ cell tumors (2%), and prostate cancer (1%). Exclusion of these patients would significantly reduce response and median survival rates.

Second, even among patients with PDC/PDAC of unknown primary, significant heterogeneity exists. In the study by Lenzi, CART analysis of 337 patients revealed different groups with widely discrepant survival times. The group with the longest median OS (40 months) included patients with PDC, lymph node involvement, and only one or two metastatic sites. By contrast, patients with non–lymph node metastases had a very poor prognosis, with a median OS of only 7 months.[4]

Sarcomatoid Carcinoma

Sarcomatoid carcinoma is a rare histologic subtype of CUP characterized by poorly differentiated carcinoma with a sarcomatoid component or a true mixed-lineage neoplasm. This rare group of patients often has an aggressive disease course and poor prognosis. In a study of 48 patients, median OS was 11 months and patients were often resistant to chemotherapy. On multivariate analysis, patients with poor performance status and high neutrophil-to-lymphocyte ratio had shorter survival.[89]

Carcinomas of Unknown Primary and Single Sites Discovered Incidentally on Resection

CUPs are notorious for unusual, isolated presentations. Such lesions may appear on the skin, in single isolated lymph nodes removed during surgery for benign unrelated conditions, and at other, even more unusual sites. Patients should be examined for primary tumors and other sites of metastasis, as described previously. If no primary tumor and no additional sites of metastasis are found, complete removal of the lesion must be ensured; this often requires additional excision with wider margins (if skin or subcutaneous). The patient may then be monitored without therapy and in selected cases are candidates for radiation. Many such patients may enjoy prolonged survival. Patients with isolated skin lesions may have an undifferentiated primary integumentary tumor with a potential for cure after adequate local surgical treatment.

CHEMOTHERAPEUTIC STRATEGIES FOR CARCINOMAS OF UNKNOWN PRIMARY

Combination regimens using newer chemotherapeutic agents have demonstrated greater benefit than have older single-agent therapies for CUP cancers. Several difficulties arise when survival and response rates reported in different chemotherapy trials are compared. For example, histologic criteria for patient selection often varied from study to study. Moreover, in older studies, IHC methods were not used to evaluate pathologic specimens. Despite these difficulties, no study has firmly established any chemotherapy regimen as the "gold standard" in CUP. The median survival in most studies, regardless of regimen, has ranged between 5 and 13 months, with response rates of less than 30% and without a significant improvement in survival (Table 53–4).

Nevertheless, patients with certain clinical subtypes (eg, peritoneal carcinomatosis and lymph node–predominant disease) do benefit from chemotherapy. Historically, cisplatin-based combination chemotherapy regimens were frequently used to treat patients with CUP. Response rates in the literature range from 12% to 26% and median survival from 5 to 7 months. Combining paclitaxel with carboplatin has modestly improved both survival and response rates. In patients with widespread metastases and poor performance status, however, systemic chemotherapy is unlikely to be beneficial, and only supportive therapy is usually indicated.

In a phase 2 study by Hainsworth and colleagues, patients with CUP ($n = 55$) received paclitaxel (200 mg/m^2 on day 1), carboplatin (AUC = 6, day 1), and oral etoposide (50 mg alternating with 100 mg days 1–10) every 21 days.[90] Most were previously untreated, with only four having received prior chemotherapy. Most patients had moderately to well-differentiated adenocarcinoma (55%) or PDC/PDAC (38%), with squamous (2%) and neuroendocrine (5%) histologic findings less prevalent. The dominant sites of disease were lymph nodes (25%), liver (16%), and lungs (16%). Approximately 24% of patients in the study had multiple sites of disease, with 42% of those having more than two metastatic sites. Response rates were equivalent in all histologic subgroups, with a reported ORR of 47% and a median OS of 13.4 months. This regimen was well tolerated, with myelosuppression the most common grade 3/4 toxicity. No treatment-related deaths were reported.

Briasoulis and colleagues[91] found equivalent response rates and median OS in CUP with carboplatin (AUC = 6) and paclitaxel (200 mg/m^2) without oral etoposide. In this phase 2 trial, patients ($n = 77$) were given a maximum of eight cycles of chemotherapy. In addition, granulocyte colony-stimulating factor was administered on days 5 to 12. The proportions of differing histologic subtypes were comparable with those in the Hainsworth study: adenocarcinoma (61%), undifferentiated (35%), and squamous (4%). Three distinct clinical subsets were present in this study: peritoneal carcinomatosis (25%, mostly women); visceral or bony metastases (43%); and predominant nodal or pleural disease (30%). The reported ORR, median response duration, and median OS were 38.7%, 6 months, and 13 months, respectively. Although response rates were equivalent for adenocarcinoma and undifferentiated carcinoma, significant differences were seen among the three clinical subsets: liver/bone or disseminated metastases (ORR 15.1%; median OS 10 months); nodal/pleural disease (ORR 47.8%; median OS 13 months); and peritoneal (ORR 68.4% [75% for women]; median OS 15 months); $P = .01$. Three patients with nodal-predominant disease had durable responses lasting longer than 2 years. Grade 3/4 neutropenia was only 4%, with two reported deaths from septicemia.

The role of cisplatin in combination with either gemcitabine or irinotecan for patients with previously untreated CUP was assessed in a phase 2 study.[92] The proportion of histologic subtypes were adenocarcinoma (60%–67%), poorly differentiated adenocarcinoma (15%–18%), undifferentiated (13%–15%), and unavailable (3%–10%). The ORR was 55% in patients receiving cisplatin and gemcitabine and 38% in those receiving cisplatin and irinotecan. The trial was not designed to make statistical comparisons between the two groups. Median survival times in the two groups were 8 months for gemcitabine and cisplatin and 6 months for irinotecan and cisplatin.

The results of docetaxel in combination with carboplatin in one small phase 2 study appear to be inferior to those of the paclitaxel/carboplatin combination in the trials mentioned. The ORR was 22%, the median OS was 8 months, and the 1-year OS rate was 29%. Differences in sites of disease and histology among these three studies may account for the discrepancy. Severe grade 3/4 myelosuppression was more frequent with docetaxel (50%) than with paclitaxel, with two reported deaths from septicemia.[93] Docetaxel was also studied in combination with gemcitabine in a phase 2 study. The ORR was 40% and median OS was 10 months.[94]

Patients with undifferentiated or PDCs not fitting into the extragonadal germ cell or neuroendocrine clinical subgroups have traditionally been given a trial of a cisplatin-based regimen. Patients with squamous cell carcinomas who require chemotherapy are also often treated effectively using a cisplatin-based regimen.

Table 45-4 Selected Phase 2 Studies in Carcinoma of Unknown Primary

Overall Survival

Author	n	Chemotherapy Regimen	Two or More Metastatic Sites (%)	ORR (%)	Median TTP (Months)	Median (Months)	1 Year (%)	2 Years (%)
Assersohn et al	45	5-FU vs	44	11.6	4.1	6.6	28	NR
	43	5-FU+ Mi		20	3.6	4.7	21	NR
Culine et al	82	AC →EP, alt q14d + GCSF	68	39	NR	10		
McDonald et al	31	Mi/P/CI 5-FU	52	27	3.4	7.7	28	
Greco et al	120	Gem/Cb/Pac	65	25	NR	9	42	23
Saghatchian et al	33	PDC/PDAC: EP × 2 → BI	57	40	8.1	9.4	NR	28
	18	Adeno: P/CI-5-FU/IFNα	44	44	8.6	16.1	NR	39
Hainsworth et al	39	Gem	NR	33	5	NR		
Dowell et al	17	Pac + 5-FU/leucovorin vs	59	19	NR	8.4		
	17	CbE	65	19	6.5			
Briasoulis et al	77	Cb + Pac	22% with 3 or more	38.7	6	13		
Greco et al	23	DP vs	73	29	NR	8	42	
	40	DCb	68	22	8	29		
Culine et al	20	HDCT + AutoSCT vs	80	42	NR	11		
	40	AC alt with EP	75	39	8			
Falkson et al	43	Mi/Epi/P vs	53	50	4.5[a]	9.4[a]		
	41	Mi	44	17	2.0	5.4		
Warner et al	33	Cb + E (PO)	91	23	NR	5.6	NR	
Hainsworth et al	55	Pac/Cb/E (PO)	67	47	NR	13.4	58	NR
Hainsworth et al	220	BEvP ± Doxo; after 1985: BEP	74	63	NR	10-year survival: 16%		
Van der Gaast et al	34	BEP × 4 → EP × 2	53	53	NR	NR		
Eagen et al	28	MiA → CAM vs	NR	14	NR	5.5	19	8
	27	MiAP → CAM		26	4.6	12	0	26
Hayashi et al	30	Carboplatin-paclitaxel vs	NR	41.2	NR	12.5	54.9	NR
Hayashi et al 30		Site-specific treatment	NR	34.7	NR	9.8	44	NR

[a]Statistically significant difference $P = .05$.

A, doxorubicin; Adeno, adenocarcinoma; alt, alternating; AutoSCT, autologous stem cell transplant; B, bleomycin; C, cyclophosphamide; Cb, carboplatin; CI, continuous infusion; D, docetaxel; Doxo, doxorubicin; E, etoposide; Epi, epirubicin; 5-FU, 5-flurouracil; Gem, gemcitabine; GCSF, granulocyte colony-stimulating factor; HDCT, high-dose chemotherapy; I, ifosfamide; IFN, interferon; M, methotrexate; Mi, mitomycin; Neuro, neuroendocrine; NR, not reported; ORR, overall response rate; P, cisplatin; Pac, paclitaxel; PDC/PDAC, poorly differentiated carcinoma/adenocarcinoma; TTP, time to progression; Undif, undifferentiated malignancy; v, vinblastine.

There has been significant interest in using ToO studies to guide selection of therapy for patients with CUP. Several trials have been designed to address this question, and one has been reported. In this trial, 130 patients underwent gene expression profiling to predict tumor origin, and then were assigned to either site-specific therapy or empiric paclitaxel and carboplatin.[95] The 1-year survival rate was 44% in the site-specific treatment group and 54.9% in the empiric chemotherapy group; $P = .264$; the authors concluded that gene expression profiling directing site-specific chemotherapy failed to improve survival compared with an empiric chemotherapy approach. However, favorable CUP subsets were excluded and there was an imbalance in predicted tumor types between arms.

The role of salvage chemotherapy in CUP is poorly defined. Gemcitabine has been published as second-line therapy in patients with previously treated CUP. In a phase 2 study by Hainsworth and colleagues,[96] gemcitabine was administered weekly at 1000 mg/m^2 (on days 1, 8, and 15 of a 28-day cycle). All patients ($n = 39$) received two cycles and were then evaluated for response. Chemotherapy was continued for a maximum of six cycles for either an objective response or stable disease. Approximately 90% of patients had failed a prior regimen containing platinum and a taxane. Most patients had either adenocarcinoma (59%) or PDC/PDAC (31%). Median time to progression was 5 months. Gemcitabine was well tolerated, with 92% of patients receiving two or more cycles. The most common grades 3–4 toxicities were fatigue/weakness and mucositis/esophagitis.

Hainsworth et al[97] reported on a combination-targeted therapy trial of bevacizumab and erlotinib in 51 patients; 25% were chemotherapy naïve with advanced bone or liver metastases, and 75% had been treated with one or two chemotherapy regimens. Responses were noted in four patients (8%), and 30 patients (59%) experienced stable disease or a minor response. The median OS duration was 8.9 months, with 42% of patients alive at 1 year.

The evolution of clinical trials examining the role of treatments based on molecular characteristics rather than site of origin has important implications for CUP and may lead to additional treatment options. In an analysis of 389 cases, 1.8% were found to be microsatellite instability-high.[98] Although treatment response data were not reported in this cohort, pembrolizumab is approved for patients with microsatellite instability-high cancer regardless of site of origin.[70] In addition, another study using next-generation sequencing of 333 patients found 30% with "potentially targetable genomic alterations."[99] Although not all genomic alterations in various cancers have been shown to be responsive to targeted therapy, one patient was found to have an NTRK1 fusion. Larotrectinib is a treatment option available to patients with TRK-fusion–positive cancers and has a role in this small patient population.[71]

Although evaluation of empiric regimens was the preferred approach in the past, with the emergence of modern molecular diagnostic trials that help define CUP subtypes, our focus has shifted from empiric combinations to more tailored regimens, especially as directed by IHC and, where helpful, ToO or mutational profiles. Further, as therapies for known cancers improve and become more selective based on evolving predictive markers, the newer therapeutic approaches should be evaluated in the appropriate CUP subtypes as well.

FUTURE TRENDS

Advances in pathology, cancer therapeutics, and clinical trial design all have the potential to benefit patients with CUP in the coming years. Pathologic advances provide opportunities to tailor IHC use based on algorithms, which can improve diagnostic yield and also conserve tissue, which may be needed for ToO studies or next-generation sequencing.[100] The role of immunotherapy has yet to be well defined in CUP, and it is currently best used in the context of a clinical trial. Furthermore, multiple biomarkers to predict the efficacy of immunotherapy are being studied, including the microsatellite-instability pathway, tumor mutational burden, and programmed cell death ligand 1, among others. Ongoing studies may address these unanswered questions.[101] Clinical trial design has evolved to include basket trials, which look at groups of patients with similar genomic alterations rather than site of origin. These approaches, along with other novel clinical trial designs, have important therapeutic implications for CUP, because they may provide evidence of benefit to this rare patient population.

SUMMARY

All patients with CUP should undergo a directed diagnostic evaluation for the primary tumor and a detailed pathologic evaluation of the metastatic specimen. A subset of patients defined by clinicopathologic criteria and considered to have favorable prognosis benefit significantly from selective or aggressive treatments. For most patients who present with advanced disseminated CUP, the prognosis remains poor, and no unique empiric combination therapy of established efficacy is available. We have moved away from the paradigm of "one treatment fits all" to a more focused approach that integrates clinical presentation, pathologic evaluation, and the evolving diagnostic tools. Molecular profiling and next-generation sequencing–based studies allow for more sophisticated ToO testing. In addition, these tools allow for therapy targeting specific mutations or molecular characteristics of a tumor to individualize CUP treatments. However, for this approach to be successful, it will require both additional molecular insights and novel drugs that are effective against specific mutations.

MD ANDERSON PRACTICE TIPS

- Adequate pathologic evaluation is the cornerstone of diagnosis. In any case of inadequate sample that may introduce sampling bias or limit pathologic workup, a repeat biopsy is strongly recommended.
- Multidisciplinary approach involving close communication between medical oncology, pathology, radiology and surgical/radiation oncology (for oligometastatic disease) is extremely valuable in devising an appropriate treatment strategy.
- Focused evaluation based on the clinicopathologic profile of the patient is recommended and is the most cost-effective and clinically effective strategy and prevents delays in treatment. Unnecessary and invasive testing should be avoided.
- Although limited data exist regarding the role of molecular profiling, we encourage use of next generation sequencing because it can provide clues with regard to putative origin and also identify a small subset of tumors where molecularly-driven therapy may be beneficial.
- Although the absolute benefit of site-specific versus empiric chemotherapy is unclear, we endorse the paradigm of tailoring therapy to a putative primary, if discernible.
- Participation in clinical trials (interventional or translational) should be encouraged for all patients and early referral to academic CUP programs be considered for select patients.

REFERENCES

1. van de Wouw AJ, Janssen-Heijnen ML, Coebergh JW, et al. Epidemiology of unknown primary tumours; incidence and population-based survival of 1,285 patients in Southeast Netherlands, 1984-1992. *Eur J Cancer*. 2002;38(3):409-413.
2. Varadhachary GR, Raber MN. Cancer of unknown primary site. *N Engl J Med*. 2014;371:757-765.
3. Greco FA, Burris HA III, Erland JB, et al. Carcinoma of unknown primary site. *Cancer*. 2000;89(12):2655-2660.
4. Hess KR, Abbruzzese MC, Lenzi R, et al. Classification and regression tree analysis of 1000 consecutive patients with unknown primary carcinoma. *Clin Cancer Res*. 1999;5(11):3403-3410.
5. Briasoulis E, Tolis C, Bergh J, Pavlidis N. ESMO minimum clinical recommendations for diagnosis, treatment and follow-up of cancers of unknown primary site (CUP). *Ann Oncol*. 2005;16(suppl 1): i75-i76.
6. Siegel R, Miller K, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70:7-30.
7. Le Chevalier T, Cvitkovic E, Caille P, et al. Early metastatic cancer of unknown primary origin at presentation. A clinical study of 302 consecutive autopsied patients. *Arch Intern Med*. 1988;148(9):2035-2039.
8. Abbruzzese JL, Abbruzzese MC, Lenzi R, et al. Analysis of a diagnostic strategy for patients with suspected tumors of unknown origin. *J Clin Oncol*. 1995;13(8):2094-2103.
9. van de Wouw AJ, Jansen RL, Speel EJ, et al. The unknown biology of the unknown primary tumour: a literature review. *Ann Oncol*. 2003;14(2):191-196.
10. Naresh KN. Do metastatic tumours from an unknown primary reflect angiogenic incompetence of the tumour at the primary site? A hypothesis. *Med Hypoth*. 2002;59(3):357-360.
11. Pantou D, Tsarouha H, Papadopoulou A, et al. Cytogenetic profile of unknown primary tumors: clues for their pathogenesis and clinical management. *Neoplasia*. 2003;5(1):23-31.
12. Atkin NB. Chromosome 1 aberrations in cancer. *Cancer Genet Cytogenet*. 1986;21(4):279-285.
13. Motzer RJ, Rodriguez E, Reuter VE, et al. Molecular and cytogenetic studies in the diagnosis of patients with poorly differentiated carcinomas of unknown primary site. *J Clin Oncol*. 1995;13(1):274-282.
14. Motzer RJ, Rodriguez E, Reuter VE, et al. Genetic analysis as an aid in diagnosis for patients with midline carcinomas of uncertain histologies. *J Natl Cancer Inst*. 1991;83(5):341-346.
15. Bar-Eli M, Abbruzzese JL, Lee-Jackson D, et al. *p53* gene mutation spectrum in human unknown primary tumors. *Anti-cancer Res*. 1993;13(5A):1619-1623.
16. Pavlidis N, Briassoulis E, Bai M, et al. The expression of *cmyc, ras,* and c-erbB-2 in patients with carcinoma of unknown primary [Abstr 1374]. *Proc Am Soc Clin Oncol*. 1994;13.
17. Soong R, Robbins PD, Dix BR, et al. Concordance between p53 protein overexpression and gene mutation in a large series of common human carcinomas. *Hum Pathol*. 1996;27(10): 1050-1055.
18. Hainsworth JD, Lennington WJ, Greco FA. Overexpression of Her-2 in patients with poorly differentiated carcinoma or poorly differentiated adenocarcinoma of unknown primary site. *J Clin Oncol*. 2000;18(3):632-635.
19. Mayordomo JI, Guerra JM, Guijarro C, et al. Neoplasms of unknown primary site: a clinicopathological study of autopsied patients. *Tumori*. 1993;79(5):321-324.
20. Schapira DV, Jaret AR. Cost of diagnosis and survival of patients with unknown primary cancer [Abstr 481]. *Proc Am Soc Clin Oncol*. 1994;13.
21. Nystrom SJ, Hornberger JC, Varadhachary GR, et al. Clinical utility of gene-expression profiling for tumor-site origin in patients with metastatic or poorly differentiated cancer: impact on diagnosis, treatment, and survival. 2012. *Oncotarget*. 3(6):620-628.
22. Milovic M, Popov I, Jelic S. Tumor markers in metastatic disease from cancer of unknown primary origin. *Med Sci Monit*. 2002;8(2):MT25-MT30.
23. Bates SE. Clinical applications of serum tumor markers. *Ann Intern Med*. 1991;115(8):623-638.
24. Abbruzzese JL, Raber MN, Frost P. The role of CA-125 in patients with unknown primary tumors [Abstr 39]. *Proc Am Soc Clin Oncol*. 1991;10.
25. Varadhachary GR. Carcinoma of unknown primary: focused evaluation. *J Natl Compr Canc Netw*. 2011;9:1406-1412.
26. National Comprehensive Cancer Network. *Occult Primary (Cancer of Unknown Primary)*, version 2.2020. https://www.nccn.org/professionals/physician_gls/pdf/occult_blocks.pdf
27. Taylor MB, Bromham MR, Arnold SE. Carcinoma of unknown primary: key radiological issues from the recent National Institute for Health and Clinical Excellence guidelines. Br J Radiol. 2012;85:661-671.
28. Bedrosian I, Mick R, Orel SG, et al. Changes in the surgical management of patients with breast carcinoma based on pre-operative magnetic resonance imaging. *Cancer*. 2003;98(3):468-473.
29. Schelfout K, Kersschot E, Van Goethem M, et al. Breast MR imaging in a patient with unilateral axillary lymphadenopathy and unknown primary malignancy. *Eur Radiol*. 2003;13(9):2128-2132.
30. Henry-Tillman RS, Harms SE, Westbrook KC, et al. Role of breast magnetic resonance imaging in determining breast as a source of unknown metastatic lymphadenopathy. *Am J Surg*. 1999;178(6):496-500.
31. Schorn C, Fischer U, Luftner-Nagel S, et al. MRI of the breast in patients with metastatic disease of unknown primary. *Eur Radiol*. 1999;9(3):470-473.
32. Olson JA Jr, Morris EA, Van Zee KJ, Linehan DC, Borgen PI. Magnetic resonance imaging facilitates breast conservation for occult breast cancer. *Ann Surg Oncol*. 2000;7:411-415.
33. Lu H, Xu YL, Zhang SP, et al. Breast magnetic resonance imaging in patients with occult breast carcinoma: evaluation on feasibility and correlation with histopathological findings. *Chin Med J (Engl)*. 2011;124;12:1790-1795.
34. Koch WM, Bhatti N, Williams MF, et al. Oncologic rationale for bilateral tonsillectomy in head and neck squamous cell carcinoma of unknown primary source. *Otolaryngol Head Neck Surg*. 2001;124:331-333.
35. Lassen U, Daugaard G, Eigtved A, et al. 18F-FDG whole body positron emission tomography (PET) in patients with unknown primary tumours (UPT). *Eur J Cancer*. 1999;35(7):1076-1082.
36. Regelink G, Brouwer J, de Bree R, et al. Detection of unknown primary tumours and distant metastases in patients with cervical metastases: value of FDG-PET versus conventional modalities. *Eur J Nucl Med Mol Imaging*. 2002;29:1024-1030.
37. Rusthoven KE, Koshy M, Paulino AC. The role of fluorodeoxyglucose positron emission tomography in cervical lymph node metastases from an unknown primary tumor. *Cancer*. 2004;101:2641-2649.
38. Waltonen JD, Ozer E, Hall NC, et al. Metastatic carcinoma of the neck of unknown primary origin. *Arch Otolaryngol Head Neck Surg*. 2009;135:1024-1029.
39. Rudmik L, Lau HY, Matthews TW, et al. Clinical utility of PET/CT in the evaluation of head and neck squamous cell carcinoma with an unknown primary: a prospective clinical trial. *Head Neck*. 2011;33;7:935-940.
40. Johansen J, Eigtved A, Buchwald C, et al. Implication of 18F-fluoro-2-deoxy-D-glucose positron emission tomography on management of carcinoma of unknown primary in the head and neck: a Danish cohort study. *Laryngoscope*. 2002;112(11):2009-2014.

41. Delgado-Bolton RC, Fernandez-Perez C, Gonzalez-Mate A, et al. Meta-analysis of the performance of 18F-FDG PET in primary tumor detection in unknown primary tumors. *J Nucl Med*. 2003;44(8):1301-1314.
42. Alberini JL, Belhocine T, Hustinx R, et al. Whole-body positron emission tomography using fluorodeoxyglucose in patients with metastases of unknown primary tumours (CUP syndrome). *Nucl Med Commun*. 2003;24(10):1081-1086.
43. Joshi U, van der Hoeven JJ, Comans EF, Herder GJ, Teule GJ, Hoekstra OS. In search of an unknown primary tumour presenting with extracervical metastases: the diagnostic performance of FDG-PET. *Br J Radiol*. 2004;77:1000-1006.
44. Moller AK, Loft A, Berthelsen AK, et al. 18F-FDG PET/CT as a diagnostic tool in patients with extracervical carcinoma of unknown primary site: a literature review. *Oncologist*. 2011;16;4:445-451.
45. Wu M, Wang B, Gil J, et al. p63 and TTF-1 immunostaining. A useful marker panel for distinguishing small cell carcinoma of lung from poorly differentiated squamous cell carcinoma of lung. *Am J Clin Pathol*. 2003;119(5):696-702.
46. Ng WK, Chow JC, Ng PK. Thyroid transcription factor-1 is highly sensitive and specific in differentiating metastatic pulmonary from extrapulmonary adenocarcinoma in effusion fluid cytology specimens. *Cancer*. 2002;96(1):43-48.
47. Chhieng DC, Cangiarella JF, Zakowski MF, et al. Use of thyroid transcription factor 1, PE-10, and cytokeratins 7 and 20 in discriminating between primary lung carcinomas and meta-static lesions in fine-needle aspiration biopsy specimens. *Cancer*. 2001;93(5):330-336.
48. Reis-Filho JS, Carrilho C, Valenti C, et al. Is TTF1 a good immunohistochemical marker to distinguish primary from metastatic lung adenocarcinomas? *Pathol Res Pract*. 2000;196(12):835-840.
49. DeYoung BR, Wick MR, Immunohistologic evaluation of metastatic carcinomas of unknown origin: an algorithmic approach. *Semin Diagn Pathol*. 2000;17:184-193.
50. Dennis JL, Vass JK, Wit EC, et al. Identification from public data of molecular markers of adenocarcinoma characteristic of the site of origin. *Cancer Res*. 2002;62(21):5999-6005.
51. Dennis JL, Hvidsten TR, Wit EC, et al. Markers of adenocarcinoma characteristic of the site of origin: development of a diagnostic algorithm. *Clin Cancer Res*. 2005;11:3766-3772.
52. Ramaswamy S, Tamayo P, Rifkin R, et al. Multiclass cancer diagnosis using tumor gene expression signatures. *Proc Natl Acad Sci U S A*. 2001;98:15149-15154.
53. Su AI, Welsh JB, Sapinoso LM, et al. Molecular classification of human carcinomas by use of gene expression signatures. *Cancer Res*. 2001;61:7388-7393.
54. Tothill RW, Kowalczyk A, Rischin D, et al. An expression-based site of origin diagnostic method designed for clinical application to cancer of unknown origin. *Cancer Res*. 2005;65:4031-4040.
55. Kerr SE, Schnabel CA, Sullivan PS, et al. Multisite validation study to determine performance characteristics of a 92-gene molecular cancer classifier. *Clin Cancer Res*. 2012;18:3952-3960.
56. Pillai R, Deeter R, Rigl CT, et al. Validation and reproducibility of a microarray-based gene expression test for tumor identification in formalin-fixed, paraffin-embedded specimens. *J Mol Diagn*. 2011;13:48-56.
57. Meiri E, Mueller WC, Rosenwald S, et al. A second-generation microRNA-based assay for diagnosing tumor tissue origin. *Oncologist*. 2012;17:801-812.
58. Varadhachary GR, Spector Y, Abbruzzese JL, et al. Prospective gene signature study using microRNA to identify the tissue of origin in patients with carcinoma of unknown primary. *Clin Cancer Res*. 2011;17:4063-4070.
59. Oien KA, Dennis JL. Diagnostic work-up of carcinoma of unknown primary: from immunohistochemistry to molecular profiling. *Ann Oncol*. 2012;23:271-277.
60. Pentheroudakis G, Golfinopoulos V, Pavlidis N. Switching benchmarks in cancer of unknown primary: from autopsy to microarray. *Eur J Cancer*. 2007;43:2026-2036.
61. Bloom G, Yang IV, Boulware D, Kwong KY, et al. Multi-platform, multi-site, microarray-based human tumor classification. *Am J Pathol*. 2004;164:9-16.
62. Ferracin M, Pedriali M, Veronese A, et al. MicroRNA profiling for the identification of cancers with unknown primary tissue-of-origin. *J Pathol*. 2011;225:43-53.
63. Horlings HM, van Laar RK, Kerst JM, et al. Gene expression profiling to identify the histogenetic origin of metastatic adenocarcinomas of unknown primary. *J Clin Oncol*. 2008;26:4435-4441.
64. Greco FA, Spigel DR, Yardley DA, Erlander MG, Ma XJ, Hainsworth JD. Molecular profiling in unknown primary cancer: accuracy of tissue of origin prediction. *Oncologist*. 2010;15:500-506.
65. Penson A, Camacho N, Zheng Y, et al. Development of genome-derived tumor type prediction to inform clinical cancer care. *JAMA Oncol*. 2020;6(1):84-91.
66. Hainsworth JD, Rubin MS, Spigel DR, et al. Molecular gene expression profiling to predict the tissue of origin and direct site-specific therapy in patients with carcinoma of unknown primary site: a prospective trial of the Sarah Cannon Research Institute. *J Clin Oncol*. 2013;31:217-223.
67. Handorf CR, Kulkami A, Grenert JP, et al. A multicenter study directly comparing the diagnostic accuracy of gene expression profiling and immunohistochemistry for primary site identification in metastatic tumors. *Am J Surg Pathol*. 2013;37(7):1067-1075.
68. Weiss L, Chu P, Schroeder BE, et al. Immunohistochemistry (IHC) vs a 92-gene cancer classifier in the diagnosis of primary site in metastatic tumors: a blinded comparator study. *J Mol Diagn*. 2013;15(2):263-269.
69. Ross JS, Wang K, Gay L, et al. Comprehensive genomic profiling of carcinoma of unknown primary site: new routes to targeted therapies. *JAMA Oncol*. 2015;1(1):40-49.
70. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science*. 2017;57(6349):409-413.
71. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N Engl J Med*. 2018;378(8):731-739.
72. Diaz LA Jr, Bardelli A. Liquid biopsies: genotyping circulating tumor DNA. *J Clin Oncol*. 2014;32(6):579-586.
73. Fenizia F, De Luca A, Pasquale R, et al. EGFR mutations in lung cancer: from tissue testing to liquid biopsy. *Future Oncol*. 2015;11(11):1611-1623.
74. Kato S, Krishnamurthy N, Banks KC, et al. Utility of genomic analysis in circulating tumor DNA from patients with carcinoma of unknown primary. *Cancer Res*. 2017;77(16):4238-4246.
75. Soffietti R, Ruda R, Mutani R. Management of brain metastases. *J Neurol*. 2002;249(10):1357-1369.
76. Ruda R, Borgognone M, Benech F, et al. Brain metastases from unknown primary tumour: a prospective study. *J Neurol*. 2001;248(5):394-398.
77. Yalin Y, Pingzhang T, Smith GI, et al. Management and outcome of cervical lymph node metastases of unknown primary sites: a retrospective study. *Br J Oral Maxillofac Surg*. 2002;40(6):484-487.
78. Issing WJ, Taleban B, Tauber S. Diagnosis and management of carcinoma of unknown primary in the head and neck. *Eur Arch Otorhinolaryngol*. 2003;260:436-443.
79. Zuur CL, van Velthuysen ML, Schornagel JH, et al. Diagnosis and treatment of isolated neck metastases of adenocarcinomas. *Eur J Surg Oncol*. 2002;28(2):147-152.

80. Pignon JP, Bourhis J, Domenge C, et al. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-analysis of chemotherapy on head and neck cancer. *Lancet*. 2000;355(9208):949-955.
81. Olson JA Jr., Morris EA, Van Zee KJ, et al. Magnetic resonance imaging facilitates breast conservation for occult breast cancer. *Ann Surg Oncol*. 2000;7(6):411-415.
82. Foroudi F, Tiver KW. Occult breast carcinoma presenting as axillary metastases. *Int J Radiat Oncol Biol Phys*. 2000;47(1):143-147.
83. Bugat R, Bataillard A, Lesimple T, et al. Standards, options and recommendations for the management of patient with carcinoma of unknown primary site. *Bull Cancer*. 2002;89(10):869-875.
84. Jackson B, Scott-Conner C, Moulder J. Axillary metastasis from occult breast carcinoma: diagnosis and management. *Am Surg*. 1995;61(5):431-434.
85. Ordonez NG. The immunohistochemical diagnosis of mesothelioma: a comparative study of epithelioid mesothelioma and lung adenocarcinoma. *Am J Surg Pathol*. 2003;27(8):1031-1051.
86. Gershenson DM, Silva EG. Serous ovarian tumors of low malignant potential with peritoneal implants. *Cancer*. 1990;65(3):578-585.
87. Strnad CM, Grosh WW, Baxter J, et al. Peritoneal carcinomatosis of unknown primary site in women. A distinctive subset of adenocarcinoma. *Ann Intern Med*. 1989;111(3):213-217.
88. Hainsworth JD, Johnson DH, Greco FA. Cisplatin-based combination chemotherapy in the treatment of poorly differentiated carcinoma and poorly differentiated adenocarcinoma of unknown primary site: results of a 12-year experience. *J Clin Oncol*. 1992;10(6):912-922.
89. Huey RW, Makawita S, Xiao L, et al. Sarcomatoid carcinoma presenting as cancers of unknown primary: a clinicopathological portrait. *BMC Cancer*. 2019;19(1):965.
90. Hainsworth JD, Erland JB, Kalman LA, et al. Carcinoma of unknown primary site: treatment with 1-hour paclitaxel, carboplatin, and extended-schedule etoposide. *J Clin Oncol*. 1997;15(6):2385-2393.
91. Briasoulis E, Kalofonos H, Bafaloukos D, et al. Carboplatin plus paclitaxel in unknown primary carcinoma: a phase II Hellenic Cooperative Oncology Group Study. *J Clin Oncol*. 2000;18(17):3101-3107.
92. Culine S, Lortholary A, Voigt J-J, et al. Cisplatin in combination with either gemcitabine or irinotecan in carcinomas of unknown primary site: results of a randomized phase II study—trial for the French Study Group on Carcinomas of Unknown Primary (GEFCAPI 01). *J Clin Oncol*. 2003;21(18):3479-3482.
93. Greco FA, Erland JB, Morrissey LH, et al. Carcinoma of unknown primary site: phase II trials with docetaxel plus cisplatin or carboplatin. *Ann Oncol*. 2000;11(2):211-215.
94. Pouessel D, Culine S, Becht C, et al. Gemcitabine and docetaxel as front-line chemotherapy in patients with carcinoma of an unknown primary site. *Cancer*. 2004;100(6):1257-1261.
95. Hayashi H, Kurata T, Takiguchi Y, et al. Randomized phase II trial comparing site-specific treatment based on gene expression profiling with carboplatin and paclitaxel for patients with cancer of unknown primary site. *J Clin Oncol*. 2019;37(7):570-579.
96. Hainsworth JD, Burris HA III, Calvert SW, et al. Gemcitabine in the second-line therapy of patients with carcinoma of unknown primary site: a phase II trial of the Minnie Pearl Cancer Research Network. *Cancer Invest*. 2001;19(4):335-339.
97. Hainsworth JD, Spigel DR, Farleg C et al. Phase II trial of bevacizumab and erlotimis in Carcinomas of unknown primary site: The Minnie Pearl Cancer Research Network. *J Clin Oncol*. 2007;25(13):1747-1752.
98. Gatalica Z, Xiu J, Swensen J, Vranic S. Comprehensive analysis of cancers of unknown primary for the biomarkers of response to immune checkpoint blockade therapy. *Eur J Cancer*. 2018;94:179-186.
99. Varghese AM, Arora A, Capanu M, et al. Clinical and molecular characterization of patients with cancer of unknown primary in the modern era. *Ann Oncol*. 2017;28(12):3015-3021.
100. Selves J, Long-Mira E, Mathieu M-C, Rochaix P, Ilié M. Immunohistochemistry for diagnosis of metastatic carcinomas of unknown primary site. *Cancers (Basel)*. 2018;10(4):108.
101. Varadhachary GR, Raghav KPS, Pant S, et al. Phase II study for the evaluation of efficacy of pembrolizumab (MK-3475) in patients with cancer of unknown primary. *J Clin Oncol*. 2017;35(suppl 15):abstract TPS3103.

54 Pediatric Cancers

Branko Cuglievan
Wafik Zaky
Richard Gorlick
Douglas Harrison

KEY CONCEPTS

- Patients with many common pediatric neoplasms, such as acute lymphoblastic leukemia (ALL), Wilms tumor, non-Hodgkin lymphoma, Hodgkin lymphoma, and germ cell tumors, have survival rates approaching or even exceeding 90%. However, progress has been limited for patients with some types of solid tumors, high-grade gliomas, and diffuse intrinsic brainstem gliomas.
- Patients with ALL, the most common cancer in children, typically present with hepatomegaly or splenomegaly, pallor, fever, and/or bruising. ALL's genetic interrogation has enabled us to employ risk-based treatment strategies that have led to a cure rate greater than 98% in some ALL subtypes. Those with unfavorable cytogenetic factors, suboptimal responses to chemotherapy, or those who relapse require treatment with aggressive regimens and will benefit from novel treatment modalities.
- Hodgkin lymphoma, the most common neoplasm among adolescents ages 15 to 19, commonly presents with painless supraclavicular or cervical adenopathy with or without the involvement of the mediastinum. Fever higher than 38 °C, drenching night sweats, and weight loss more than 10% of body weight within 6 months have been classified as "B symptoms" and affect staging and prognosis. Interim assessment with 18-fluorodeoxyglucose–positron emission tomography scan has allowed recognizing favorable responders who benefit from less toxic therapy.
- In children, the central nervous system (CNS) neoplasms are mostly infratentorial. Patients present with increased intracranial pressure, which manifests as macrocephaly, vomiting, and developmental delay in infants and headache, vomiting, blurred vision, and altered mental status in older children. A gross total resection is the surgery goal, whenever it is safe and feasible. Chemotherapy and radiation therapy typically follow for the malignant CNS tumors except for chemoresistant tumors like ependymoma.
- Non-neural solid tumors vary considerably by histology, tumor cell of origin, symptom spectrum, age at presentation, treatment, and outcome. The majority are treated with a multidisciplinary approach that includes surgical resection, radiation, and/or systemic chemotherapy. In some instances, like neuroblastoma and Wilms tumor, treatment is also determined by the patient's risk status, which incorporates biologic features.
- In pediatric cancer survivors, long-term side effects of therapy include cardiovascular dysfunction in those exposed to anthracyclines and/or radiation, neurocognitive deficits, endocrinopathies, and secondary CNS tumors in patients who received radiation to the CNS, and breast and thyroid cancer for those exposed to radiation to the chest.

Over the past five decades, the treatment of children and adolescents with cancer has improved dramatically.[1] Patients with many common pediatric neoplasms, such as acute lymphoblastic leukemia (ALL), Wilms tumor (WT), non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), and germ cell tumors, have survival rates approaching or even exceeding 90%.[2] However, progress has been limited for patients with some types of solid tumors, high-grade gliomas, and diffuse intrinsic brainstem gliomas. As in adults, pediatric patients who present with metastatic disease, who have a disease that does not respond to standard frontline therapies, and/or who have disease relapse face a grim prognosis despite intensive multimodal treatments that in survivors can cause long-term morbidity and disability.[3] Thus, cancer is the leading cause of disease-related morbidity and mortality in childhood and is second only to accidents as a cause of pediatric death in the United States and other developed countries.[1]

Understanding the proteomic and genomic landscapes of pediatric diseases may enable us to implement novel treatment strategies. Unfortunately, the relative rarity of these cancers precludes the substantive preclinical research necessary to find and develop potential therapeutic targets and limits the number of patients who can be enrolled in trials of novel therapeutic strategies. Furthermore, extrapolating the clinical activity and safety of the novel agents employed in adults is not always conceivable; the etiology and biology of pediatric cancer differ from those of adult cancer (Fig. 54–1).[2]

In this chapter, we present a few examples of common pediatric tumors and briefly describe some of the most important therapeutic advances for each.

PEDIATRIC LEUKEMIA

Acute Lymphoblastic Leukemia

ALL is the most common cancer diagnosed in children and adolescents in the United States.[1] ALL originates in a B- or T-lymphocyte precursor that proliferates and disrupts normal hematopoiesis. The disease can involve the liver, spleen, lymph nodes, thymus, meninges, and gonads.[4] Patients typically present with hepatomegaly or splenomegaly, pallor, fever, and/or bruising. Some patients demonstrate central nervous system (CNS) disease and have clinical evidence of cranial nerve involvement at diagnosis. A lumbar puncture can confirm the presence of leukemic blasts in that site with bone marrow aspirate and biopsies used to make the diagnosis.

Immunophenotyping, a critical element of the initial workup of patients with ALL, can differentiate between T-cell precursors and B-cell precursors and between these cell types and mature B cells.[4] The extensive genetic interrogation of ALL has enabled us to classify the disease into prognostically and therapeutically essential subtypes and identify candidate molecules for targeted therapeutics.[4]

Some high-risk features are: (1) age less than 1 year or more than 10 years, (2) an initial white blood cell count more than 50,000 µL, (3) CNS involvement, (4) testicular involvement, (5) T-lineage ALL, and (6) suboptimal induction response. Unfavorable cytogenetic factors include hypodiploidy (<44 chromosomes or a DNA index <0.81), Philadelphia chromosome (Ph+); t(9;22)(q34.1; q11.2); *BCR-ABL1,* t(v;11q23.3); *KMT2A*-rearranged, BCR-ABL1-like (Ph-like); and iAMP21.

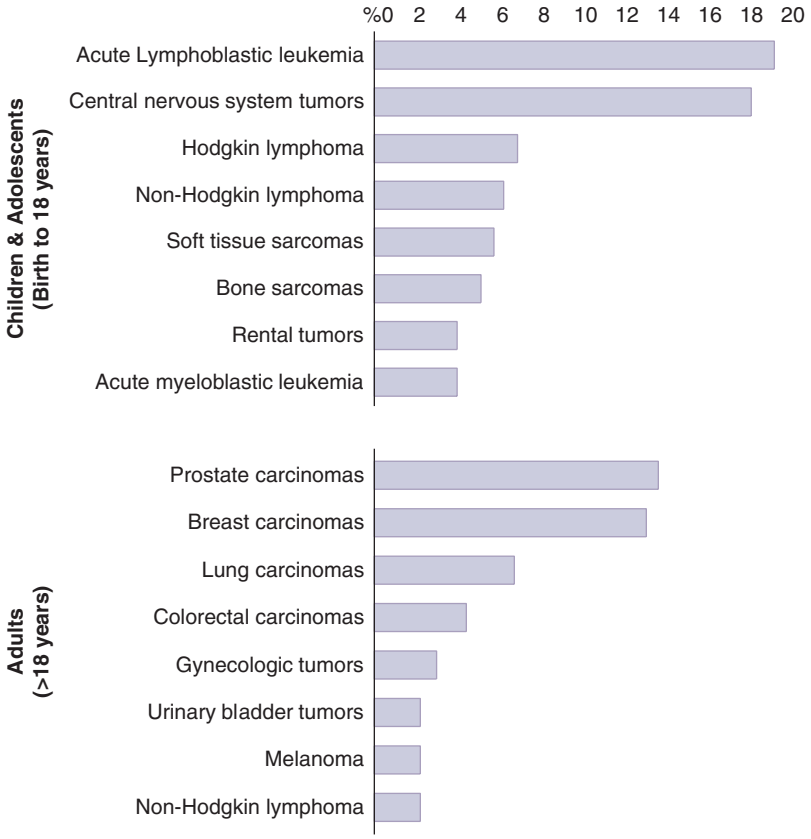


FIGURE 54–1 Graph demonstrating the different spectrum of neoplasms in children and adults.

Favorable cytogenetics are precursor B subtypes with *ETV6-RUNX1* translocation and high hyperdiploid ALL (>50 chromosomes or a DNA index >1.16) with simultaneous trisomy 4 and 10.[5,6]

With the use of risk-directed treatment and supportive care, patients with ALL have a 5-year overall survival (OS) rate of approximately 80%; for patients with some ALL subtypes, the cure rate is greater than 98%.[7]

Space precludes describing upfront treatment, which is usually on the Children's Oncology Group treatment protocols, so we will focus on novel therapies in this chapter.

Blinatumomab is a bispecific T-cell engager antibody construct that directs CD3-positive effector memory T-cells to target CD19-positive leukemia cells. The efficacy of blinatumomab in pediatric patients with relapsed/refractory ALL was demonstrated in an international, single-arm phase 1/2 study (NCT01471782).[8] Similarly, inotuzumab ozogamicin, a humanized CD22 monoclonal antibody conjugated to calicheamicin, elicited complete remissions in 67% of 51 pediatric patients with overt marrow disease. No patient developed sinusoidal obstruction syndrome during inotuzumab therapy; however, 11 of 21 (52%) patients who underwent hematopoietic stem cell transplantation after inotuzumab developed sinusoidal obstruction syndrome.[9] CD19 single-targeting chimeric antigen receptor T-cell therapy has recently emerged as a new modality to treat B-lineage malignancies.[10] Numerous current pediatric frontline ALL protocols integrate immunotherapy. The Children's Oncology Group is conducting randomized trials of blinatumomab plus cytotoxic chemotherapy in standard-risk patients with ALL (AALL1731, NCT03914625), inotuzumab plus cytotoxic chemotherapy in high-risk patients with ALL (AALL1732, NCT03959085), and tisagenlecleucel in high-risk patients with ALL with minimal residual disease (AALL1721, NCT03876769).[10]

Acute Myeloid Leukemia

Pediatric acute myeloid leukemia (AML) accounts for approximately 15% of all pediatric leukemias and has an incidence of seven cases per million among children younger than 15 years.[11] AML is characterized for being a profoundly heterogeneous disease at both the molecular and clinical levels. For more than three decades, numerous international cooperative groups have sought to develop a therapeutic strategy fundamentally composed of four or five phases of intensive chemotherapy consisting of an anthracycline and cytarabine backbone.[12] Patients who have high-risk mutations or whose disease relapses undergo allogeneic hematopoietic stem cell transplantation.[7,11,12] In recent clinical trials, the 5-year event-free survival rates of pediatric patients with AML have been 49% to 64%[7,13]; however, bone marrow relapse still occurs in as much as one-third of cases.[14] This subset of patients continues to have poor long-term outcomes, with an OS rate of less than 40%.[12] For pediatric patients with AML, the main treatment objective is the achievement of a complete remission that can be consolidated with a potentially curative hematopoietic stem cell transplantation.[7,13,14] Patients who do not have a complete remission after reinduction therapy with salvage chemotherapy or those who have a subsequent relapse have little chance of cure.[13] Making additional progress against this aggressive hematologic disease requires novel drugs directed toward distinct pathways and new molecular targets.

In 2014, the Children's Oncology Group conducted a phase 3 trial of the antibody-drug conjugate gemtuzumab ozogamicin, which targets CD33, and revealed decreased rates of relapse compared with conventional chemotherapy only.[15] CPX-351, a liposomal formulation of cytarabine and daunorubicin, demonstrated favorable responses in pediatric patients with relapsed AML.[16] Recently, the BCL-2 inhibitor venetoclax has shown promising activity in combination with hypomethylating agents and low-dose cytarabine.[17]

PEDIATRIC LYMPHOMA

Hodgkin Lymphoma

HL is the most common neoplasm among adolescents ages 15 to 19 years, with an estimated incidence of 29 cases per million.[1] The World Health Organization classification divides HL into two main types: classic HL and nodular lymphocyte–predominant HL.[18]

Classic HL, which accounts for most cases of childhood HL in the United States, is characterized by the presence of giant multinucleated Reed-Sternberg cells. Virtually all Reed-Sternberg cells express CD30, whereas 75% to 85% express CD15.[19] CHL is further divided into four subtypes according to pathologic features: (1) nodular sclerosis (the most common subtype in adolescents and young adults); (2) mixed cellularity; (3) lymphocyte-rich; and (4) lymphocyte-depleted. Epstein-Barr virus-positive CHL is frequently present in mixed cellularity classic HL, in males, and in developing countries. Nodular lymphocyte–predominant HL, which is more indolent than CHL, expresses CD20 but rarely expresses CD30 or CD15.[19]

Patients with HL commonly present with painless supraclavicular or cervical adenopathy with or without the involvement of the mediastinum.[20] Fever higher than 38 °C, drenching night sweats, and weight loss more than 10% body weight in 6 months have been classified as "B symptoms" and affect staging and

prognosis.[21] Physical examination, thoracic radiography, computed tomography (CT), and 18-fluorodeoxyglucose–positron emission tomography are used to determine the stage through the Ann Arbor Staging System.[21]

Children and adolescents with HL have had a 5-year survival rate of 94% since 2002, compared with an 81% survival rate in the early 1970s.[2,3] In the United States, the Children's Oncology Group has studied the ABVE-PC regimen (comprising doxorubicin bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide) and its derivatives across risk groups.[22] Radiotherapy of the involved field or node given at lower doses (15–25 Gy) is used mostly in patients with suboptimal responses and high disease burden.[22] Brentuximab vedotin, an antibody-drug conjugate comprising an anti-CD30 antibody conjugated by a protease-cleavable linker to the potent antimicrotubule agent monomethyl auristatin E, is approved for relapsed HL.[23] The Children's Oncology Group has evaluated the brentuximab vedotin-AVEPC regimen for high-risk HL in a phase 3 trial (NCT02166463); the results are pending. The composite results of trials NCT02181738 and NCT01592370 demonstrated that nivolumab, a humanized IgG4-κ monoclonal antibody against programmed cell death receptor–1, has clinically meaningful activity against classic HL.[24] Currently, the Children's Oncology Group is conducting a phase 3 randomized study of nivolumab versus brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine in patients with newly advanced classic HL (NCT03907488). The prognosis for relapsed HL is generally favorable given the use of high-dose chemotherapy and autologous hematopoietic stem cell transplantation.[21]

Non-Hodgkin Lymphoma

NHL comprises a varied group of malignant lymphoid neoplasms that arise from B- or T-cell precursors, mature B cells, or mature T-cells.[18,25] Most NHLs are high-grade and aggressive. The NHL section of this chapter focuses on mature B-cell NHL. Numerous subtypes of NHL that occur in adults rarely occur in children.

Burkitt lymphoma, an aggressive neoplasm that arises from germinal center B cells, frequently presents in the abdomen, head, and neck.[26] Less common sites of involvement are the testes, bone, bone marrow, skin, and CNS. Burkitt lymphoma can have a 24-hour doubling time and often undergoes spontaneous tumor lysis. The tumor cells express a mature B-cell phenotype that typically lacks the terminal deoxynucleotidyl transferase and is positive for pan-B-cell markers (CD19, CD20, CD22, and CD79a) and surface immunoglobulin with either κ or λ light chains.[26] Burkitt lymphoma expresses distinguishing chromosomal translocations juxtaposing the c-*myc* oncogene and immunoglobulin locus regulatory elements such as t(8;14) and, more rarely, t(8;22) or t(2;8). Cytogenetic evidence of c-*myc* rearrangement is the gold standard for the diagnosis of Burkitt lymphoma.[19] Cases with "double-hit" translocations involving *MYC* and *BCL6*, and rare cases with "triple-hit" translocations involving *MYC, BCL2,* and *BCL6,* are more common in adults.

Diffuse large B-cell lymphoma represents 10% to 20% of pediatric NHL.[25] Most patients present with enlarging symptomatic masses in the neck or abdomen, or, in the case of primary mediastinal large B-cell lymphoma, the mediastinum.[19] Unlike Burkitt lymphoma, diffuse large B-cell lymphoma less often involves the CNS and bone marrow.[19] The Murphy Staging System is the most widely used staging scheme for NHL.[27]

In pediatrics, the treatment for Burkitt lymphoma and diffuse large-cell lymphoma is usually identical. In the United States, the Children's Oncology Group has added rituximab to baseline chemotherapy with FAB/LMB-96 therapy with excellent outcomes.[28] Primary mediastinal B-cell lymphoma carries a worse prognosis in pediatric patients, and many centers in the United States treat these patients with the dose-adjusted EPOCH-R regimen (etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and rituximab; typically given for six cycles) with filgrastim and no radiation therapy.[29] The safety and effectiveness of chimeric antigen receptor T-cell therapy in pediatric patients with relapsed or refractory mature B-cell NHL are being evaluated in clinical trials (NCT03610724, NCT02625480).[30]

CHILDHOOD CENTRAL NERVOUS SYSTEM TUMORS

CNS tumors are the most common childhood cancer and the leading cause of cancer-related mortality in this population.[31] The overall incidence rate is 5.65 to 11.20 per 100,000 population, depending on the age group. Approximately 4700 pediatric CNS tumors are diagnosed each year in the United States. According to a recently published report of the Surveillance, Epidemiology, and End Results (SEER) program, the most common location is the infratentorial tumor (43.2%), followed by the supratentorial (40.9%), the spinal cord (4.9%), and multiple sites (11%).

Many environmental factors have been interrogated with only exposure to ionizing radiation associated with increased risk of CNS tumors (ie, meningioma), whereas allergy and atopic diseases were associated with decreased risk (ie, glioma).[31] Furthermore, having a first-degree relative with a CNS tumor has been shown to increase the risk twofold.[31]

The clinical presentation of a patient with a CNS tumor depends on the tumor location, stage, and patient age at diagnosis. The most common presentation is increased intracranial pressure, which presents as macrocephaly, vomiting, and developmental delay in infants and as headache, vomiting, blurred vision, and altered mental status in older children. Depending on location, patients may have motor weakness, sensory changes, seizures, bowel or bladder symptoms, ataxia and dysarthria, or cranial nerve neuropathies. Endocrine abnormalities are common in midline tumors like craniopharyngioma and germ cell tumors.

The OS has improved in the last few decades owing to advances in imaging, chemotherapy, modalities of radiation therapy, as well as surgical navigation techniques. A gross total resection is the goal, whenever it is safe and feasible. Chemotherapy and radiation therapy typically follow for the malignant CNS tumors, except for chemoresistant tumors like ependymoma.

Low-Grade Gliomas

Low-grade gliomas (LGGs) are the most common pediatric CNS tumors and associated with two cancer predisposition syndromes, neurofibromatosis I (NF1) and tuberous sclerosis syndrome. Surgical resection, if feasible, is the most effective therapeutic option, with complete resection of LGG leading to greater than 90% survival, whereas less than total resection leads to nearly 60% survival. Further therapy depends on several factors, including tumor location, amount of residual tumor, patient age, and/or association with NF1. For progressive LGG, first-line chemotherapy is a combination of vincristine and carboplatin. In a study of children with progressive LGG, 56% had an objective response and 3-year progression-free survival (PFS) was 68%.[32] Recently, molecular testing of progressive LGG has identified translocations of BRAF in 70% of LGGs, whereas the BRAF V600E mutation occurs in 5% to 10%, with potential response to selumetinib and vemurafenib, respectively.[33]

High-Grade Gliomas

High-grade gliomas (HGGs) including diffuse intrinsic pontine glioma (DIPG) are common CNS tumors in children. Their outcome remains poor despite the use of multimodal therapy with surgery, radiation therapy, and chemotherapy. For hemispheric HGG, the strongest prognostic factors are the extent of resection and histologic grade. Temozolomide as a radiosensitizer followed by adjuvant temozolomide had a 3-year PFS and OS of 11% and 22%, respectively.[34] This study demonstrated comparable survival with less toxicity than nitrosourea-based regimens, resulting in temozolomide becoming standard treatment. On the other hand, adding temozolomide did not add survival benefit to patients with DIPG, with a median survival similar to radiation therapy alone at 10 months. Focal radiation therapy remains the standard of care for newly diagnosed DIPG, with more than 200 clinical trials over the last three decades failing to show superior outcome to radiation alone.[35] Recently, whole-genome, whole-exome, and methylation profiling have identified six molecular subgroups in pediatric HGG, with each subgroup having its own clinical characteristic and driving genomics.[36] Frequent somatic mutations in histone H3 genes, *TP53* and *ACVR1*, have been reported in DIPG recently.[37] Fusion genes were also found in nearly half of DIPGs involving the neurotrophin receptor genes, *NTRK1* and *NTRK2*. Mutations targeting receptor tyrosine kinase–RAS-PI3K signaling, histone modification or chromatin remodeling, and cell cycle regulation were found in 68%, 73%, and 59% of pediatric HGGs, respectively, including in midline gliomas.

Medulloblastoma

Medulloblastoma is the most common pediatric malignant CNS tumor, with a peak age of incidence at 5 years. Medulloblastoma is known to be associated with familial cancer syndrome in less than 1% of patients, Gorlin (PTCH mutation, Sonic Hedgehog [SHH] receptor) and Turcot (mismatch repair genes) syndromes. Age younger than 3 years at diagnosis, residual tumor after resection, anaplastic histology, and metastatic disease are high-risk features and associated with poor outcome. Children with localized disease have a greater than 80% 5-year PFS compared with disseminated disease, which has less than 40% 5-year PFS.[38] Treatment typically is multidisciplinary, including surgery, chemotherapy, and radiation in newly diagnosed children older than 3 years. An alternative treatment approach for patients younger than 3 years old is to avoid radiation and use high-dose chemotherapy and autologous stem cell rescue.[39] Recent genomic studies have identified four subtypes of medulloblastoma with distinct cellular origins, clinical characteristics, and outcome, namely WNT, Sonic Hedgehog (SHH), Group 3, and Group 4.[40] The WNT and Group 3 subtypes have the best and worst prognosis, respectively. MYC amplification, 17p loss, and p53 mutation are other markers associated with poor outcome regardless of the molecular subgroup.

Ependymoma

Ependymoma accounts for 10% of childhood CNS tumors, with 70% occurring in the posterior fossa. The mean age of patients is 6 years at diagnosis. Genome-wide DNA methylation patterns, have led to the recognition of nine molecular subgroups across all three

anatomic compartments including supratentorial, posterior fossa, and the spinal locations.[41] More than 70% of supratentorial ependymomas express the *C11orf95–RELA* gene fusion, which is a downstream target of nuclear factor-κB signaling. Despite recent identification of driver oncogenes and molecular subtypes of ependymoma, treatment remains challenging. Surgery is the primary treatment modality, with the extent of surgical resection a major prognostic factor. Residual disease, younger age, anaplastic histology, and posterior fossa location are associated with poor outcome. Treatment of brain ependymomas consists of attempting complete surgical resection and adjuvant radiation therapy. The benefit of adjuvant chemotherapy to surgical resection and radiation therapy has been investigated in the Children's Oncology Group trial, with final results pending. Spinal myxopapillary ependymoma is a grade I neoplasm with spinal dominance, and the preferred standard of care is surgical resection followed by adjuvant focal radiation therapy for residual or progressive disease.

NON-NEURAL SOLID TUMORS

Although non-neural solid tumors (NNSTs) individually are markedly less common than leukemia and CNS tumors in the pediatric population, when grouped together they make up approximately 44% of all pediatric malignancies in patients under the age of 20.[42] NNSTs vary considerably by histology, tumor cell of origin, symptom spectrum, age at presentation, treatment, and outcome. The majority are treated with a multidisciplinary approach that includes surgical resection, radiation therapy, and/or systemic chemotherapy. They are typically divided broadly between malignancies that develop from primitive embryonic structures—such as neuroblastoma and WT—and sarcomas. Pediatric sarcomas will be further differentiated between those that arise from bone such as osteosarcoma and Ewing sarcoma versus those that develop from soft tissue such as rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma.

Neuroblastoma

Neuroblastoma is the most common pediatric NNST, with approximately 650 new cases diagnosed in the United States annually.[43] Neuroblastoma is derived from cells that originate from the primordial neural crest, which will eventually give rise to the sympathetic nervous system. The median age at diagnosis is 23 months, with the vast majority of patients diagnosed before age 5 years.[44] The most common primary location for neuroblastoma is the adrenal gland, accounting for 65% of cases. The remainder will develop along the sympathetic ganglia lining the spinal cord.[44] Neuroblastoma is a catecholamine-secreting tumor, and urinary catecholamines—specifically homovanillic acid and vanillylmandelic acid—are elevated in the majority of children with neuroblastoma. Neuroblastoma metastasizes to bone, bone marrow, and liver (less commonly to the CNS and lungs). Staging includes chest abdomen and pelvis CT, bone scintigraphy, bilateral bone marrow biopsies, and iodine-123 metaiodobenzylguanidine study to document the extent of disease.[44] Treatment is determined by a patient's risk status, which incorporates biologic features—including pathologic information and genetic alterations such as the presence of amplification of the proto-oncogene N-*myc*, patient age, and stage.[45] In certain cases, low-risk patients may be cured with surgical resection alone. Patients with intermediate-risk disease sustain high event-free survival and OS but often will require systemic chemotherapy and/or surgical resection.[45] Historically, patients with high-risk disease fared poorly despite extensive therapy that included intensive chemotherapy, surgical resection of the primary, and autologous stem cell transplant. Recent advances in immunotherapy have led to the incorporation of anti-GD2 antibody therapy with dinutuximab, which targets the GD2 glycoprotein, which exhibits high expression in neuroblastoma into frontline and salvage therapy. The addition of dinutuximab to neuroblastoma therapy has improved OS from 46.5% to 66.5% for patients with high-risk neuroblastoma.[46]

Wilms Tumor

WT is the most common pediatric malignancy of the kidney, with 500 diagnosed cases annually in the United States.[47] WT maintains a peak age at diagnosis of 2 to 3 years and arises from primitive embryonic renal precursors. Histology is prognostic in WT. Classical WT is composed of varying proportions of three cell types: blastemal, epithelial, and stromal. The presence of anaplasia in the tumor imports a worse prognosis and delineates unfavorable histology.[48] Two loci (WT1 on chromosome 11p13 and WT2 on chromosome 11p15) have been linked to a predisposition to WT. Several genetic syndromes associated with mutations in these loci are associated with an increased incidence of WT, including Beckwith-Wiedemann syndrome and WAGR syndrome, among others.[49] Despite this genetic association, the majority of WT cases are sporadic with no genetic propensity identified. WT metastasizes to the lungs, liver, lymphatic system, and rarely to the contralateral kidney. Similar to neuroblastoma, treatment is stratified by a patient's individual risk status, which incorporates stage as well as specific biologic features. Patients with WT have excellent outcomes and are treated with a multidisciplinary approach that will include surgical resection (usually via nephrectomy) in addition to systemic chemotherapy and, in some cases,

consolidative radiation therapy depending on the stage of the tumor.[48]

Sarcomas

Sarcomas make up 13% of all pediatric malignancies diagnosed under age 20 years.[42] The most common pediatric sarcoma of bone is osteosarcoma, with approximately 400 new cases diagnosed in the United States annually.[50] Osteosarcoma has a predilection for the metaphysis of long bones, although it can arise in the axial skeleton as well. Patients are typically treated with systemic chemotherapy and surgical resection of the primary tumor as well as sites of metastatic disease. Osteosarcoma is generally not radiosensitive, and radiation therapy is typically not done.[51,52] Ewing sarcoma is the second most common pediatric bone sarcoma, with approximately 200 children diagnosed annually in the United States.[50] The tumor most commonly arises in the diaphysis of long bones, although it can also arise in the axial skeleton or in soft tissue sites. The tumor is thought to develop from primitive embryonic cells that give rise to the parasympathetic nervous system. The presence of the EWS-FLI-1 translocation confirms the diagnosis of Ewing sarcoma.[53] Patients are treated with intensive systemic chemotherapy as well as surgical resection and/or radiation therapy because the tumor is highly radiosensitive.[54,55] Rhabdomyosarcoma is the most common soft tissue sarcoma seen in pediatric patients, with approximately 350 cases diagnosed annually in the United States.[47] Because it shares markers of primitive embryonic precursors of skeletal muscle, it was historically thought to be a tumor of primitive muscle precursors. However, rhabdomyosarcoma may develop in areas of the body where no skeletal muscle exists, thus the cell of origin for rhabdomyosarcoma remains an area of active research.[56] Treatment typically is multidisciplinary and includes systemic chemotherapy, radiation therapy, and/or surgical resection, which is determined by an extensive risk classification system that incorporates histologic subtype and cytogenetics, tumor-node-metastasis stage, and the location of the primary tumor.[57–60] Pediatric sarcomas most commonly metastasize to the lungs or other bony sites. The presence of metastatic disease at diagnosis is a poor prognostic indicator. Staging evaluation includes CT or magnetic resonance imaging of the primary tumor, chest CT to evaluate for pulmonary metastases, and bone scintigraphy to evaluate for bone metastases. Recent data have suggested that ^{18}FDG-PET/CT may be more effective to identify bone or soft tissue metastases.[61–63]

Outcomes for pediatric sarcomas have not changed in several decades, obviating the need for novel molecular targets and approaches. Recent work has focused on improved understanding of the biology behind these tumors to identify novel agents that can be tested in early-phase clinical trials. These include but are not limited to tyrosine kinase inhibitors, histone deacetylase inhibitors, mechanistic target of rapamycin inhibitors, immunomodulatory agents such as nivolumab, and chimeric antigen receptor T-cell therapies, all of which show promise, and are under active investigation. The hope is that a better understanding of sarcoma biology will yield novel targets to exploit and lead to improved outcomes (Table 54–1).

CHILDHOOD CANCER SURVIVORSHIP

Epidemiology of Childhood Cancer Survivors

Cure rates for children with cancer have improved dramatically over the past 70 years, with current cure rates estimated to be approximately 80%.[64] This has led to a large and increasing population—as many as 500,000 survivors currently living in the United States—of childhood cancer survivors (those who are alive 5 years after their initial diagnosis) who have unique physical, mental, and psychosocial health needs.

Late Effects in Childhood Cancer Survivors

As cure rates for children and adolescents diagnosed with cancer were improved, it became important to understand the degree to which patients' cancer diagnoses and treatment impacted their lives moving forward. The Childhood Cancer Survivorship Study (CCSS) was one of the first and largest cohort studies to report the long-term outcomes for young patients treated for cancer.[65] The CCSS reported that the lifespan of childhood cancer survivors is significantly lower than the general population.[66] Early deaths between 5 and 10 years post diagnosis were mostly secondary to disease relapse or disease progression. Importantly, two-thirds of survivors will have at least one chronic health condition, whereas one-third will have at least one severe or life-threatening illness.[67] Long-term side effects of therapy, those occurring more than 5 years after diagnosis, are common and span all areas of health and well-being. Risk factors for some of the most severe late effects include: exposure to anthracyclines and/or radiation for the development of cardiovascular dysfunction; radiation to the CNS for the development of neurocognitive deficits, endocrinopathies, and secondary CNS tumors; and radiation to the chest for the development of breast and thyroid cancer.[68–70] Survivors at risk for late effects should be seen in a specialized survivorship program and the Children's Oncology Group

Table 54–1

Pediatric Neoplasm	Novel Agents	Molecular Target
Leukemia		
Acute lymphoblastic leukemia	Blinatumomab	Bispecific T-cell engager; targets CD19
	Inotuzumab	ADC; targets CD22
	Tisagenlecleucel	Chimeric antigen receptor T-cell therapy; targets CD19
Acute myelogenous leukemia	Gemtuzumab ozogamicin	ADC; targets CD33
	CPX-351	Liposomal formulation of cytarabine and daunorubicin
	Venetoclax	BCL-2 inhibitor
Lymphoma		
Hodgkin lymphoma	Brentuximab vedotin	ADC; targets CD30
	Nivolumab, pembrolizumab	Anti–PD-1
Non-Hodgkin lymphoma	Axicabtagene ciloleucel	Chimeric antigen receptor T-cell therapy; targets CD19
Central Nervous System Tumors		
	Selumetinib, vemurafenib, trametinib	MEK 1/2 inhibitor
	Veliparib	PARP inhibitor
	Dabrafenib	BRAF inhibitor
	Vorinostat, entinostat	HDAC inhibitor
	Bevacizumab	VEGF-A inhibitor
	Pembrolizumab, nivolumab	Anti–PD-1
	Indoximod	IDO inhibitor
Non-Neural Solid Tumors		
	Dinutuximab	Anti-GD2
	Crizotinib	ALK and ROS1 inhibitor
	Pembrolizumab, nivolumab	Anti–PD-1
	Ipilimumab	Anti–CTLA-4
	Pazopanib	VEGFR, PDGFR and FGFR Inhibitor
	Cabozantinib	C-MET, VEGFR-2 and AXL Inhibitor
	Palbociclib	CDK4 and CDK6 Inhibitor

publishes guidelines for the risk-based screening and management of late effects (www.survivorshipguidelines.org).

Improvements in Long-Term Survival

Long-term outcomes for children and adolescents treated for cancer are improving, with patients diagnosed in the 1990s living significantly longer than patients diagnosed in the 1970s.[71] This is likely the result of both more effective upfront therapies, resulting in fewer late relapses, as well as reduction in some of the most toxic therapies. For example, anthracycline doses are capped for most patients to reduce cardiotoxicity, patients with ALL receive intrathecal chemotherapy instead of cranial spinal radiation, patients with CNS tumors rarely receive radiation therapy before the age of 2, and fewer patients with HL receive radiation to the chest because of response-based treatment.[22,72] With the use of newer immunotherapies, it will be important to determine the potential late effects associated with these novel treatments.

CONCLUSION

We have made remarkable advances in pediatric cancer treatment outcomes. The challenge for the future is to identify and employ novel treatment strategies for pediatric neoplasms whose outcomes remain suboptimal and have not changed in decades. New treatments will lead to more progress and even better outcomes.

MD ANDERSON PRACTICE TIPS

- The efficacy of blinatumomab in pediatric patients with relapsed/refractory ALL was demonstrated in an international, single-arm phase 1/2 study and will now be incorporated in the frontline treatment of ALL. Blinatumomab, CD19 single-targeting chimeric antigen receptor T-cell therapy, and stem cell transplant can be considered in the relapse setting.
- In relapsed AML, the use of CPX-351, a liposomal formulation of cytarabine and daunorubicin, demonstrated favorable responses and will now be randomized as a frontline strategy. Recently, the BCL-2 inhibitor venetoclax has shown promising activity in combination with hypomethylating agents and low-dose cytarabine and should be considered in treatment-refractory cases.
- In HL, novel anti-PD1 nivolumab and anti-CD30 antibody conjugate brentuximab vedotin have shown meaningful activity in treatment-refractory cases. The use of these agents as part of frontline therapy or instead of autologous stem cell transplant in a relapsed setting is being studied.
- Molecular testing of LGGs has identified translocations of BRAF in 70% of LGG, whereas the *BRAF* V600E mutation occurs in 5% to 10%, with a potential response to selumetinib and vemurafenib, respectively.
- In medulloblastoma, recent genomic studies have identified four subtypes with distinct cellular origins, clinical characteristics, and outcome, namely WNT, Sonic Hedgehog (SHH), Group 3, and Group 4. The WNT and Group 3 subtypes have the best and worst prognosis, respectively. Patients in inferior-outcome molecular subgroups are encouraged to participate in clinical trials.
- Outcomes for pediatric sarcomas have not changed in several decades, obviating the need for novel molecular targets and approaches. The use of tyrosine kinase inhibitors, histone deacetylase inhibitors, mechanistic target of rapamycin inhibitors, immunomodulatory agents such as nivolumab, and chimeric antigen receptor T-cell therapies all show promise and are under active investigation.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin.* 2018;68(1):7-30.
2. Smith MA, Seibel NL, Altekruse SF, et al. Outcomes for Children and Adolescents With Cancer: Challenges for the Twenty-First Century. *J Clin Oncol.* 2010;28(15):2625-2634.
3. Castellino SM, Geiger AM, Mertens AC, et al. Morbidity and mortality in long-term survivors of Hodgkin lymphoma: a report from the Childhood Cancer Survivor Study. *Blood.* 2011;117(6):1806-1816.
4. Pui C-H, Jeha S. New therapeutic strategies for the treatment of acute lymphoblastic leukaemia. *Nat Rev Drug Discov.* 2007;6(2):149-165.
5. Den Boer ML, van Slegtenhorst M, De Menezes RX, et al. A subtype of childhood acute lymphoblastic leukaemia with poor treatment outcome: a genome-wide classification study. *Lancet Oncol.* 2009;10(2):125-134.
6. Cooper SL, Brown PA. Treatment of pediatric acute lymphoblastic leukemia. *Pediatr Clin North Am.* 2015;62(1):61-73.
7. Pui C-H, Carroll WL, Meshinchi S, Arceci RJ. Biology, risk stratification, and therapy of pediatric acute leukemias: an update. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology.* 2011;29(5):551-565.
8. Locatelli F, Whitlock JA, Peters C, et al. Blinatumomab versus historical standard therapy in pediatric patients with relapsed/refractory Ph-negative B-cell precursor acute lymphoblastic leukemia. *Leukemia.* 2020;34:2473-2478.
9. Bhojwani D, Sposto R, Shah NN, et al. Inotuzumab ozogamicin in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. *Leukemia.* 2019;33(4):884-892.
10. Inaba H, Pui C-H. Immunotherapy in pediatric acute lymphoblastic leukemia. *Cancer Metastasis Rev.* 2019;38(4):595-610.
11. Creutzig U, van den Heuvel-Eibrink MM, Gibson B, et al. Diagnosis and management of acute myeloid leukemia in children and adolescents: recommendations from an international expert panel. *Blood.* 2012;120(16):3187-3205.
12. Zwaan CM, Kolb EA, Reinhardt D, et al. Collaborative efforts driving progress in pediatric acute myeloid leukemia. *J Clin Oncol.* 2015;33(27):2949-2962.
13. Kaspers GJ, Zimmermann M, Reinhardt D, et al. Improved outcome in pediatric relapsed acute myeloid leukemia: results of a randomized trial on liposomal daunorubicin by the International BFM Study Group. *J Clin Oncol.* 2013;31(5):599-607.
14. Gorman MF, Ji L, Ko RH, et al. Outcome for children treated for relapsed or refractory acute myelogenous leukemia (rAML): a Therapeutic Advances in Childhood Leukemia (TACL) Consortium study. *Pediatr Blood Cancer.* 2010;55(3):421-429.
15. Gamis AS, Alonzo TA, Meshinchi S, et al. Gemtuzumab ozogamicin in children and adolescents with de novo acute myeloid leukemia improves event-free survival by reducing relapse risk: results from the randomized phase III Children's Oncology Group trial AAML0531. *J Clin Oncol.* 2014;32(27):3021-3032.
16. Absalon M, O'Brien MM, Phillips CL, et al. A phase I/pilot study of CPX-351 for children, adolescents and young adults with recurrent or refractory hematologic malignancies. *J Clin Oncol.* 2016;34(suppl 15):10541.
17. Karol SE, Alexander TB, Budhraja A, et al. Venetoclax in combination with cytarabine with or without idarubicin in children with relapsed or refractory acute myeloid leukaemia: a phase 1, dose-escalation study. *Lancet Oncol.* 2020;21(4):551-560.
18. Swerdlow SH, Campo E, Harris NL, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. WHO Press; 2008:439.
19. Allen CE, Kelly KM, Bollard CM. Pediatric lymphomas and histiocytic disorders of childhood. *Pediatr Clin North Am.* 2015;62(1):139-165.
20. Canellos GP, Rosenberg SA, Friedberg JW, Lister TA, DeVita VT. Treatment of Hodgkin lymphoma: a 50-year perspective. *J Clin Oncol.* 2014;32(3):163-168.
21. Mauz-Körholz C, Metzger ML, Kelly KM, et al. Pediatric Hodgkin lymphoma. *J Clin Oncol.* 2015;33(27):2975-2985.
22. Friedman DL, Chen L, Wolden S, et al. Dose-intensive response-based chemotherapy and radiation therapy for children and adolescents with newly diagnosed intermediate-risk hodgkin lymphoma: a report from the Children's Oncology Group Study AHOD0031. *J Clin Oncol.* 2014;32(32):3651-3658.
23. Locatelli F, Mauz-Koerholz C, Neville K, et al. Brentuximab vedotin for paediatric relapsed or refractory Hodgkin's lymphoma and anaplastic large-cell lymphoma: a multicentre, open-label, phase 1/2 study. *Lancet Haematol.* 2018;5(10):e450-e461.
24. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med.* 2014;372(4):311-319.
25. Sandlund JT, Downing JR, Crist WM. Non-Hodgkin's lymphoma in childhood. *N Engl J Med.* 1996;334(19):1238-1248.
26. Hecht JL, Aster JC. Molecular biology of Burkitt's lymphoma. *J Clin Oncol.* 2000;18(21):3707-3721.
27. Murphy SB. Classification, staging and end results of treatment of childhood non-Hodgkin's lymphomas: dissimilarities from lymphomas in adults. *Semin Oncol.* 1980;7(3):332-339.
28. Reiter A, Klapper W. Recent advances in the understanding and management of diffuse large B-cell lymphoma in children. *Br J Haematol.* 2008;142(3):329-347.
29. Dunleavy K, Pittaluga S, Maeda LS, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. *N Engl J Med.* 2013;368(15):1408-1416.
30. Erker C, Harker-Murray P, Burke MJ. Emerging immunotherapy in pediatric lymphoma. *Future Oncol.* 2016;12(2):257-270.
31. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2011-2015. *Neuro Oncol.* 2018;20(suppl 4):iv1-iv86.
32. Ater JL, Xia C, Mazewski CM, et al. Nonrandomized comparison of neurofibromatosis type 1 and non-neurofibromatosis type 1 children who received carboplatin and vincristine for progressive low-grade glioma: a report from the Children's Oncology Group. *Cancer.* 2016;122(12):1928-1936.
33. Garcia MA, Solomon DA, Haas-Kogan DA. Exploiting molecular biology for diagnosis and targeted management of pediatric low-grade gliomas. *Future Oncol.* 2016;12(12):1493-1506.
34. Cohen KJ, Pollack IF, Zhou T, et al. Temozolomide in the treatment of high-grade gliomas in children: a report from the Children's Oncology Group. *Neuro Oncol.* 2011;13(3):317-323.
35. Khatua S, Zaky W. Diffuse intrinsic pontine glioma: time for therapeutic optimism. *CNS Oncol.* 2014;3(5):337-348.
36. Jones C, Karajannis MA, Jones DTW, et al. Pediatric high-grade glioma: biologically and clinically in need of new thinking. *Neuro Oncol.* 2017;19(2):153-161.
37. Buczkowicz P, Hoeman C, Rakopoulos P, et al. Genomic analysis of diffuse intrinsic pontine gliomas identifies three molecular subgroups and recurrent activating ACVR1 mutations. *Nat Genet.* 2014;46(5):451-456.
38. Packer RJ, Gajjar A, Vezina G, et al. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. *J Clin Oncol.* 2006;24(25):4202-4208.
39. Cohen BH, Geyer JR, Miller DC, et al. Pilot study of intensive chemotherapy with peripheral hematopoietic cell support for children less than 3 years of age with malignant brain tumors,

the CCG-99703 Phase I/II Study. A report from the Children's Oncology Group. *Pediatr Neurol.* 2015;53(1):31-46.
40. Taylor MD, Northcott PA, Korshunov A, et al. Molecular subgroups of medulloblastoma: the current consensus. *Acta Neuropathol.* 2012;123(4):465-472.
41. Pajtler KW, Witt H, Sill M, et al. Molecular classification of ependymal tumors across all CNS compartments, histopathological grades, and age groups. *Cancer Cell.* 2015;27(5):728-743.
42. Ries L, Smith M, Gurney J, et al. National Cancer Institute, SEER Program. NIH Press; 1999(99-4649):1975-1995.
43. Goodman M, Gurney J, Smith M, Olshan A. Sympathetic nervous system tumors. *Cancer Incidence and Survival Among Children and Adolescents: United States SEER Program 1975-1995*. National Cancer Institute; 1999.
44. Park JR, Eggert A, Caron H. Neuroblastoma: biology, prognosis, and treatment. *Hematol Oncol Clin North Am.* 2010;24(1):65-86.
45. Pinto NR, Applebaum MA, Volchenboum SL, et al. Advances in risk classification and treatment strategies for neuroblastoma. *J Clin Oncol.* 2015;33(27):3008-3017.
46. Yu AL, Gilman AL, Ozkaynak MF, et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. *N Engl J Med.* 2010;363(14):1324-1334.
47. Ries LAG. Renal tumors. *Cancer Incidence and Survival Among Children and Adolescents: United States SEER Program 1975-1995*. National Cancer Institute; 1999.
48. Dome JS, Graf N, Geller JI, et al. Advances in Wilms tumor treatment and biology: progress through international collaboration. *J Clin Oncol.* 2015;33(27):2999-3007.
49. Treger TD, Chowdhury T, Pritchard-Jones K, Behjati S. The genetic changes of Wilms tumour. *Nature Rev Nephrol.* 2019;15(4):240-251.
50. Gurney JG, Swensen AR, Bulterys M. Malignant bone tumors ICCC VIII. *Cancer Incidence and Survival Among Children and Adolescents: United States SEER Program 1975-1995*. National Cancer Institute; 1999.
51. Bielack SS, Kempf-Bielack B, Delling G, et al. Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1,702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols. *J Clin Oncol.* 2002;20(3):776-790.
52. Meyers PA, Heller G, Healey J, et al. Chemotherapy for nonmetastatic osteogenic sarcoma: the Memorial Sloan-Kettering experience. *J Clin Oncol.* 1992;10(1):5-15.
53. de Alava E. Ewing sarcoma, an update on molecular pathology with therapeutic implications. *Surg Pathol Clin.* 2017;10(3):575-585.
54. Grier HE, Krailo MD, Tarbell NJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. *N Engl J Med.* 2003;348(8):694-701.
55. Womer RB, West DC, Krailo MD, et al. Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology Group. *J Clin Oncol.* 2012;30(33):4148-4154.
56. Skapek SX, Ferrari A, Gupta AA, et al. Rhabdomyosarcoma. *Nature Rev Dis Primers.* 2019;5(1):1.
57. Walterhouse DO, Pappo AS, Meza JL, et al. Shorter-duration therapy using vincristine, dactinomycin, and lower-dose cyclophosphamide with or without radiotherapy for patients with newly diagnosed low-risk rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. *J Clin Oncol.* 2014;32(31):3547-3552.
58. Arndt CA, Stoner JA, Hawkins DS, et al. Vincristine, actinomycin, and cyclophosphamide compared with vincristine, actinomycin, and cyclophosphamide alternating with vincristine, topotecan, and cyclophosphamide for intermediate-risk rhabdomyosarcoma: Children's Oncology Group Study D9803. *J Clin Oncol.* 2009;27(31):5182-5188.
59. Breneman JC, Lyden E, Pappo AS, et al. Prognostic factors and clinical outcomes in children and adolescents with metastatic rhabdomyosarcoma--a report from the Intergroup Rhabdomyosarcoma Study IV. *J Clin Oncol.* 2003;21(1):78-84.
60. Weigel BJ, Lyden E, Anderson JR, et al. Intensive multiagent therapy, including dose-compressed cycles of ifosfamide/etoposide and vincristine/doxorubicin/cyclophosphamide, irinotecan, and radiation, in patients with high-risk rhabdomyosarcoma: a report from the Children's Oncology Group. *J Clin Oncol.* 2016;34(2):117-122.
61. Quartuccio N, Treglia G, Salsano M, et al. The role of fluorine-18-fluorodeoxyglucose positron emission tomography in staging and restaging of patients with osteosarcoma. *Radiol Oncol.* 2013;47(2):97-102.
62. Treglia G, Salsano M, Stefanelli A, Mattoli MV, Giordano A, Bonomo L. Diagnostic accuracy of (1)(8)F-FDG-PET and PET/CT in patients with Ewing sarcoma family tumours: a systematic review and a meta-analysis. *Skeletal Radiol.* 2012;41(3):249-256.
63. Federico SM, Spunt SL, Krasin MJ, et al. Comparison of PET-CT and conventional imaging in staging pediatric rhabdomyosarcoma. *Pediatr Blood Cancer.* 2013;60(7):1128-1134.
64. Robison LL, Hudson MM. Survivors of childhood and adolescent cancer: life-long risks and responsibilities. *Nat Rev Cancer.* 2014;14(1):61-70.
65. Leisenring WM, Mertens AC, Armstrong GT, et al. Pediatric cancer survivorship research: experience of the Childhood Cancer Survivor Study. *J Clin Oncol.* 2009;27(14):2319.
66. Armstrong GT, Liu Q, Yasui Y, et al. Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. *J Clin Oncol.* 2009;27(14):2328.
67. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med.* 2006;355(15):1572-1582.
68. Mulrooney DA, Yeazel MW, Kawashima T, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *BMJ.* 2009;339:b4606.
69. Kenney LB, Yasui Y, Inskip PD, et al. Breast cancer after childhood cancer: a report from the Childhood Cancer Survivor Study. *Ann Intern Med.* 2004;141(8):590-597.
70. Gurney JG, Kadan–Lottick NS, Packer RJ, et al. Endocrine and cardiovascular late effects among adult survivors of childhood brain tumors: Childhood Cancer Survivor Study. *Cancer.* 2003;97(3):663-673.
71. Armstrong GT, Chen Y, Yasui Y, et al. Reduction in late mortality among 5-year survivors of childhood cancer. *N Engl J Med.* 2016;374(9):833-842.
72. Vora A, Andreano A, Pui C-H, et al. Influence of cranial radiotherapy on outcome in children with acute lymphoblastic leukemia treated with contemporary therapy. *J Clin Oncol.* 2016;34(9):919.

This page intentionally left blank

55 Cancer Genomics

Jason A. Willis
Jennifer B. Goldstein
Zhijing Zhang
Andy Futreal

KEY CONCEPTS

- The cancer genomics era has been driven by rapid technological and computational advancements, which have enabled large-scale multidimensional analyses of rare and common cancers and precursor lesions.
- The vast majority of human cancers are characterized by both inter- and intratumor molecular heterogeneity, which adds further complexity to the identification of robust and clinically useful biomarkers.
- Clonal molecular evolution is evident throughout multiple stages of tumor development and has critical implications for the development of treatment resistance and metastasis.
- Driven by the development of cost-effective and robust clinical next-generation sequencing (NGS) assays, somatic mutation profiling has been broadly integrated into clinical practice for patients with hematologic malignancies and advanced solid tumors. The long-term clinical benefit of comprehensive mutation profiling remains to be defined.
- Despite the widespread application of tumor mutation profiling in practice, interpretation of the results and therapeutic decision making remains challenging. Institutional resources and/or publicly available decision tools should be consulted to help guide providers and patients.
- Large-scale studies such as the NCI-MATCH study and the MD Anderson IMPACT study, provide a critical framework for matching patients with biomarker-driven clinical trials, which is a hallmark of precision oncology.

CANCER GENES: HISTORICAL PERSPECTIVE

Over the past 50 years, multiple discoveries have had an impact on our understanding of key genomic events that influence the development of malignant growth. After many large-scale sequencing projects of cancer genomes, we now understand that many genetic alterations in specific cancer genes are responsible for the development and progression of the disease. These alterations may occur at the level of the patient's germline, predisposing to inherited forms of cancer that may develop in many tissues throughout the body. Genetic alterations may also be somatic, or newly acquired changes within the genes of an individual cell or group of cells over time, and a result of environmental stresses. Somatic alterations may come in many forms, including single-base substitutions, insertions or deletions of DNA fragments, rearrangements and rejoining of DNA from alternative locations in the genome, and copy number increases and reductions. Should these alterations affect key cancer genes, malignancy may develop.

In the early 1970s, the study of retroviruses that reverse transcribe RNA into DNA found that certain retroviruses, when incorporated into host cells, have the ability to transform normal cells into rapidly dividing tumors.[1] Rous sarcoma virus, isolated by Peyton Rous, was the first retrovirus found to cause sarcoma in chickens.[2] Later, hybridization studies proved that the Rous sarcoma virus gene, termed *v-src*, was homologous to a highly conserved eukaryotic gene, *c-src*. *Src* became the first known viral oncogene.[3] In contrast to highly transforming retroviruses, weakly transforming viruses can insert themselves into the genome near proto-oncogenes—normal genes that when mutated give rise to an oncogene—and induce cancer. Activation of proto-oncogenes to oncogenes, through activating point mutations, gene amplification, or

chromosomal translocation events, can occur independent of retroviral transformation and cause cancer.

In 1981, Shih and colleagues showed that normal NIH3T3 mouse fibroblast cells could be made cancerous by the introduction of total genomic DNA from human cancers.[4] Isolation of the specific DNA segment responsible for this transforming activity led to the identification of the first naturally occurring, human cancer–causing sequence change—the single-base G > T substitution that causes a glycine-to-valine substitution in codon 12 of the *HRAS* gene.[5] These experiments demonstrated the causal relationship between oncogenic mutations and cancer. The discovery of *HRAS* and many other oncogenes altered our understanding of cancer and expanded our knowledge of driver mutations that can be targeted to treat disease.

Another commonly referenced class of cancer-related genes is the tumor suppressor gene. Such genes are frequently involved in cell-cycle regulation, inhibition of cellular proliferation, and DNA repair. When functioning normally, they act as barriers to unregulated tumor growth. However, dysfunction of both copies of the gene are usually required to initiate tumor development because only one functioning copy is needed to regulate the cell. In 1971, Alfred Knudson was the first to theorize about the role of tumor suppressor genes in cancer development.[6] He described the two-hit hypothesis: The development of cancer was caused by the loss of inherited regulatory genes that functioned to suppress tumor formation, subsequently followed by the somatic loss of the normal homologous allele. In nonhereditary forms, both alleles would be somatically affected.[6,7]

The first tumor suppressor gene to be identified was the retinoblastoma (*RB*) gene, found to cause childhood cancers of the retina. In the hereditary form, one copy of the *RB* gene is usually defective, with a second mutation or deletion of the normal gene leading to early cancer development. Hereditary forms frequently affect the bilateral eyes. Sporadic retinoblastoma is much rarer and occurs when there is homozygous deletion or somatic mutation of both normal copies of the gene. Sporadic retinoblastoma usually presents later in life than the hereditary form and usually effects only one eye.

In the mid-1980s, Webster Cavenee and colleagues localized the retinoblastoma gene to a small region on chromosome 13 and found that both the inherited and sporadic varieties had the same secondary abnormalities, leading to homozygosity of mutations in the *RB* region.[8] In 1986, Friend et al isolated human complementary DNA mapping to the *RB* gene.[9] The following year, Fung[10] and Lee[11] both cloned *RB* using chromosome walking.[10,11] Huang and colleagues later proved a causative relationship between the defective *RB* gene and cancer by performing rescue experiments of the neoplastic phenotype in *RB*-mutated retinoblastoma cells with wild-type *RB*.[12] Aside from retinoblastoma, many tumors have subsequently been found to have defects in the *RB* gene, which may play a role in the establishment of these cancers.

NEXT-GENERATION TOOLS IN THE CANCER GENOMICS ERA

Pivotal studies of the 1980s and 1990s gave rise to the fundamental concept of cancer as a genetic disease. However, it was the completion of the Human Genome Project[13] in April 2003, and subsequent publication of the first human reference genome, that created a new era of opportunity for systematic discovery and characterization of somatic alterations in cancers.[14–16] This era has expanded rapidly in both scale and scope—that is, moving beyond a catalog of somatic DNA alterations and toward higher-order aspects of tumor biology.

Early studies of vertebrate and invertebrate genomes relied heavily on Sanger's "dideoxy method," in which a single large DNA fragment of interest (up to ~1000 base pairs [bp] in length) is amplified and then sequenced using chain-terminating polymerase chain reaction (PCR) with fluorescently-labeled nucleotides.[17] Indeed, de novo assembly of the first reported human genome succeeded largely through the implementation of costly and labor-intensive Sanger sequencing efforts in parallel, which simultaneously highlights its robustness and limitations as a sequencing approach in the context of complex diseases.[18] Achieving a better understanding of complex genetic diseases on a population level required novel high-throughput approaches that prioritized cost efficiency and scale. Accordingly, within the past two decades, this challenge has been met with the rapid development and application of next-generation sequencing (NGS) methods.[14,15,19]

To better appreciate the advantages and limitations offered by NGS technology, it is helpful to consider at least two important characteristics shared across the variety of platforms currently in use.[20–22] First, the majority of NGS technology development has centered on short-read sequencing, wherein a library of millions of variable-length DNA fragments are read simultaneously using a polymerase- or ligation-based sequencing-by-synthesis reaction, producing reads of 35 to 400 bp. Paired-end short-read sequencing is a variation of this approach in which both ends of each small DNA fragment are read. Among other properties, short-read sequencing enables massive parallelization, which consequently lowers the per-base pair and per-run costs of DNA sequencing. Importantly, however, making use of short-read NGS output (which can range from 600 megabases [Mb] to 15 gigabases [Gb] of data in a single instrument run)

also requires the computationally intensive and error-prone step of realigning (or mapping) individual reads to a reference genome. Therefore, in parallel with the emergence of novel sequencing-by-synthesis chemistries, a multitude of computational tools have been developed to robustly and efficiently align short-read NGS data against a reference genome.[23] This step may then be followed by any number of downstream analyses, most importantly the detection of single-nucleotide variations (SNVs), short insertions or deletions (indels), and large structural alterations (such as copy number gain, loss, or translocation) all by comparison with a reference genome. A second shared characteristic of NGS technology is the ability to process DNA from multiple samples in parallel. This is achieved through in vitro capture, barcoding, amplification, and pooling of small DNA fragments isolated from different samples of interest. The NGS output is then demultiplexed computationally so that reads for each sample can be analyzed separately. Commonly used next-generation platforms include the Illumina and Ion Torrent systems. In just more than a week, a solitary run on an Illumina HiSeq 4000 sequencer can generate 200 GB of data.

Building on this technological platform, cancer genomics studies have applied NGS towards a number of different goals, each focused on interrogating unique aspects of complex tumor biology. With respect to systematic discovery of DNA mutations in cancer, common NGS applications include whole-genome, whole-exome, and targeted-exome sequencing of tumor samples. NGS-based approaches are also widely used for the analysis of messenger RNA (mRNA-seq) and epigenetic markers.

In research settings, DNA from bulk fresh/frozen tumor tissue is sequenced and compared against a "normal" or (germline) reference genome, which is derived either from a matched normal tissue sample from the same individual patient or a panel of unmatched normal tissue samples from a population of patients. By comparison against the normal reference genome, the goal of tumor NGS DNA analysis is to identify somatic (rather than germline) mutations. More recently, single-cell sequencing (eg, single-cell RNA-seq) has massively expanded our insights into the clonal structure of tumor cell and stromal cell populations within a single sample.[24]

INSIGHTS FROM LARGE-SCALE SEQUENCING OF CANCER GENOMES

The overarching goal of the cancer genomics era has been to discover novel and clinically meaningful insights into the pathogenesis and molecular evolution of cancers. Toward this goal, several large-scale profiling studies have been undertaken over the past 10 years, including The Cancer Genome Atlas and the International Cancer Genome Consortium. Together, these studies have set out to systematically characterize the multidimensional landscape of several different tumor types.[25,26] In the sections below, we summarize key insights gained from this work.

Tumor Mutation Burden and Mutation Signatures

Although some cancer types may be driven by a single alteration alone, others may contain driver mutations in multiple different genes, each contributing to various aspects of tumor initiation, invasion, proliferation, and metastasis. For example, leukemias and other hematologic malignancies tend to harbor somatic mutations in approximately 9.6 genes per tumor.[27,28] By comparison, solid organ tumors such as colon, breast, brain, and pancreas contain an average of 33 to 66 genes with coding sequence mutations.[28] Within these solid tumors, the most common type of somatic alterations are SNVs (90.7% missense, 7.6% nonsense, and 1.7% alterations of splice sites or untranslated regions) and the remainder are indels.[28]

In many cases, the difference between the mutational landscape of one tumor type versus another is a reflection of varying toxic environmental factors or mutational processes that are prevalent within each tumor type. This phenomenon can be observed not only with respect to the number of mutations in a given tumor (ie, tumor mutation burden), but also the specific distribution of SNVs (ie, a mutation signature). As an example, acquired or inherited defects in DNA repair mechanisms—such as in the Fanconi pathway, the DNA mismatch repair pathway (Lynch syndrome), or the proofreading domains of DNA polymerases *POLE* or *POLD1*—are associated with markedly increased tumor mutation burden.[29,30] Even tumors of the same type may display a wide distribution of mutation frequencies. In 2013, Lawrence et al published a study examining 27 different cancer types, showing a wide variance in the frequency of nonsynonymous mutations that ranged more than 1000-fold across cancers within a given subtype (Fig. 55–1).[31] As previously described, this study showed a high frequency of mutations in melanoma and lung cancer, thought to be caused by ultraviolet radiation and tobacco carcinogen exposure, respectively, with more than 100 mutations/Mb. The frequency of mutations in melanoma and lung cancers was also quite variable, however, ranging from 0.1 to 100 mutations/Mb. Although less extreme than the latter cancers, mutation frequencies observed in acute myelogenous leukemia ranged widely from 0.01 to 10 mutations/Mb. This was despite the overall low number of mutations (0.37/Mb).[31] Furthermore,

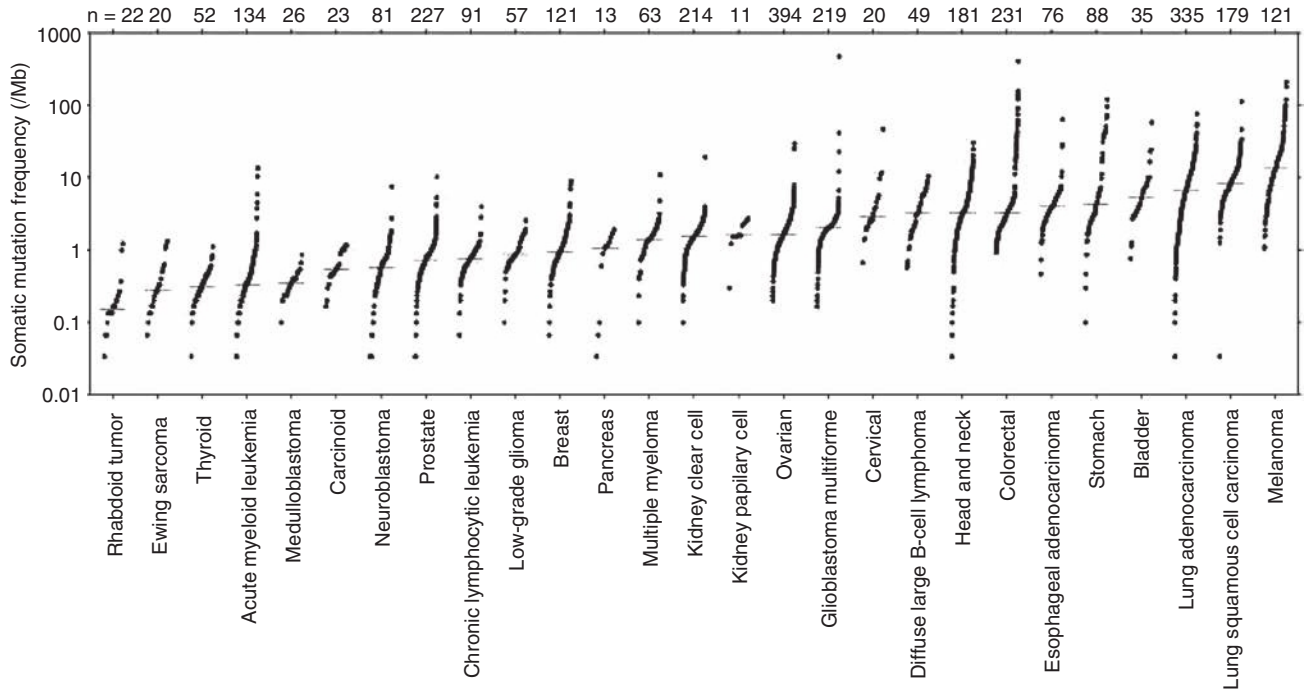


FIGURE 55–1 Whole-exome somatic mutation frequencies in 3083 tumor-normal pairs. Each dot represents a tumor-normal pair. The *y* axis is the total somatic mutation frequency. Tumor types are ordered on the *x* axis (lowest to highest) by their median somatic mutation frequency. (Reproduced with permission from Lawrence MS, Stojanov P, Polak P, et al. Mutational heterogeneity in cancer and the search for new cancer-associated genes. *Nature*. 2013;499[7457]:214-218.)

Alexandrov and colleagues analyzed NGS sequencing data from 7042 cancers and demonstrated that these tumors exhibited greater than 20 discrete mutational signatures based on the distribution of transition and transversion alterations. Some signatures could be found across cancer types (ie, APOBEC cytidine deaminase signature), and other signatures were found in a single cancer class. Kataegis, or regional hypermutation, was also found in many cancers.[32]

Despite the number of mutations present, not all mutations contribute to the production and growth of tumor cells. Identifying the background mutation rates for tumors as described previously was integral to our understanding of those genes that play a key role in the development of the tumor and confer a selective growth advantage. These alterations in genes are termed *driver* mutations. Those genes that are present within the tumor but do not contribute to tumor formation are deemed *passenger* mutations.[33] Driver mutations may not all contribute to tumor growth in the same manner, and some driver mutations may be integral to certain steps of tumor development (proliferation vs invasion). Common driver mutations that occur in cancer genes include *PTEN, EGFR, TP53, IDH1, RB1, KRAS,* and *BRAFI.*[34] In addition, some mutations originally deemed passenger mutations may become drivers once treatment leads to eradication of sensitive clones and provides a niche for already present, resistant clones to develop.[35]

Functional Impact of Structural Alterations in Cancer

Chromosomal gains, losses, and translocations are some commonly observed hallmarks of cancer. Somatic copy number alterations may span the entire chromosome or one arm of a chromosome, although they may be limited to particular regions of the genome.[36] It has been reported that an average cancer cell may have gains or losses involving a quarter of its chromosomes, with smaller, local events affecting about 10% of the genome.[37] Many of these focal events occur in "peak" regions, affecting a median of 6 to 7 genes (although up to 150–200 genes in some cases). Because of the broader effect of amplification and deletion events, it is difficult to interpret which genetic alterations contribute to carcinogenesis.[38,39]

Chromosomal translocations are associated with both hematologic and solid organ malignancies, particularly leukemias, lymphomas, and sarcomas. In some tumors, translocations can result in the fusion of genes normally found at a distance from each other or bring genes closer to enhancer or promoter elements, resulting in alteration in their normal expression patterns. The number of translocations may differ between

cancers depending on their degree of genomic instability.[40] As discussed further in the chapter, translocations can become targets for cancer treatment.

Tumor Heterogeneity and Clonal Evolution

Molecular and phenotypic heterogeneity is a hallmark of human cancer. As outlined above, not only do different tumor types harbor varying numbers of mutations, but even different sets of driver mutations can give rise to the same tumor type. Conventionally, this is referred to as *intertumoral*. In melanoma, for example, *BRAF* mutations are present in about 50% to 60% of patients, allowing for the majority, but not all, patients to benefit from *BRAF* inhibitors.[41,42] Intertumoral heterogeneity therefore may have profound implications for antineoplastic drug development, because an individual patient's tumor may respond to a drug differently depending on the presence or absence of the target of interest. The challenges of integrating NGS profiling in clinical development are outlined later in this chapter.

Furthermore, although mutations may vary among individuals with the same type of cancer, individual tumors and/or their metastatic lesions may also have cells with distinct mutations and, by extension, phenotypes. This is termed *intratumoral* heterogeneity.[43] This added complexity may account for partial responses to treatment and therapeutic resistance within an individual when treated with chemotherapy or targeted agents. Two classically described theories regarding the development of intratumoral heterogeneity include the cancer stem cell hypothesis and the clonal evolution model. In the cancer stem cell hypothesis, it is suggested that a small, distinct population of cells retain the ability to grow and divide. These cells are responsible for the maintenance of the tumor. As is seen with noncancerous stem cells throughout the body, epigenetic modifications can cause these cells to differentiate into their biologically diverse nonrenewable constituents. These diverse, differentiated cancer cells compose the bulk of the tumor, yet do not necessarily contribute to its expansion and tumorigenic potential.[44] In the clonal evolution model, with time, genetic and epigenetic events accumulate in cells; if these changes confer a competitive advantage, they will allow selective growth of distinct clones that survive over others.[44] It is possible that both phenomena can occur in the same tumor. Figure 55–2 depicts the two models.[45]

The expansion of subclones may occur in a linear or branched fashion.[46] In 2012, Gerlinger and colleagues published a paper in the *New England Journal of Medicine* using multiregional whole-exome sequencing of four renal cell carcinoma samples to elucidate the subclonal architecture and branched evolution of the disease. They found that the majority of driver alterations were subclonal, which acted as a confounder when identifying pertinent driver mutations. This study also demonstrated the unconventional pattern of mutations with regional patterns of heterogeneity. Mutational convergence was also seen with multiple subclonal mutations found in the same driver genes, however at different loci.[43]

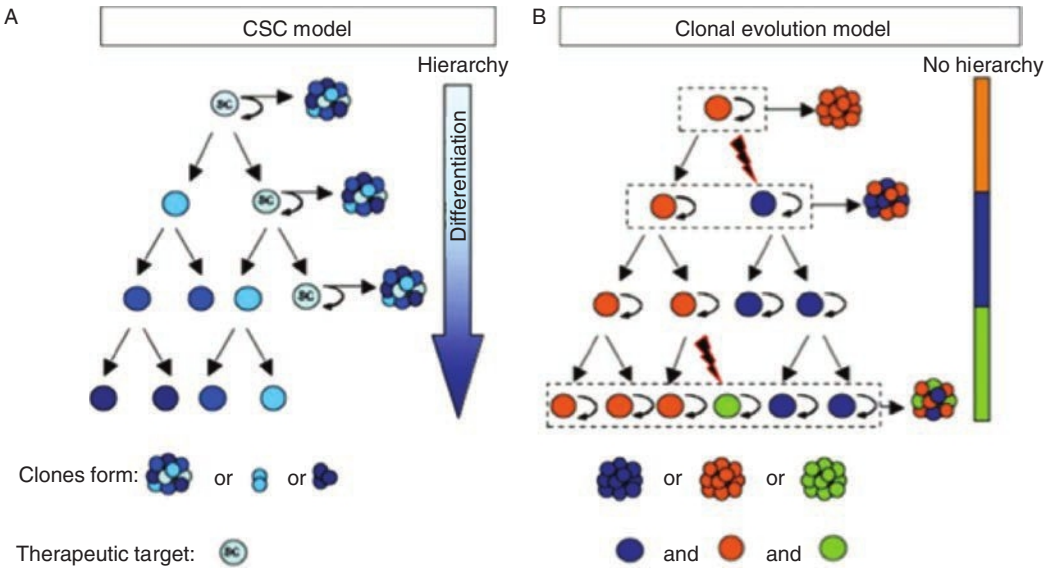


FIGURE 55–2 Models of intratumoral heterogeneity. (A). The cancer stem cell model: a specialized subpopulation of cancer cells possesses the capacity of self-renewal and differentiation. This leads to formation of a hierarchical lineage system of subclones (B). The clonal evolution model: genetic mutations lead to multiple cell populations without distinct cellular hierarchy. Most cells are assumed to retain self-renewing capacity. CSC, cancer stem cell. (Adapted with permission from Laks DR, Visnyei K, Kornblum HI. Brain tumor stem cells as therapeutic targets in models of glioma. *Yonsei Med J.* 2010;51[5]:633-640.)

In stark contrast to the former study, in 2015, Zhang and colleagues and Bruin and colleagues published two studies concurrently in *Science* examining multiregional samples from non–small cell lung cancer specimens.[47,48] Unlike renal cell carcinoma, the mutational architecture of the lung-cancer specimens showed more limited branching of subclones, with the majority of driver mutations being truncal. Patients whose disease relapsed also had a higher degree of subclonal mutations than those whose disease did not. Smoking-related mutations decreased over time, despite an increase in APOBEC-associated mutations. This may speak to an etiology of treatment resistance as a result of increased diversity of alterations.[47] Similar conclusions have also been made in the case of colorectal cancers.[49,50] Dang et al performed whole-genome and targeted deep sequencing of paired primary and metastatic tumor samples in patients with metastatic colorectal cancer. Although many truncal driver mutations were shared between primary and metastatic tumors, their analyses also revealed evidence of subclonal heterogeneity between different metastatic foci (including clones that were not observed in the primary tumor). This finding suggests polyclonal seeding from both the primary tumor and, potentially, metastatic tumors as well.

Altogether, these studies highlight vast differences between the patterns of intratumoral heterogeneity between cancer subtypes and the need for a greater understanding of how such heterogeneity impacts personalized cancer therapy. Indeed, the optimal framework or model for understanding clonal evolution in cancers remains the subject of intense study and debate.[51,52]

Molecular Landscapes of Premalignancy

Importantly, the molecular complexity of cancer revealed through large-scale NGS profiling must also be reconciled with (and refine) classic models of tumorigenesis. In a simplified model, the stepwise transformation of normal human tissue into invasive/malignant tumors is driven by sequential acquisition and selection of mutations that give a growth advantage to the cells in which they occur. In Fig. 55–3, we show how this model has been used to describe the acquisition of mutations during progression of myeloproliferative neoplasia and how this has an impact on clinical outcomes.[53] Here, for example, myeloproliferative neoplasms have been classified as *JAK2* or *TET2* mutation–positive or –negative. Those positive for both mutations can then be further examined to assess whether the order of mutation acquisition has an impact on phenotype, clinical presentation, and outcomes. The *TET2*-first tumors gain a self-renewal advantage but do not overdivide. Secondary *JAK2* mutants then compete with the *TET2*-alone clones, leading to overpopulation of terminal cells. When

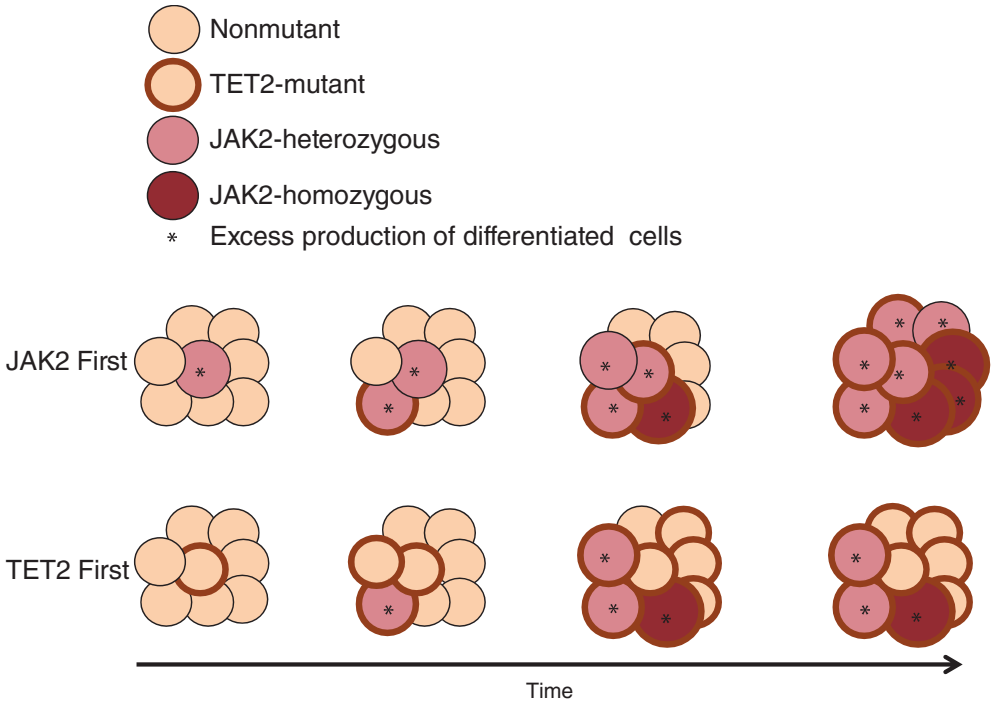


FIGURE 55–3 **Multistep cancer progression of myeloproliferative neoplasia: order of mutation acquisition influences the evolution of disease. This model depicts single hematopoietic units acquiring mutations over time.**

JAK2 homozygosity occurs as a last event, this clone has limited space to expand. This may account for the slower clinical presentation of *TET2*-first mutants. The *JAK2*-first mutants produce excess differentiated cells. After secondary *TET2* mutation acquisition, stem cells obtain a self-renewal advantage, and *JAK2–TET2–* mutant cells expand.

Loss of heterozygosity of *JAK2* V617F (either before or after *TET2* mutation) leads to expansion and resultant excess of differentiated cells. Subsequently, *JAK2*-first patients present more frequently as having polycythemia vera and have an elevated risk of thrombotic events.

An accurate understanding of the sequence of mutational events leading to cancer will allow us to build more reliable tumor models that recapitulate the evolution of the cells from normal to malignant phenotype. Furthermore, this understanding will guide the development of novel, personalized approaches for cancer interception and early detection. Toward this end, multiple large-scale collaborative efforts are now ongoing, under the umbrella of the National Institutes of Health precancer atlas initiative, to systematically characterize the landscape of pre-invasive and normal human tissue.[54] Thus far, one important perspective gained from these efforts is the prevalence of cancer-associated somatic DNA mutations in histologically normal tissue, a phenomenon conventionally known as "field cancerization."[55] For example, in 2019, Yizhak and colleagues performed next-generation RNA sequencing of approximately 6700 normal tissue samples from 29 different anatomic sites.[56] Their analyses revealed evidence of a mosaic clonal expansion of histologically normal cells with cancer gene and hotspot mutations. The rate of somatic mosaicism was highest in sun-exposed skin, lung, and esophageal tissue and was positively correlated with age, which provides evidence for both environmental and age-related mutagenic processes.

CLINICAL CANCER GENOMICS

As our understanding of the molecular landscape of cancer has grown, so has the endeavor to translate novel insights into improved clinical outcomes for patients. Indeed, the integration of cancer genomics into clinical oncology practice is itself a rapidly evolving field that faces unique challenges.[57,58] Namely, as opposed to research cancer genomics, which uses highly selected fresh-frozen tumor tissue samples, clinical cancer genomics applications must perform robustly in the setting of limited tissue *quantity* (eg, diminutive tumor biopsy or surgical specimens) and *quality* (eg, controlling for artifacts resulting from formalin-fixation and paraffin-embedding [FFPE] or normal tissue contamination). Moreover, clinical cancer genomics applications must yield results on a clinically meaningful timescale (ie, short turnaround time).

A comprehensive review of the history of clinical cancer genomics is beyond the scope of this chapter. However, it is important to highlight milestone developments that have helped address the aforementioned challenges, especially in regard to DNA sequencing. First, with respect to limited tissue quantity, a key advancement was the development of clinical NGS assays that are suited to low-input DNA.[59,60] Before this refinement, clinical assays were limited to so-called "hotspot" mutation testing, whereby only a subset of commonly mutated exon(s) or codon(s) in known cancer genes were targeted for sequencing. However, the adaptation of enhanced PCR amplification or target enrichment methods enabled rapid expansion beyond hotspots toward full-exon coverage of an entire gene panel or whole-exome sequencing. Second, accounting for the variable quality of clinical tumor specimens required further optimization of preprocessing steps. Although FFPE is widely used for archiving clinical tissue specimens, it is also known to introduce a number of artifacts in downstream sequencing (eg, C>T transitions and increased mutation calls) as a result of nucleic acid fragmentation, DNA crosslinks, or abasic sites.[61–64] Therefore, a key refinement in clinical genomic testing has been to improve methods for DNA extraction, deparaffinization, and downstream bioinformatic filtering. Similarly, it was critical to account for the fact that many clinical biopsy specimens are truly admixtures of neoplastic and non-neoplastic (normal) tissue, which has the effect of diluting mutated DNA fragments against a library of otherwise normal DNA (eg, 1 sequencing read out of 100 may harbor a mutation, implying a variant allele frequency of 1%). As such, deep sequencing (1000× coverage) and microdissection to reduce normal tissue contamination became important strategies to achieve adequate sensitivity for subclonal mutations with low variant allele frequency.

Altogether, methodologic enhancement over the past 10 years has resulted in analytical validation and integration of a number of clinical genomic assays into Clinical Laboratory Improvement Amendments (CLIA)–accredited laboratories, each with capability to detect somatic SNVs, indels, structural alterations and/or gene fusions at low-allele fractions across a wide panel of genes. This includes commercially available assays such as Oncomine, FoundationOne® (by Foundation Medicine) and Tempus, as well as institutional assays such as the Memorial Sloan Kettering–Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) assay.[65–68] Notably, in addition to single variant detection, many common assays will also report tumor mutation burden and microsatellite instability, which are now established as clinically relevant biomarkers. At MDACC, we have iteratively

developed and deployed a tissue-based multigene NGS assay, targeting a panel of known cancer genes (146, as of this writing) that are commonly mutated in multiple tumor types. In addition to having adequate FFPE tumor sample, the assay requires the collection of a whole-blood specimen from the patient, which yields a source of germline DNA to serve as a control. Efforts are currently underway to expand our institutional assay to include more than 600 cancer-related genes, tumor mutation burden, and microsatellite status.

Another landmark development in the past several years has been the use of liquid biopsies. Although serum-based biomarkers are commonly used to diagnose and track cancer progression, these indicators are often not elevated or are nonspecific. In addition, they are often prognostic rather than predictive of response to therapy. Furthermore, although the tissue-based assays described above are used in many clinical contexts, it is important to acknowledge that many factors (eg, tumor location and the patient's clinical status) can make tumor biopsies technically challenging, high risk, or nondiagnostic. This is particularly a problem with solid tumors, where intratumor heterogeneity may result in subclonal mutations remaining undetected. To address these challenges, the principle innovation underlying liquid biopsies relies upon the capture of circulating tumor cells or circulating tumor DNA (ctDNA) in the bloodstream to serve as a noninvasive source for sequencing.[69] This information can then be used as a surrogate for analysis of the tumor itself.[70] Notably, ctDNA provides a real-time snapshot of the global somatic landscape for an individual cancer, which helps avoid the pitfalls of relying on a single primary or metastatic tumor as the source for tumor tissue. In 2008, Maheswaran et al demonstrated the ability to detect epidermal growth factor receptor (*EGFR*) mutations in circulating lung-cancer cells.[71] They showed that deleterious EGFR activating mutations could be detected in circulating tumor cells from 92% of patients and in 33% of matched free-plasma DNA. As was the case for tissue-based genomic assays, a number of commercially available ctDNA genomic assays—such as FoundationOne Liquid CDx and Guardant360 CDx—have been validated and deployed in CLIA-accredited clinical laboratory environments. In more recent years, circulating tumor cells and ctDNA-based mutation profiles have become surrogate markers in clinical trials.[72] In 2017, MDACC formed a multiyear partnership with Guardant Health, Inc, to develop an institutional ctDNA-based liquid biopsy. Currently, our institutional liquid biopsy assay targets the exons of 70 known cancer genes and has been deployed into clinical practice.

Routine clinical genomic testing has been integrated into the standard-of-care at MDACC in accordance with the guidelines and approvals set forth by the institutional Molecular Testing Evaluation Committee, which was established as a formal mechanism to critically appraise published literature to determine whether there is sufficient scientific *and* clinical interest for the routine use of any given genomic assay. In the case of either tissue-based or ctDNA-based somatic mutation profiling, individual providers interpret the results to determine which mutations, if any, may be actionable for the patient receiving care. This includes decision making with respect to standard-of-care therapies and also referral to biomarker-specific clinical trials. Notably, a number of tools have been developed in this setting to help guide clinical decision making. In 2017, an MDACC team lead by Meric-Bernstam published a novel resource called the Precision Oncology Decision Support (PODS),[73] which is an online tool (publicly available at www.personalizedcancertherapy.org) that reports functional annotation, relevant targeted therapies, and matched clinical trials for any given somatic alteration. Similar resources are available from the My Cancer Genome (http://mycancergenome.com) and OncoKB projects.[74,75]

PRECISION ONCOLOGY IN THE CANCER GENOMICS ERA

With the advent of NGS, as well as improvements in molecular biology (immunohistochemistry, fluorescent in situ hybridization, PCR), our ability to characterize tumors has improved. This expansion in our knowledge base has led to many breakthroughs in drug development of targeted agents. One of the first breakthroughs for targeted therapy was the discovery of the BCR-ABL translocation as the main driver for a majority of chronic myelogenous leukemia (CML) cases and a smaller subset of acute lymphoblastic leukemia.[76,77] In the 1990s, while performing a high-throughput screen for tyrosine kinase inhibitors, Novartis developed the compound STI-571 (imatinib). Druker et al conducted the first clinical trial of STI-571, demonstrating its ability to inhibit proliferation of BCR-ABL–positive CML.[78] This trial paved the way for imatinib's approval by the Food and Drug Administration (FDA) in 2001 for CML.

The success of imatinib marked an era of rapid targeted therapy development and regulatory approval. In 1998, the targeted monoclonal antibody trastuzumab was approved to treat metastatic breast cancer.[79] In 2011, the small-molecule inhibitor vemurafenib was approved by the FDA to treat metastatic melanoma.[80] These agents, and many more, are discussed in detail throughout the manual; they are highlighted here in Table 55–1, which includes a list of the FDA-approved targeted cancer therapies.[81] Note that this table does not include targeted immunotherapies, hormonal agents, or cell-cycle inhibitors discussed in other chapters.

Table 55–1 FDA-Approved Targeted Therapies

Agent	Target(s)	FDA-Approved Indication(s)
Ado-trastuzumab emtansine (Kadcyla)	HER2 (ERBB2/neu)	Breast cancer (HER2+)
Afatinib (Gilotrif)	EGFR (HER1/ERBB1), HER2 (ERBB2/neu)	Non–small cell lung cancer (EGFR exon 19 deletions or exon 21 substitution [L858R] mutations)
Axitinib (Inlyta)	KIT, PDGFRβ, VEGFR1/2/3	Renal cell carcinoma
Bevacizumab (Avastin)	VEGF ligand	Cervical cancer Colorectal cancer Ovarian and fallopian cancer Glioblastoma Non–small cell lung cancer Peritoneal cancer Renal cell carcinoma
Bosutinib (Bosulif)	ABL	Chronic myelogenous leukemia (Philadelphia chromosome–positive)
Cabozantinib (Cometriq)	FLT3, KIT, MET, RET, VEGFR2	Medullary thyroid cancer
Ceritinib (Zykadia)	ALK	Non–small cell lung cancer (ALK fusion)
Cetuximab (Erbitux)	EGFR (HER1/ERBB1)	Colorectal cancer (KRAS wild type) Squamous cell cancer of the head and neck
Crizotinib (Xalkori)	ALK, MET	Non–small cell lung cancer (ALK fusion)
Dabrafenib (Tafinlar)	BRAF	Melanoma (*BRAF* V600 mutation)
Dasatinib (Sprycel)	ABL	Chronic myelogenous leukemia (Philadelphia chromosome–positive) Acute lymphoblastic leukemia (Philadelphia chromosome–positive)
Erlotinib (Tarceva)	EGFR (HER1/ERBB1)	Non–small cell lung cancer Pancreatic cancer
Everolimus (Afinitor)	mTOR	Pancreatic neuroendocrine tumor Renal cell carcinoma Nonresectable subependymal giant cell astrocytoma associated with tuberous sclerosis Breast cancer (HR^+, $HER2^-$)
Gefitinib (Iressa)	EGFR (HER1/ERBB1)	Non–small cell lung cancer with known prior benefit from gefitinib (limited approval)
Ibrutinib (Imbruvica)	BTK	Mantle cell lymphoma Chronic lymphocytic leukemia Waldenström macroglobulinemia
Idelalisib (Zydelig)	PI3Kδ	Chronic lymphocytic leukemia Follicular B-cell non-Hodgkin lymphoma Small lymphocytic lymphoma
Imatinib (Gleevec)	KIT, PDGFR, ABL	Gastrointestinal stromal tumor (KIT^+) Dermatofibrosarcoma protuberans Multiple hematologic malignancies, including Philadelphia chromosome–positive ALL and CML
Lapatinib (Tykerb)	HER2 (ERBB2/neu), EGFR (HER1/ERBB1)	Breast cancer ($HER2^+$)
Lenvatinib (Lenvima)	VEGFR2	Thyroid cancer
Nilotinib (Tasigna)	ABL	Chronic myelogenous leukemia (Philadelphia chromosome–positive)
Olaparib (Lynparza)	PARP	Ovarian cancer (BRCA mutation)
Panitumumab (Vectibix)	EGFR (HER1/ERBB1)	Colorectal cancer (KRAS wild type)

(*Continued*)

Table 55–1 FDA-Approved Targeted Therapies *(Cont.)*

Agent	Target(s)	FDA-Approved Indication(s)
Pazopanib (Votrient)	VEGFR, PDGFR, KIT	Renal cell carcinoma
Pertuzumab (Perjeta)	HER2 (ERBB2/neu)	Breast cancer (HER2$^+$)
Ponatinib (Iclusig)	ABL, FGFR1-3, FLT3, VEGFR2	Chronic myelogenous leukemia Acute lymphoblastic leukemia (Philadelphia chromosome–positive)
Ramucirumab (Cyramza)	VEGFR2	Gastric cancer or gastroesophageal junction (GEJ) adenocarcinoma Non–small cell lung cancer
Regorafenib (Sitara)	KIT, PDGFRβ, BRAF, RET, VEGFR1/2/3	Colorectal cancer Gastrointestinal stromal tumors
Ruxolitinib (Jakafi)	JAK1/2	Myelofibrosis
Sorafenib (Nexavar)	VEGFR, PDGFR, KIT, RAF	Hepatocellular carcinoma Renal cell carcinoma Thyroid carcinoma
Temsirolimus (Torisel)	mTOR	Renal cell carcinoma
Trametinib (Mekinist)	MEK	Melanoma (BRAF V600 mutation)
Trastuzumab (Herceptin)	HER2 (ERBB2/neu)	Breast cancer (HER2$^+$) Gastric cancer (HER2$^+$)
Vandetanib (Caprelsa)	EGFR (HER1/ERBB1), RET, VEGFR2	Medullary thyroid cancer
Vemurafenib (Zelboraf)	BRAF	Melanoma (*BRAF* V600 mutation)
Vismodegib (Erivedge)	PTCH, Smoothened	Basal cell carcinoma
Ziv-aflibercept (Zaltrap)	PIGF, VEGFA/B	Colorectal cancer
Axitinib (Inlyta)	KIT, PDGFRβ, VEGFR1/2/3	Renal cell carcinoma

Recently, the FDA has required biomarker testing in conjunction with efficacy results for targeted therapy approval. One way to develop trials in line with new FDA standards is the creation of basket clinical trials, which are a relatively new clinical trial paradigm where, in principle, recruitment is based on the molecular aberration rather than the underlying tumor histology. In these trials, patients with multiple different tumor types may be receiving the same treatment. The MDACC Battle Umbrella trials have been conducted with a similar principle; patients with late-stage lung cancer were assigned to an arm of therapy based on their biomarker profile. This allowed for testing of multiple targeted therapies in a timelier fashion.

In 2015, the National Cancer Institute (NCI) launched the NCI-MATCH (Molecular Analysis for Therapy Choice) trial, with plans to initially enroll 1000 patients on targeted drug combination therapies based on molecular alterations by pathway rather than on tumor histology. Participants are randomly assigned to receive a drug specific for that genetic alteration or a treatment unknown to be particularly effective on that pathway.[82] Recently, the NCI-MATCH investigators have reported that 37.6% of 5954 patients enrolled in the study were found to have an actionable alteration, but only 17.8% could ultimately be assigned to participate in a matched drug arm.[83] These results add to a growing body of evidence showing that large-scale genomic-matched clinical trials are technically feasible, but further refinements are necessary to extend the benefits of this approach to a wider population of patients.

CONCLUSIONS

The cancer genomics era has yielded massive amounts of information and several key biological insights into the pathogenesis of many human cancers. Deep sequencing as well as single-cell sequencing has enabled us to better understand the clonal evolution of cancer, intratumoral heterogeneity, and mechanisms of resistance. Over time, this has translated into the identification of targetable somatic alterations and novel therapeutic approaches. Furthermore, decreasing costs and methodologic improvements over the past 10 years have also led to the robust integration of cancer genomics assays in clinical laboratory settings. The long-term feasibility and benefit(s) of tumor molecular profiling remain the subjects of intense study and debate. Yet ultimately the goal of this era remains true: to improve patient outcomes and quality of life.

MD ANDERSON PRACTICE TIPS

- Although the long-term benefits remain to be demonstrated, tissue- or liquid biopsy–based comprehensive tumor mutation profiling should be considered a standard-of-care for specific subsets of patients at MDACC.
- Decision-making tools such as PODS are freely available to help providers at MDACC interpret results and identify actionable alterations for individual patients.
- Tumor mutation profiles represent a snapshot of a complex and continually evolving molecular landscape. Repeat tissue biopsies and/or serial liquid biopsies may be indicated in specific settings where the loss or emergence of a biomarker (eg, a mutation conferring resistance) would lead to a change in therapy.
- Tumor mutation profiling should not be a substitute for germline genetic testing. Therefore, patients in whom a hereditary cancer syndrome is suspected should be referred for clinical genetic counseling and testing, if indicated.
- Basket trials or umbrella trials should be considered for patients found to have actionable mutations based on clinical tumor profiling.
- Cross-comparison of mutation profiles from different NGS assays should be done with extreme caution, because multiple factors (eg, exon coverage, sensitivity, preprocessing) can impact the detectability of any given mutation in one assay compared with another.

REFERENCES

1. Varmus HE. Form and function of retroviral proviruses. *Science.* 1982;216:812-820.
2. Rous PA. Transmissible avian neoplasm (sarcoma of the common fowl) by Peyton Rous, MD; *Experimental Medicine.* 1910;12:696-705. *J Exp Med.* 979;150:738-753.
3. Frame MC. Src in cancer: deregulation and consequences for cell behaviour. *Biochim Biophys Acta* 2002;1602:114-130.
4. Shih C, Padhy LC, Murray M, Weinberg RA. Transforming genes of carcinomas and neuroblastomas introduced into mouse fibroblasts. *Nature.* 1981290:261-264.
5. Reddy EP, Reynolds RK, Santos E, Barbacid M. A point mutation is responsible for the acquisition of transforming properties by the T24 human bladder carcinoma oncogene. *Nature.* 1982;300:149-152.
6. Knudson AG Jr. Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci U S A.* 1971;68:820-823.
7. Knudson AG Jr, Strons LC. Mutation and cancer: a model for Wilms' tumor of the kidney. *JNCI: J Natl Cancer Inst.* 1972;48:313-324.
8. Cavenee WK, Dryja TP, Phillips RA, et al. Expression of recessive alleles by chromosomal mechanisms in retinoblastoma. *Nature.* 1983;305:779-784.
9. Friend SH, Bernards R, Rogelj S, et al. A human DNA segment with properties of the gene that predisposes to retinoblastoma and osteosarcoma. *Nature.* 1986;323:643-646.
10. Fung YK, Murphree AL, T'Ang A, et al. Structural evidence for the authenticity of the human retinoblastoma gene. *Science.* 1987;236:1657-1661.
11. Lee WH, Bookstein R, Hong F, et al. Human retinoblastoma susceptibility gene: cloning, identification, and sequence. *Science.* 1987;235:1394-1399.
12. Huang HJ, Yee JK, Shew JY, et al. Suppression of the neoplastic phenotype by replacement of the RB gene in human cancer cells. *Science.* 1988;242:1563-1566.
13. Collins FS, Morgan M, Patrinos A. The Human Genome Project: lessons from large-scale biology. *Science.* 2003;300:286-290.
14. Goodwin S, McPherson JD, McCombie WR. Coming of age: ten years of next-generation sequencing technologies. *Nat Rev Genet.* 2016;17:333-351.
15. van Dijk EL, Jaszczyszyn Y, Naquin D, Thermes C. The third revolution in sequencing technology. *Trends Genet.* 2018;34:666-681.
16. Stratton MR, Campbell PJ, Futreal PA. The cancer genome. *Nature.* 2009;458:719-724.
17. Sanger F, Nicklen S, Coulson AR. DNA sequencing with chain-terminating inhibitors. *Proc Natl Acad Sci U S A.* 1977;74:5463-5467.
18. Schloss JA. How to get genomes at one ten-thousandth the cost. *Nat Biotechnol.* 2008;26:1113-1115.
19. Pettersson E, Lundeberg J, Ahmadian A. Generations of sequencing technologies. *Genomics.* 2009;93:105-111.
20. Levy SE, Myers RM. Advancements in next-generation sequencing. *Annu Rev Genomics Hum Genet.* 2016;17:95-115.
21. Mardis ER. Next-generation sequencing platforms. *Annu Rev Anal Chem (Palo Alto Calif).* 2013;6:287-303.
22. Meyerson M, Gabriel S, Getz G. Advances in understanding cancer genomes through second-generation sequencing. *Nat Rev Genet.* 2010;11:685-696.
23. Ye H, Meehan J, Tong W, Hong H. Alignment of short reads: a crucial step for application of next-generation sequencing data in precision medicine. *Pharmaceutics.* 2015;7:523-541.
24. Baslan T, Hicks J. Unravelling biology and shifting paradigms in cancer with single-cell sequencing. *Nat Rev Cancer.* 2017;17:557-569.
25. Cancer Genome Atlas Research Network. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature.* 2008;455:1061-1068.
26. Wood LD, Parsons DW, Jones S, et al. The genomic landscapes of human breast and colorectal cancers. *Science.* 2007;318:1108-1113.
27. Miller DG. On the nature of susceptibility to cancer. The presidential address. *Cancer.* 1980;46:1307-1318.
28. Vogelstein B, Papadopoulos N, Velculescu VE, et al. Cancer genome landscapes. *Science.* 2013;339:1546-1558.
29. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of human colon and rectal cancer. *Nature.* 2012;487:330-337.
30. Palles C, Cazier J-B, Howarth KM, et al. Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas. *Nat Genet.* 2013;45:136-144.
31. Lawrence MS, Stojanov P, Polak P, et al. Mutational heterogeneity in cancer and the search for new cancer-associated genes. *Nature.* 2013;499:214-218.
32. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. *Nature.* 2013;500:415-421.
33. Greenman C, Stephens P, Smith R, et al. Patterns of somatic mutation in human cancer genomes. *Nature.* 2007;446:153-158.
34. Tamborero D, Gonzalez-Perez A, Perez-Llamas C, et al. Comprehensive identification of mutational cancer driver genes across 12 tumor types. *Sci Rep.* 2013;3:2650.
35. Roche-Lestienne C, soenen-Cornu V, Grardel-Duflos N, et al. Several types of mutations of the Abl gene can be found in chronic myeloid leukemia patients resistant to STI571, and they can preexist to the onset of treatment. *Blood.* 2002;100:1014-1018.
36. Sebat J, Lakshmi B, Troge J, et al. Large-scale copy number polymorphism in the human genome. *Science.* 2004;305:525-528.
37. Beroukhim R, Mermel CH, Porter D, et al. The landscape of somatic copy-number alteration across human cancers. *Nature.* 2010;463:899-905.
38. Chin L, Hahn WC, Getz G, Meyerson M. Making sense of cancer genomic data. *Genes Dev.* 2011;25:534-555.
39. Garraway LA, Lander ES. Lessons from the cancer genome. *Cell.* 2013;153:17-37.
40. Bunting SF, Nussenzweig A. End-joining, translocations and cancer. *Nat Rev Cancer.* 2013;13:443-454.
41. Curtin JA, Fridlyand J, Kageshita T, et al. Distinct sets of genetic alterations in melanoma. *N Engl J Med.* 2005;353:2135-2147.
42. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. *Nature.* 2002;417:949-954.
43. Gerlinger M, Rowan AJ, Horswell S, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *N Engl J Med.* 2012;366:883-892.
44. Shackleton M, Quintana E, Fearon ER, Morrison SJ. Heterogeneity in cancer: cancer stem cells versus clonal evolution. *Cell.* 2009;138:822-829.
45. Laks DR, Visnyei K, Kornblum HI. Brain tumor stem cells as therapeutic targets in models of glioma. *Yonsei Med J.* 2010;51:633-640.
46. Swanton C. Intratumor heterogeneity: evolution through space and time. *Cancer Res.* 2012;72:4875-4882.
47. de Bruin EC, McGranahan N, Mitter R, et al. Spatial and temporal diversity in genomic instability processes defines lung cancer evolution. *Science.* 2014;346:251-256.
48. Zhang J, Fujimoto J, Zhang J, et al. Intratumor heterogeneity in localized lung adenocarcinomas delineated by multiregion sequencing. *Science.* 2014;346:256-259.
49. Dang HX, Krasnick BA, White BS, et al. The clonal evolution of metastatic colorectal cancer. *Sci Adv.* 2020;6:eaay9691.
50. Wei Q, Zhong X, Li L, et al. Multiregion whole-exome sequencing of matched primary and metastatic tumors revealed genomic heterogeneity and suggested polyclonal seeding in colorectal cancer metastasis. *Ann Oncol.* 2017;28:2135-2141.

51. Turajlic S, Sottoriva A, Graham T, Swanton C. Resolving genetic heterogeneity in cancer. *Nat Rev Genet.* 2019;20:404-416.
52. Williams MJ, Sottoriva A, Graham TA. Measuring clonal evolution in cancer with genomics. *Annu Rev Genomics Hum Genet.* 2019;20:309-329.
53. Ortmann CA, Kent DG, Nangalia J, et al. Effect of mutation order on myeloproliferative neoplasms. *N Engl J Med.* 2015;372:601-612.
54. Spira A, Yurgelun MB, Alexandrov L, et al. Precancer atlas to drive precision prevention trials. *Cancer Res.* 2017;77:1510-1541.
55. Curtius K, Wright NA, Graham TA. An evolutionary perspective on field cancerization. *Nat Rev Cancer.* 2018;18:19-32.
56. Yizhak K, Aguet F, Kim J, et al. RNA sequence analysis reveals macroscopic somatic clonal expansion across normal tissues. *Science.* 2019;364:eaaw0726.
57. Shaw KR, Maitra A. The status and impact of clinical tumor genome sequencing. *Annu Rev Genomics Hum Genet.* 2019;20:413-432.
58. Berger MF, Mardis ER. The emerging clinical relevance of genomics in cancer medicine. *Nat Rev Clin Oncol.* 2018;15:353-365.
59. Gray PN, Dunlop CL, Elliott AM. Not all next generation sequencing diagnostics are created equal: understanding the nuances of solid tumor assay design for somatic mutation detection. *Cancers (Basel).* 2015;7:1313-1332.
60. Vigliar E, Malapelle U, De Luca C, Bellevicine C, Troncone G. Challenges and opportunities of next-generation sequencing: a cytopathologist's perspective. *Cytopathology* 2015;26:271-283.
61. Bass BP, Engel KB, Greytak SR, Moore HM. A review of preanalytical factors affecting molecular, protein, and morphological analysis of formalin-fixed, paraffin-embedded (FFPE) tissue: how well do you know your FFPE specimen? *Arch Pathol Lab Med.* 2014;138:1520-1530.
62. Do H, Dobrovic A. Sequence artifacts in DNA from formalin-fixed tissues: causes and strategies for minimization. *Clin Chem.* 2015;61:64-71.
63. Goetz L, Bethel K, Topol EJ. Rebooting cancer tissue handling in the sequencing era: toward routine use of frozen tumor tissue. *JAMA.* 2013;309:37-38.
64. Srinivasan M, Sedmak D, Jewell S. Effect of fixatives and tissue processing on the content and integrity of nucleic acids. *Am J Pathol.* 2002;161:1961-1971.
65. Beaubier N, Tell R, Lau D, et al. Clinical validation of the tempus xT next-generation targeted oncology sequencing assay. *Oncotarget.* 2019;10:2384.
66. Cheng DT, Mitchell TN, Zehir A, et al. Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT): a hybridization capture-based next-generation sequencing clinical assay for solid tumor molecular oncology. *J Mol Diagn.* 2015;17:251-264.
67. Frampton GM, Fichteholtz A, Otto GA, et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. *Nat Biotechnol.* 2013;31:1023-1031.
68. Lih C-J, Harrington RD, Sims DJ, et al. Analytical validation of the next-generation sequencing assay for a nationwide signal-finding clinical trial: molecular analysis for therapy choice clinical trial. *J Mol Diagn.* 2017;19:313-327.
69. Nagrath S, Sequist LV, Maheswaran S, et al. Isolation of rare circulating tumour cells in cancer patients by microchip technology. *Nature.* 2007;450:1235-1239.
70. Cristofanilli M, Budd GT, Ellis MJ, et al. Circulating tumor cells, disease progression, and survival in metastatic breast cancer. *N Engl J Med.* 2004;351:781-791.
71. Maheswaran S, Sequist LV, Nagrath S, et al. Detection of mutations in EGFR in circulating lung-cancer cells. *N Engl J Med.* 2008;359:366-377.
72. Janku F, Angenendt P, Tsimberidou AM, et al. Actionable mutations in plasma cell-free DNA in patients with advanced cancers referred for experimental targeted therapies. *Oncotarget.* 2015;6:12809-12821.
73. Kurnit KC, Bailey AM, Zeng J, et al. "Personalized Cancer Therapy": a publicly available precision oncology resource. *Cancer Res.* 2017;77:e123-e126.
74. Levy MA, Lovly CM, Pao W. Translating genomic information into clinical medicine: lung cancer as a paradigm. *Genome Res.* 2012;22:2101-2108.
75. Chakravarty D, Gao J, Phillips SM, et al. OncoKB: a precision oncology knowledge base. *JCO Precision Oncology*, 2017;1-16.
76. Hungerford D, Nowell P. A minute chromosome in human chronic granulocytic leukemia. *Science.* 1960;132:1497-1499.
77. Kurzrock R, Gutterman JU, Talpaz M. The molecular genetics of Philadelphia chromosome-positive leukemias. *N Engl J Med.* 1988;319:990-998.
78. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med.* 2001;344:1031-1037.
79. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med.* 344, 2001;344:783-792.
80. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med.* 2011;364:2507-2516.
81. United States Food & Drug Administration. Table of Pharmacogenomic Biomarkers in Drug Labeling. Accessed May 15, 2021. https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling
82. Redig AJ, Janne PA. Basket trials and the evolution of clinical trial design in an era of genomic medicine. *J Clin Oncol.* 2015;33:975-977.
83. Flaherty KT, et al. Molecular landscape and actionable alterations in a genomically guided cancer clinical trial: National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH). *J Clin Oncol.* 2020;38:3883-3894.

This page intentionally left blank

56 Immuno-oncology

Bilal A. Siddiqui
Sangeeta Goswami
James P. Allison
Padmanee Sharma

KEY CONCEPTS

- Immune checkpoint therapy (ICT) targeting cytotoxic T lymphocyte antigen-4 (CTLA-4) or programmed cell death protein 1 or programmed cell death ligand 1 (PD-L1) has changed the clinical course of many cancers, with some patients achieving survival benefit and durable responses lasting for years.
- The most commonly used biomarkers for ICT are tissue PD-L1 expression, tumor mutational burden, and mismatch repair deficiency or microsatellite instability.
- Significant efforts are underway to discover biomarkers for optimal patient selection and develop combinatorial strategies to improve response.
- Immune-related adverse events (irAEs) can affect any organ and require prompt recognition and early intervention is critical.
- Chimeric antigen receptor (CAR) T-cells are engineered with a synthetic antigen receptor with high affinity for a tumor antigen coupled with a T-cell signaling domain. There are now three CAR T-cell (CAR T therapeutics approved by the Food and Drug Administration for patients with hematologic malignancies). CAR T-cells have unique toxicities, including cytokine release syndrome and immune effector cell–associated neurotoxicity syndrome, which require a high index of suspicion.
- Future areas of investigation in cancer immunotherapy include rational targeting of other immune checkpoints, refinement of CAR T-cell therapies and other cellular therapies, testing of immunotherapy earlier in the disease state (eg, neoadjuvant), combinatorial strategies, improved understanding of irAEs, and development of predictive biomarkers for toxicities and response.

THE PROMISE OF IMMUNOTHERAPY

Although the ability of the immune system to recognize and eradicate cancer was first postulated in the 19th century, proof of principle remained elusive until the 20th century. As early as 1884, Anton Chekhov observed in a letter that: "It has long been noted that the growth of malignant tumors halts for a time when this disease [erysipelas] is present."[1] Beginning in the 1890s, William Coley developed a mixture of heat-killed bacteria (Coley's toxin) that was found to induce complete tumor regression in certain patients with sarcoma and subsequently studied in various types of cancer through the 1960s with mixed clinical benefit.[2] The concept of stimulating the immune system using bacterial elements was further validated with the development of intravesical bacillus Calmette–Guérin (BCG) for superficial bladder cancer, which promotes a nonspecific inflammatory immune response and clinical benefit.[3] Over time, the discovery of the major histocompatibility complex (MHC) and T-cell receptor (TCR) in the 1980s provided insight into T-cell function that led to a number of clinical trials.[4,5] Unfortunately, many early clinical trials failed because an incomplete understanding of T-cell function. As further research led to deeper understanding of mechanisms of T-cell function, including co-stimulation and co-inhibition, the field of cancer immunotherapy has expanded rapidly with the emergence of treatments that have yielded survival advantages for many patients, such as immune checkpoint therapies (ICTs) and chimeric

antigen receptor T-cell (CAR T) therapy. Immunotherapy is now firmly established as a pillar of cancer treatment, alongside chemotherapy, radiation, and surgery.

The basic principles that guide cancer immunology are (1) immune surveillance, (2) immune editing, and (3) immune tolerance.[6] *Immune surveillance* involves scanning and eliminating the transformed nascent cells by the immune system. Although it was shown that tumor-specific antigens could be recognized by cytotoxic T lymphocytes, it was increasingly understood that antigen recognition alone was insufficient to promote immunogenicity.[7] These findings gave rise to the concept of *immune editing*, which describes how tumor cells exploit different mechanisms to become less immunogenic and eventually evade immune recognition. Immune editing involves three phases: (1) an elimination phase similar to the original concept of immune surveillance, in which host immunity serves as an extrinsic tumor suppressor; (2) an equilibrium phase, in which tumor cells survive but are held in check by the immune system; and (3) and an escape phase, when tumor cells with reduced immunogenicity or the capacity to attenuate or subvert immune responses grow into clinically apparent cancers. Finally, the principle of *immune tolerance* argues that tumor cells may not only become less immunogenic themselves but exert changes in host immunity to induce a state of functional quiescence.

These principles have formed the bedrock of development for cancer immunotherapy, as insight has been gained into interactions between tumor and host immunity, as well as the mechanisms of regulation of T-cell function. Understanding of these immunologic principles led to clinical development of immunotherapeutic agents, which will be discussed in the following sections.

IMMUNE CHECKPOINT THERAPY

T-cell activation is finely balanced by co-stimulatory and co-inhibitory molecules to prevent excess activation and autoimmunity (Fig. 56–1) and requires two main signals.[8] The first signal of T-cell activation requires interaction of the TCR on naïve T-cells with MHC molecules on antigen-presenting cells (APCs).[9] The second co-stimulatory signal requires the binding of CD28 on T-cells with B7 (CD80/86) molecules on APCs.[9] Whereas the role of T-cell co-stimulation was well-recognized for many years, the discovery of the inhibitory checkpoint cytotoxic T lymphocyte antigen-4 (CTLA-4) heralded a paradigm shift in cancer immunotherapy by providing a pathway to release T-cell inhibition and promote antitumor immunity.[10] An array of ICTs targeting the inhibitory checkpoints CTLA-4, programmed cell death protein 1 (PD-1), and programmed cell death ligand 1 (PD-L1) have been approved for a wide variety of indications and continue to evolve rapidly as novel combinations and other checkpoints are explored. The current Food and Drug Administration (FDA)–approved landscape of ICTs is listed in Table 56–2. This section aims to provide a brief overview of FDA-approved ICTs across tumor types; full details for each cancer are available in their respective chapters.

Inhibitory Checkpoints: CTLA-4

CTLA-4 is expressed by activated T-cells and competes with the co-stimulatory molecule CD28 for binding to its ligands (B7, CD80/86), thereby serving as a negative regulator of T-cell responses. Preclinical studies in murine models demonstrated that inhibition of CTLA-4 enhanced antitumor immune responses, leading to durable regression of syngeneic tumors.[10] These results led to the development of ipilimumab, a fully human immunoglobulin (Ig) G1 monoclonal antibody (mAb) against CTLA-4, which has been approved by the FDA as monotherapy in patients with unresectable or metastatic melanoma and as adjuvant treatment for patients with melanoma with pathologic involvement of regional lymph nodes larger than 1 mm who have undergone complete resection (Table 56–2).

In a randomized phase III trial, patients with metastatic melanoma received either ipilimumab with or without a peptide (gp100) vaccine or vaccine treatment alone. Ipilimumab monotherapy improved median overall survival (OS), and approximately 20% of patients who received ipilimumab had long-term survival of greater than 3 years, which led to the initial FDA approval of ipilimumab.[11] Another phase III trial in previously untreated metastatic melanoma compared ipilimumab plus dacarbazine chemotherapy to dacarbazine alone and showed a survival advantage with ipilimumab.[12] In the adjuvant setting, ipilimumab was compared with placebo investigated in patients with high-risk stage III melanoma after complete resection and demonstrated median recurrence-free survival of 46.5% for ipilimumab versus 34.8% for placebo.[13] A pooled analysis of 10 prospective and two retrospective studies showed ipilimumab increased long-term survival of approximately 20% of patients, with survival of 10 years noted for some patients.[14] Ipilimumab is currently the only FDA-approved mAb against CTLA-4, although another humanized IgG2 mAb targeting CTLA-4, tremelimumab, is under active investigation.[15]

Inhibitory Checkpoints: PD-1 and PD-L1

PD-1 is another negative regulator of T-cell response that is mainly expressed by activated CD4 and CD8 T-cells as well as APCs.[16] PD-1 has two ligands, PD-L1 and PD-L2, with distinct expression profiles. The

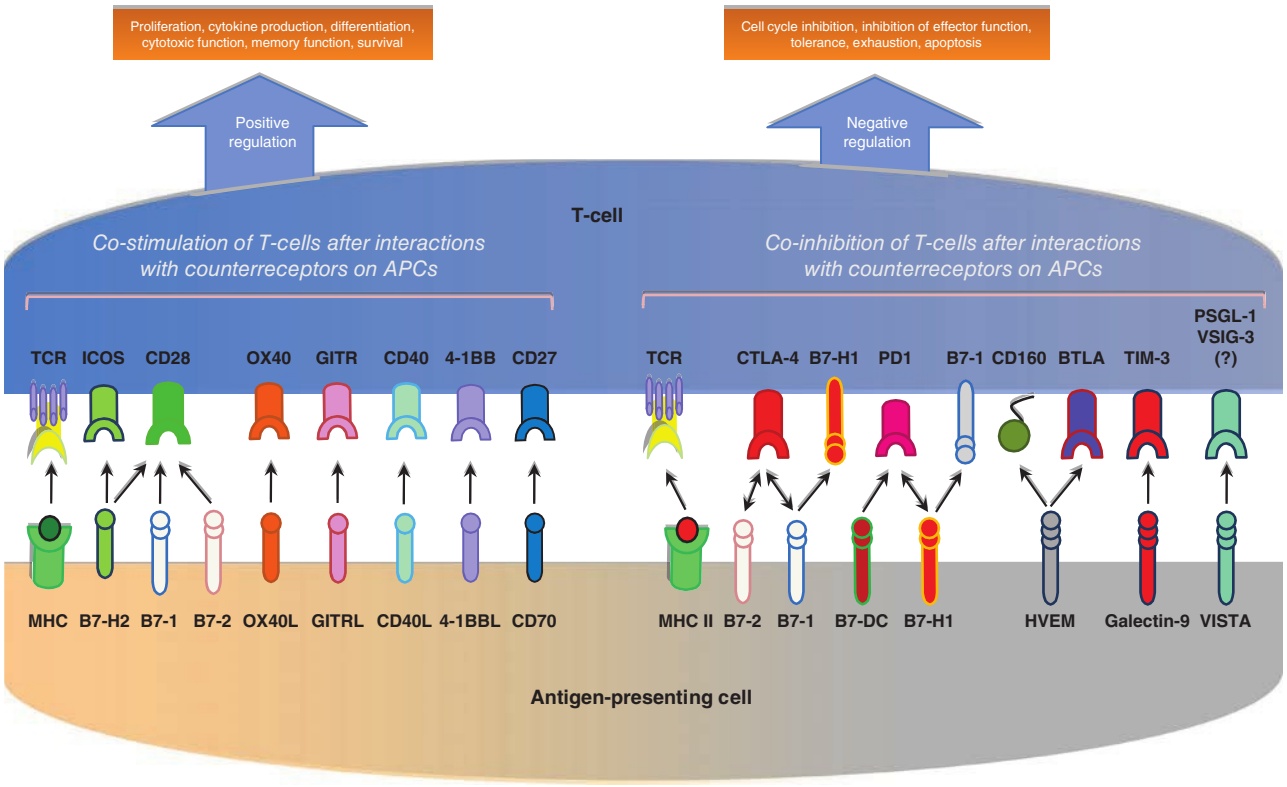


FIGURE 56–1 **T-cell activation begins with interaction of the T-cell receptor (TCR) on a T-cell with major histocompatibility complex (MHC) bound to antigen on an antigen-presenting cell (APC) (signal 1); activation of the T-cell requires additional signals that are provided by the interaction between CD28 and other co-stimulatory molecules (signal 2). T-cell activation is inhibited by co-inhibitory molecules such as cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed cell death protein 1 (PD-1). BTLA, B- and T-lymphocyte attenuator; CD40L, CD40 ligand; GITR, glucocorticoid-induced tumor necrosis factor receptor; GITRL, GITR ligand; HVEM, Herpesvirus entry mediator; ICOS, inducible T-cell co-stimulator; MHC, major histocompatibility complex; OX40, OX40 ligand; PSGL-1, P-selectin glycoprotein ligand-1; TIM-3, T-cell immunoglobulin and mucin-domain containing-3; VSIG-3, V-set and immunoglobulin domain containing 2.**

TABLE 56–1 Anti- and Protumor Arms of the Immune System

	Antitumor	Protumor
	Innate: Mature dendritic cell Tumor-associated macrophage (M1 phenotype) Tumor-associated neutrophil (N1)	Innate: Immature dendritic cell Tumor-associated macrophage (M2 phenotype) Tumor-associated neutrophil (N2)
Cellular compartment	NK cells Adaptive: CD8+ T-cells CD4+ T-cells: Th-1, Th-9, Th-17	Adaptive: CD4+ T-cells: Th-9, Th-17 T-regulatory cells
Soluble factors (cytokines)	Granzyme B, IL-1 a,b, IL-2, IL-6, IFN-g, IL-12, IL-17	TGF-b, IL-2, IL-4, IL-6, IL-10, IL-17, IL-23

IFN, interferon; IL, interleukin; NK, natural killer; TGF, transforming growth factor.

PD-L1 ligand is expressed not only on APCs but also on T-cells, B cells, and nonhematopoietic cells, including tumor cells. Expression of PD-L2 is largely restricted to APCs, including macrophages and myeloid dendritic cells (DCs), as well as mast cells. In preclinical studies, mAbs against PD-1 and PD-L1 resulted in reduction of tumor metastasis and growth in a number of experimental tumor models, which have led to an enormous array of clinical trials and a FDA approvals in various tumor types.[17,18] Currently, there are six mAbs against PD-1 (nivolumab, pembrolizumab, cemiplimab) and PD-L1 (durvalumab, atezolizumab, avelumab) FDA approved in a diverse array of cancers, including skin, genitourinary, lung, head and neck,

TABLE 56–2 List of Food and Drug Administration–Approved Immune Checkpoint Therapies as of September 1, 2020

Immune Checkpoint Therapy	Disease	Indications	References
Anti–CTLA-4			
Ipilimumab	Melanoma	Metastatic or unresectable	11,12,14
	Melanoma	High-risk stage III after complete resection (adjuvant)	13
Anti–PD-1			
Nivolumab	Colorectal cancer	Metastatic, MSI-H or dMMR, after treatment with a fluoropyrimidine, oxaliplatin, and irinotecan	65
	Esophageal cancer	Unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy	196
	Head and neck cancer, squamous cell carcinoma	Recurrent or metastatic with progression on or after platinum-based therapy	57
	Hepatocellular carcinoma	After treatment with sorafenib	58
	Hodgkin lymphoma, classical	Relapsed or progressed after autologous hematopoietic stem cell transplant and brentuximab vedotin or after three or more lines of systemic therapy that included autologous transplant	67
	Melanoma	Metastatic or unresectable	19,20
	Melanoma	Lymph node involvement or metastatic disease after complete resection (adjuvant)	21
	Non–small cell lung cancer	Metastatic, progressive after platinum-based chemotherapy	42,43
	Renal cell carcinoma	Advanced, after antiangiogenic therapy	30
	Small cell lung cancer	Metastatic, progression after platinum-based chemotherapy and at least one other line of therapy	45
	Urothelial carcinoma	Locally advanced or metastatic with disease progression during or after platinum-containing therapy or disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing therapy	36
Pembrolizumab	Any solid tumor	Unresectable or metastatic MSI-H or dMMR solid tumors that have progressed after prior treatment with no satisfactory alternate treatment options	71,72
	Any solid tumor	Unresectable or metastatic TMB-H (≥10 mut/Mb) solid tumors that have progressed on prior treatment with no satisfactory alternative treatment options	73
	Cervical cancer	Recurrent or metastatic, with tumor PD-L1 CPS ≥1 and disease progression on *or* after chemotherapy	70
	Colorectal cancer	Unresectable or metastatic MSI-H or dMMR tumors that have progressed after treatment with fluoropyrimidine, oxaliplatin, and irinotecan *or* first-line treatment	66,197
	Cutaneous squamous cell carcinoma	Recurrent or metastatic cutaneous squamous cell carcinoma not curable by surgery or radiation	29
	Esophageal cancer	Recurrent locally advanced or metastatic squamous cell, with tumor PD-L1 CPS ≥10 and disease progression after one or more prior lines of systemic therapy	63,64
	Gastric cancer	Recurrent locally advanced or metastatic, with tumor PD-L1 CPS ≥1 and disease progression on or after two or more prior lines of therapy, including fluoropyrimidine- and platinum-containing chemotherapy, and if appropriate, HER2/neu-targeted therapy	61,62

TABLE 56–2 List of Food and Drug Administration–Approved Immune Checkpoint Therapies as of September 1, 2020 (*Cont.*)

Immune Checkpoint Therapy	Disease	Indications	References
	Head and neck cancer, squamous cell carcinoma	First-line treatment for metastatic or unresectable recurrent disease with tumor PD-L1 CPS ≥1 or subsequent treatment with disease progression on or after platinum-containing chemotherapy	54,55
	Hepatocellular carcinoma	After treatment with sorafenib	59,60
	Hodgkin lymphoma, classical	Relapsed or refractory after three or more prior lines of therapy	68
	Melanoma	Metastatic or unresectable	22,198
	Melanoma	Lymph node involvement after complete resection (adjuvant)	23
	Merkel cell carcinoma	Recurrent locally advanced or metastatic	24,25
	Non-small cell lung cancer	First-line stage III (not candidates for resection or definitive chemoradiation) or metastatic disease and with tumor PD-L1 expression TPS ≥1% without *EGFR* or *ALK* tumor alterations or metastatic with PD-L1 TPS ≥1% with disease progression on or following platinum-containing chemotherapy and EGFR or ALK-directed therapy if genomic alterations present	47,48
	Primary mediastinal B-cell lymphoma	Refractory disease or relapse after two or more lines of therapy	69
	Small cell lung cancer	Metastatic, with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy	49
	Urothelial carcinoma	High-risk, BCG-unresponsive, non–muscle-invasive bladder cancer with carcinoma in situ with or without papillary tumors, ineligible for or declined cystectomy	35
	Urothelial carcinoma	Locally advanced or metastatic disease ineligible for cisplatin-based chemotherapy with tumor PD-L1 CPS ≥10 or platinum ineligible regardless of PD-L1 status or patients with disease progression during or after platinum-based chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-based chemotherapy	31,33,34
Cemiplimab	Cutaneous squamous cell carcinoma	Metastatic or locally advanced	27,28
Anti–PD-L1			
Atezolizumab	Non–small cell lung cancer	Metastatic disease, with progression during or after platinum-containing therapy (with progression on *EGFR*- or *ALK*-directed therapy if indicated) *or* frontline for tumors with PD-L1 tumor cells ≥50% or PD-L1 immune cells ≥10% without *EGFR* or *ALK* alterations	50–52
	Urothelial carcinoma	Locally advanced or metastatic disease ineligible for cisplatin-based chemotherapy with tumor PD-L1 immune cells ≥5% or patients with disease progression during or after platinum-based chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-based chemotherapy	37,38

(*Continued*)

TABLE 56–2 List of Food and Drug Administration–Approved Immune Checkpoint Therapies as of September 1, 2020 (*Cont.*)

Immune Checkpoint Therapy	Disease	Indications	References
Avelumab	Merkel cell carcinoma	Metastatic disease	26
	Urothelial carcinoma	Locally advanced or metastatic, with disease progression during or after platinum-based chemotherapy or disease progression within 12 months of neoadjuvant or adjuvant platinum-based therapy	39
	Urothelial carcinoma	Maintenance treatment for locally advanced for metastatic UC that has not progressed with first-line platinum-containing chemotherapy	41
Durvalumab	Non–small cell lung cancer	Unresectable stage III disease after concurrent platinum-based chemotherapy and radiation therapy	53
	Urothelial carcinoma	Locally advanced or metastatic with disease progression during or after platinum-containing chemotherapy or disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy	40
Anti–CTLA-4 + anti–PD-1			
Ipilimumab + nivolumab	Colorectal cancer	Metastatic, MSI-H or dMMR, after treatment with fluoropyrimidine, oxaliplatin, and irinotecan	83
	Hepatocellular carcinoma	After treatment with sorafenib	81
	Melanoma	Metastatic or unresectable, previously untreated	77,78
	Non–small cell lung cancer	Metastatic or recurrent, without *EGFR* or *ALK* genomic tumor alterations	82
	Renal cell carcinoma	Advanced, intermediate, or poor risk, previously untreated	79,80
Anti–PD-(L)1 + targeted therapy			
Pembrolizumab + lenvatinib	Endometrial carcinoma	Advanced, non–MSI-H and dMMR with progression after prior systemic therapy and not candidate for curative surgery or radiation	94
Atezolizumab + vemurafenib + cobimetinib	Melanoma	BRAF V600 mutation-positive unresectable or metastatic melanoma	93
Pembrolizumab + axitinib	Renal cell carcinoma	Advanced, first line	91
Avelumab + axitinib	Renal cell carcinoma	Advanced, first line	92
Atezolizumab + bevacizumab	Hepatocellular carcinoma	Unresectable or metastatic hepatocellular carcinoma, first line	199
Anti–PD-(L)1+ chemotherapy			
Atezolizumab + nab-paclitaxel	Breast cancer	Unresectable locally advanced or metastatic, triple negative, with PD-L1 immune cells ≥1%	90
Atezolizumab + bevacizumab + paclitaxel + carboplatin	Non–small cell lung cancer	First line for metastatic, nonsquamous, without *EGFR* or *ALK* genomic tumor alterations	86
Atezolizumab + nab-paclitaxel/ carboplatin	Non–small cell lung cancer	Metastatic, without *EGFR* or *ALK* genomic tumor alterations	87

TABLE 56–2 List of Food and Drug Administration–Approved Immune Checkpoint Therapies as of September 1, 2020 (*Cont.*)

Immune Checkpoint Therapy	Disease	Indications	References
Atezolizumab + etoposide/ carboplatin	Small cell lung cancer	Extensive-stage, first-line treatment	88
Durvalumab + etoposide/ platinum	Small cell lung cancer	Extensive-stage, first-line treatment	89
Pembrolizumab + 5-FU/platinum	Head and neck cancer, squamous cell	First-line treatment for metastatic or unresectable recurrent disease	56
Pembrolizumab + pemetrexed/ platinum	Non–small cell lung cancer	Metastatic, nonsquamous, without *EGFR* or *ALK* genomic tumor alterations	84
Pembrollizumab + carboplatin/(nab) paclitaxel	Non–small cell lung cancer	Metastatic, squamous	85

ALK, anaplastic lymphoma kinase; BCG, Bacillus Calmette-Guerin; CPS, combined positive score; CTLA-4, cytotoxic T-cell lymphocyte antigen-4; dMMR, deficient mismatch repair; EGFR, epidermal growth factor receptor; 5-FU, fluorouracil; MSI-H, high microsatellite instability; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; TKI, tyrosine kinase inhibitor; TMB-H, high tumor mutational burden; TPS, tumor proportion score; UC, urothelial carcinoma.

lymphoma, gynecologic, gastrointestinal (GI), and select tumor-agnostic indications. These indications are summarized in Table 56–2.

Skin Cancers

Two phase III trials supported the approval of nivolumab in refractory unresectable or metastatic melanoma, as well as first-line treatment for patients with metastatic melanoma. A phase III study of nivolumab in advanced melanoma after ipilimumab achieved an objective response rate (ORR) of 31.7% for nivolumab versus 10.6% for chemotherapy alone.[19] Another trial in previously untreated metastatic melanoma without BRAF mutation showed an improved 1-year OS in patients treated with nivolumab (72.9%) compared with dacarbazine (42.1%), with a subgroup analysis showing survival advantage regardless of PD-L1 expression status on tumor cells.[20] In the adjuvant setting, a phase III study comparing nivolumab with ipilimumab demonstrated improved 12-month recurrence-free survival (70.5%; 95% confidence interval [CI], 66.1–74.5) compared with ipilimumab (60.8%; 95% CI, 56.0–65.2).[21]

Pembrolizumab has also been approved for melanoma in the metastatic or unresectable as well as the adjuvant setting. A randomized phase III trial of frontline pembrolizumab versus ipilimumab yielded 1-year estimates of survival of 74.1% for pembrolizumab and 58.2% for ipilimumab, with lower rates of high-grade toxicity with pembrolizumab.[22] A subsequent post-hoc analysis after a median follow-up period of 57.7 months reported a median OS of 32.7 months (95% CI, 24.5–41.6) for pembrolizumab versus 15.9 months (95% CI, 13.3–22.0) for ipilimumab. In the adjuvant setting for high-risk, completely resected stage III melanoma, 1 year of pembrolizumab was compared with placebo; at a median follow-up of period 15 months, the 1-year recurrence-free survival rate was 75.4% (95% CI, 71.3–78.9) with pembrolizumab versus 61.0% (95% CI, 56.5–65.1) with placebo.[23]

Immune checkpoint therapy (ICT) has transformed the care of other cutaneous malignancies for which the treatment landscape has historically been limited. In metastatic Merkel cell carcinoma, both the anti–PD-1 pembrolizumab (as well as in locally advanced disease) and the anti–PD-L1 avelumab are FDA approved.[24–26] Finally, the anti–PD-1 mAbs cemiplimab and pembrolizumab have been FDA approved in advanced cutaneous squamous cell carcinoma, a disease that previously lacked any approved systemic therapies.[27–29]

Genitourinary Cancers

As a single agent, nivolumab is approved for advanced or metastatic renal cell carcinoma (RCC) in the second-line setting after antiangiogenic therapy. In a phase III trial of nivolumab versus everolimus, OS was 25.0 months with nivolumab (95% CI, 21.8 to not estimable) versus 19.6 months with everolimus (95% CI, 17.6–23.1). Anti–PD-1 combinations with anti–CTLA-4 mAbs or tyrosine kinase inhibitors (TKIs) for RCC are discussed section later.[30]

For urothelial carcinoma, five anti–PD-(L)1 therapies have been approved. Pembrolizumab was initially approved in the second-line setting after

platinum-based chemotherapy. In a phase III study, patients with recurrent or progressive advanced urothelial carcinoma after platinum-based chemotherapy pembrolizumab demonstrated a survival advantage over investigator's choice chemotherapy (hazard ratio [HR] for death, 0.73; 95% CI, 0.37–0.88; $P = .005$).[31] Pembrolizumab also gained additional indications in the first line for locally advanced or metastatic, cisplatin-ineligible urothelial carcinoma with a PD-L1–expression combined positive score (CPS) of 10% or greater and for high-risk, non–muscle-invasive bladder cancer unresponsive to BCG with or without papillary tumor.[32–35] Nivolumab has also been approved in the second-line setting after platinum-based therapy.[36]

The anti–PD-L1 mAb atezolizumab is approved for patients with locally advanced and metastatic urothelial carcinoma who are cisplatin ineligible and whose tumors express PD-L1 (with PD-L1–infiltrating immune cells ≥5% of tumor area), in cisplatin-ineligible patients regardless of PD-L1 status, and in the second line after platinum-based chemotherapy. In a phase III trial of platinum-treated locally advanced or metastatic urothelial carcinoma, atezolizumab was compared with physician's choice chemotherapy with a primary endpoint of OS tested hierarchically in prespecified populations by PD-L1 expression status. No difference in OS was observed, although the safety profile for atezolizumab was favorable compared with chemotherapy.[37,38] Two other anti–PD-L1 mAbs, avelumab and durvalumab, have also been approved in second-line urothelial carcinoma.[39,40] More recently, avelumab garnered an indication for maintenance treatment after platinum-based first-line therapy on the basis of a phase III study demonstrating an OS of 21.4 months vs 14.3 months for best supportive care (HR, 0.56; 95% CI, 0.40–0.79; $P = .0003$).[41]

Lung Cancers

Whereas ICT was initially approved in non–small cell lung cancer (NSCLC), FDA indications have now expanded to include small cell lung cancer (SCLC) as well. ICT and chemotherapy combinations are discussed in subsequent sections. For nivolumab, phase III clinical trials in both squamous and nonsquamous NSCLC demonstrated survival advantage versus docetaxel chemotherapy after progression after first-line chemotherapy.[42,43] In these FDA approvals, patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should have had disease progression on approved targeted therapy before receiving nivolumab. Notably, a phase III trial comparing first-line nivolumab with platinum-based chemotherapy in patients with PD-L1–positive (≥5%) NSCLC did not demonstrate a difference in progression-free survival (PFS).[44] Nivolumab has also been approved for metastatic SCLC in patients with progression after platinum-based therapy and at least one other line of therapy.[45]

Pembrolizumab monotherapy has been FDA approved for metastatic NSCLC in patients with tumors with PD-L1 expression tumor proportion score (TPS) 1% or greater, both in the first line and in subsequent lines after platinum-based chemotherapy (with targeted treatment for patients with EGFR or ALK aberrations as indicated), as well as in patients with stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation. In a phase II/III study of pembrolizumab versus docetaxel in previously treated patients with advanced NSCLC (squamous and nonsquamous) with PD-L1 TPS of 1% or greater, improved survival with pembrolizumab was observed, including in patients with TPS of 50% or greater.[46] In the frontline setting, a phase III trial of pembrolizumab versus platinum doublet therapy in patients with PD-L1 TPS of 50% or greater showed a median OS was 30.0 months with pembrolizumab (95% CI, 18.3 to not reached) versus 14.2 months with chemotherapy (95% CI, 9.8–19.0) at a median follow-up period of 25.2 months.[47] Additionally, a phase III trial of frontline pembrolizumab versus platinum-based chemotherapy in patients with locally advanced or metastatic NSCLC with PD-L1 TPS of 1% or greater also demonstrated improvement in OS.[48] Pembrolizumab has also been approved by the FDA for patients with metastatic SCLC with progression on or after platinum-based therapy and at least one other line of therapy.[49]

Anti–PD-L1 therapies have also garnered approval in the treatment of patients with metastatic NSCLC. A phase III trial compared atezolizumab versus docetaxel and showed an OS benefit in the intention-to-treat population for atezolizumab (median OS, 13.8 months; 95% CI, 11.8–15.7 months) versus docetaxel (9.6 months; 95% CI. 8.6–11.2 months).[50,51] In the front line setting, a phase III trial of patients with metastatic NSCLC and PD-L1 expression on tumor or immune cells of 1% or greater demonstrated a statistically significant improvement in OS compared with platinum-chemotherapy in patients with high PD-L1 expression (20.2 months vs 13.1 months; HR, 0.59; 95% CI, 0.40–0.89; $P = .0106$).[52] Finally, the anti–PD-L1 mAb durvalumab carries a unique indication in patients with NSCLC as adjuvant treatment after concurrent chemoradiation for locally advanced, unresectable stage III disease that has not progressed after two to three cycles of chemoradiation. In a phase III study, consolidation therapy for 1 year (durvalumab vs placebo) after chemoradiation demonstrated a median PFS of 16.8 months in the durvalumab arm (95% CI, 13.0–18.1) versus 5.6 months in the placebo arm (95% CI, 4.6–7.8).[53]

Head and Neck Cancers

Pembrolizumab was initially FDA approved for the recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with progression on chemotherapy in a phase 1b study.[54,55] In previously untreated patients, a phase III trial in recurrent or metastatic HNSCC randomized one to one to one to pembrolizumab versus pembrolizumab plus chemotherapy (platinum and fluorouracil) versus cetuximab plus chemotherapy with improvements in OS in both the pembrolizumab combination and single-agent pembrolizumab arms, leading to the approval of pembrolizumab alone or in combination for patients with PD-L1 CPS of 1 or greater.[56] Nivolumab has also been approved for platinum-refractory recurrent squamous cell carcinoma of the head and neck. A phase III trial of nivolumab versus single-agent systemic therapy after platinum-based chemotherapy demonstrated an OS of 7.5 months for nivolumab compared with OS of 5.1 months with standard single-agent therapy.[57]

Gastrointestinal and Hepatobiliary Cancers

In hepatocellular carcinoma (HCC), both nivolumab and pembrolizumab have been approved after prior sorafenib.[58,59] Notably, although a phase III trial of pembrolizumab versus placebo in second-line HCC showed improvement in OS (13.9; [95% CI, 11.6–16.0] vs 10.6 months; [95% CI, 8.3–13.5]), it did not reach the prespecified criteria for statistical significance.[60] In gastric cancer, pembrolizumab is approved for previously treated patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 (CPS ≥1). In a phase III trial of first-line pembrolizumab or pembrolizumab plus chemotherapy versus chemotherapy in patients with PD-L1 CPS 1 or greater, HER-2–negative advanced gastric cancer, pembrolizumab was found to be noninferior to chemotherapy for OS per prespecified margins, although the combination was not superior to chemotherapy alone.[61,62] For esophageal cancer, pembrolizumab has been approved for recurrent locally advanced or metastatic squamous cell carcinoma with PD-L1 positivity (CPS ≥10) and disease progression after one or more prior lines of systemic therapy.[63] In a phase III trial of second-line pembrolizumab versus investigator's choice chemotherapy (paclitaxel, docetaxel, or irinotecan), pembrolizumab demonstrated an OS benefit in patients with CPS of 10 or greater (9.3 months vs 6.7 months; HR, 0.69; 95% CI, 0.52–0.93; $P = .0074$).[64] Finally, in colorectal cancer, to date, the benefit of anti–PD-1 therapy has been limited to the high microsatellite instability (MSI-H) and deficient mismatch repair (dMMR) population. Both nivolumab and pembrolizumab are approved for MSI-H and dMMR colorectal cancer that as progressed after treatment with fluoropyrimidine and oxaliplatin or irinotecan.[65,66]

Other Cancers and Tumor-Agnostic Indications

ICTs have made headway in certain hematologic malignancies, notably in Hodgkin lymphoma, in which Reed-Sternberg cells have frequent amplification of chromosome 9p24.1, leading to overexpression of PD-L1. A phase I study of nivolumab in relapsed or refractory Hodgkin lymphoma demonstrating an ORR of 87% led to the approval in classical Hodgkin lymphoma for patients who have relapsed or progressed after autologous hematopoietic stem cell transplant and brentuximab vedotin or after three or more lines of systemic therapy that included autologous stem cell transplant.[67] Pembrolizumab also demonstrated activity in heavily pretreated patients and has been approved for refractory or relapsed classical Hodgkin lymphoma after three or more prior lines of therapy.[68] In non-Hodgkin lymphoma, pembrolizumab demonstrated activity in primary mediastinal large B-cell lymphoma and has been approved for patients with refractory disease or who have relapsed after two or more prior lines of therapy.[69] In gynecologic malignancies, pembrolizumab has been FDA approved for recurrent or metastatic cervical cancer in patients who tumors express PD-L1 with a CPS of 1 or greater, with disease progression on or after chemotherapy.[70]

Finally, in 2017, pembrolizumab garnered the first tumor-agnostic approval of a cancer treatment based on a common biomarker for unresectable and metastatic solid tumors with dMMR. In a phase II trial, 41 patients with progressive metastatic carcinoma with or without dMMR were treated with pembrolizumab, with objective response rates of 40% for dMMR colorectal cancers, 71% for dMMR noncolorectal cancer, and 0% in mismatch repair proficient colorectal cancer.[71] In a subsequent study across 12 tumor types, objective responses were observed in 53% of patients, with complete responses (CRs) in 21% of patients.[72] Pembrolizumab has also been approved for patients with high tumor mutational burden (TMB), defined as 10 mutations/megabase, on the basis of a preplanned analysis of patients in a phase II basket study of advanced solid tumors, in which the ORR was 29% (95% CI, 21–39), with 4% complete response (CR) and 25% partial response (PR) rates.[73]

Combination Anti–CTLA-4 and Anti–PD-(L)1

Because anti–CTLA-4 and anti–PD-1 target distinct inhibitory pathways in T-cells, preclinical studies have shown that concurrent targeting of CTLA-4 and PD-1 can improve therapeutic efficacy when compared to

the monotherapies.[74–76] The combination of ipilimumab and nivolumab has now been FDA approved for patients with melanoma (metastatic or unresectable), HCC, RCC, and colorectal cancer (metastatic, microsatellite unstable, or dMMR).

In a phase III trial comparing ipilimumab, nivolumab, and the combination in patients with untreated, unresectable or metastatic melanoma, the combination demonstrated statistically superior survival.[77] In the long-term follow-up, the estimated 5-year OS was 52% for the combination versus 44% for nivolumab and 26% for ipilimumab.[78] In advanced or metastatic clear cell RCC (intermediate or poor risk), the combination of ipilimumab and nivolumab was compared with sunitinib. A median follow-up period of 25.2 months demonstrated an 18-month OS rate of 75% with nivolumab plus ipilimumab and 60% with sunitinib and ORR of 42% versus 27% with CR rate of 9% versus 1%.[79] These findings were confirmed with extended follow-up (median, 32.4 months).[80] In patients with HCC previously treated with sorafenib, ipilimumab plus nivolumab demonstrated activity with an ORR of 31% and 24 months OS of 40%.[81] In a phase III study of metastatic or recurrent NSCLC, ipilimumab plus nivolumab was compared with chemotherapy and demonstrated an OS of 17.1 months (95% CI, 15.2–19.9) with the combination versus 13.9 months (95% CI, 12.2–15.1) for chemotherapy.[82] Finally, the combination of ipilimumab and nivolumab has also been approved by the FDA for patients with previously treated MSI-H or dMMR metastatic colorectal cancer on the basis of a trial showing an ORR of 55%, with a disease control rate for 12 weeks or longer of 80%.[83] Combination anti–CTLA-4 and anti–PD-(L)1therapy is currently under active investigation for a range of tumor types.

Combination Immune Checkpoint Therapy and Chemotherapy

ICT in combination with chemotherapy has demonstrated benefit in at least four tumor types to date: NSCLC, SCLC, HNSCC, and triple-negative breast cancer. A phase III clinical trial tested chemotherapy (cisplatin or carboplatin with pemetrexed) with or without pembrolizumab as a first line in patients with PD-L1–unselected, nonsquamous NSCLC lung cancer without driver mutations and demonstrated a 12-month OS of 69.2% in the pembrolizumab-combination group versus 49.4% in the placebo-combination group (HR, 0.49; 95% CI, 0.38–0.64; P <.001).[84] Another phase III trial tested chemotherapy (carboplatin with either paclitaxel or nab-paclitaxel) with pembrolizumab or placebo in PD-L1–unselected patients with squamous NSCLC population. This trial demonstrated an improvement in the co-primary endpoints of OS and PFS for the combination arm (OS, 15.9 months vs 11.3 months, HR, 0.64; 95% CI, 0.49–0.85, P <.001; PFS, 6.4 months vs 4.8 months; HR for progression or death, 0.56; 95% CI, 0.45–0.70; P <.001), leading to approval.[85] Atezolizumab in combination with chemotherapy has also been studied in two phase III trials of patients with NSCLC. A phase III study of carboplatin, paclitaxel, and bevacizumab with and without atezolizumab in PD-L1–unselected nonsquamous NSCLC demonstrated improvements in PFS and OS (19.2 vs 14.7 months; HR for death, 0.78; 95% CI, 0.64–0.96) for the atezolizumab arm.[86] Additionally, a phase III trial comparing chemotherapy (carboplatin, nab-paclitaxel) with or without atezolizumab demonstrated improvement for the combination in OS (18.6 months [95% CI, 16.0–21.2] vs 13.9 months [95% CI, 12.0–18.7]) and PFS (7.0 months [95% CI, 6.2–7.3] vs 5.5 months [4.4–5.9]).[87]

In extensive-stage SCLC, a phase III study of atezolizumab with or without carboplatin–etoposide (induction phase) followed by a maintenance phase of atezolizumab or placebo demonstrated, at a median follow-up of period 13.9 months, median OSs were 12.3 months for atezolizumab and 10.3 months for placebo (HR for progression or death, 0.77; 95% CI, 0.62–0.96; P = .02), leading to the approval of this combination.[88] The anti–PD-L1 mAb durvalumab has also been approved for extensive-stage SCLC in combination with platinum chemotherapy and etoposide. In a phase III clinical trial, patients with untreated extensive-stage SCLC were randomized to platinum–etoposide and either durvalumab alone or in combination with the anti–CTLA-4 mAb tremelimumab. In a planned interim analysis, durvalumab plus platinum–etoposide prolonged median OS compared with chemotherapy alone (13.0 months [95% CI, 11.5–14.8] vs 10.3 months [95% CI, 9.3–11.2; HR, 0.73 95% CI, 0.59–0.91; P = .0047]).[89]

In triple-negative breast cancer, the combination of atezolizumab and nab-paclitaxel was approved in patients with PD-L1 tumor-infiltrating immune cell staining of 1% or greater on the basis of a phase III trial of nab-paclitaxel with or without atezolizumab showing significant improvement with the combination in PFS (7.2 vs 5.5 months, HR, 0.62; 95% CI, 0.49–0.78; P <.001) and an OS benefit in PD-L1 positive patients (25.0 vs 15.5 months; HR for death, 0.62; 95% CI, 0.45–0.86).[90] Finally, in HNSCC, the combination of pembrolizumab with fluoropyrimidine and platinum-based chemotherapy has been approved, as described earlier.[56]

Combination Immune Checkpoint Therapy and Targeted Therapy

ICT in combination with targeted therapy has been well-studied in patients with RCC, with two approvals for the TKI axitinib with either pembrolizumab or

avelumab. A phase III trial in first-line advanced RCC compared pembrolizumab plus axitinib versus sunitinib and demonstrated improved OS in the entire study population (18-month OS, 82% vs 72% with the combination), most notably in intermediate- or poor-risk disease.[91] On the other hand, when first-line avelumab in combination with axitinib was compared with sunitinib in a phase III trial, an improvement in PFS was observed with the combination (13.8 vs 8.4 months).[92] The combination of atezolizumab and bevacizumab has been studied in the frontline setting in a phase III trial versus sorafenib testing the co-primary endpoints of OS and PFS; the 12-month OS was 67.2% with bevacizumab versus 54.6% with sorafenib (HR, 0.58; 95% CI, 0.42–0.79; $P<.001$), and median PFS was 6.8 months versus 4.3 months, respectively (HR for progression or death, 0.59; 95% CI, 0.47–0.76; $P<.001$). Additionally, a major area of interest in melanoma is the combination of ICT with BRAF and MEK inhibition. In a phase III study of vemurafenib and cobimetinib with or without atezolizumab, the addition of atezolizumab prolonged PFS at a median follow-up period of 18.9 months: 15.1 months for atezolizumab versus 10.6 months for control (HR, 0.78; 95% CI, 0.63–0.97; $P = .025$).[93] Finally, in endometrial carcinoma, the combination of pembrolizumab with lenvatinib has demonstrated activity and earned FDA approval.[94]

Biomarkers of Response to Immune Checkpoint Therapy

Despite the substantial clinical success of immune checkpoint therapies, including durable responses in certain patients, only subsets respond to therapy. Therefore, considerable effort is underway to identify predictive biomarkers to optimize patient selection for therapy. Broadly speaking, categories of putative biomarkers under study include (1) target expression (eg, surface expression of PD-L1), (2) tumor-specific features (eg, TMB), (3) tumor microenvironment, and (4) host features (eg, the gut microbiome).[95]

With respect to target expression, the assay most often used is PD-L1 expression on tumor and/or immune cells by immunohistochemistry. Although a number of studies have demonstrated that PD-L1 expression on tumor cells correlates with clinical response across multiple tumor types (eg, urothelial cancer and NSCLC), other studies have demonstrated conflicting results, with significant response rates in certain patients with PD-L1–negative tumors.[38,96,97] Additionally, PD-L1 is not a static marker; therefore, variations in time and area of sampling may also influence the level of PD-L1 expression. Dynamic biomarker assessments, such as the observation that sustained inducible T-cell co-stimulatory (ICOS) expression on CD4 T-cells correlates with survival of melanoma patients treated with anti–CTLA-4 therapy represents one potential path forward.[98] Therefore, although these assays have been approved as companion diagnostics, differences in antibodies, tissue handling techniques, and thresholds have limited the uniform application of PD-L1 expression as a predictive biomarker for ICT.[95]

A number of tumor-intrinsic biomarkers have been explored, including TMB and neoantigen load, DNA damage repair (DDR) pathways, viral infections (eg, Merkel cell polyoma virus), MHC expression, and transcriptional signatures.[95] High TMB has been associated with response to ICT in several cancer types, including melanoma and NSCLC, potentially because of the formation of neoantigens that are recognized by the immune system and may be met with compensatory upregulation of inhibitory immune checkpoints by the tumor cell.[99,100] As described earlier, pembrolizumab has now been approved for TMB-high tumors across tumor types.[73] Intriguingly, however, certain tumor types with a low TMB have been associated with high response rates to ICT, such as clear cell RCC, implying that TMB must be considered in the context of other potential biomarkers.[101] Further areas of investigation into TMB as a predictive biomarker include validation of thresholds of TMB, assay development, and deeper understanding of the immunogenicity of different mutations.[95] Although a number of bioinformatics algorithms are available to predict potential immunogenic neoantigens from mutations and human leukocyte antigen (HLA) phenotype, these have not yet been shown to be clearly superior to TMB.[95] In addition, DDR pathways play a key role in response to ICT, as described earlier with the tumor-agnostic approval of pembrolizumab in dMMR and MSI-H patients.[72] Other repair defects associated with response to ICT that have been reported include the DNA polymerases POLE and POLD1[102,103] and those with defects in homologous-recombination DNA repair, such as BRCA1/2, in which the generation of double-stranded breaks and release of cytosolic DNA can lead to activation of cGAS-STING, promotion of type I interferon (IFN) signaling, and upregulation of PD-L1.[104–106]

The tumor microenvironment is also a critical avenue of exploration for biomarker development. Increased tumor-infiltrating lymphocytes (TILs) have been associated with response to ICT in melanoma and in breast cancer.[107,108] Notably, a spectrum of tumor-infiltrating T-cell populations have been identified, with evidence indicating that ICT targets specific subsets of these infiltrating cells.[75] Anti–PD-1 therapy has been demonstrate to induce expansion of specific tumor-infiltrating exhausted-like CD8 T-cell subsets, whereas anti–CTLA-4 therapy has been shown to induce expansion of ICOS+ Th1-like CD4 effector cells, as well as engaging subsets of exhausted-like CD8

T-cells.[75] Classification systems have been proposed incorporating PD-L1 expression and TILs, though these require clinical validation.[109] Beyond the T-cell compartment, B cells and tertiary lymphoid structures have also been found to be associated with response to ICT in patients with melanoma and RCC.[110] Several transcriptional signatures have also been identified that are associated with response to ICT, such as markers of IFN-γ signaling.[111,112]

Finally, host factors independent of the primary tumor are also emerging, including the gut microbiome, systemic immune elements, and germline genetic polymorphisms.[95] In one study of patients with melanoma, a significant association was observed between response to anti–PD-1 therapy and commensal microbial composition, including *Bifidobacterium longum, Collinsella aerofaciens,* and *Enterococcus faecium*.[113] A separate study similarly demonstrated significant differences in the diversity and composition of the gut microbiome in patients with melanoma who responded to anti–PD-1 versus those who did not.[114] These findings have raised the possibility that modulation of the gut microbiome, perhaps through fecal microbiota transplantation, may offer an avenue to improve response to ICT. Other elements of host immunity in circulating immune cells have been identified as possible biomarkers; in one study, distinct subsets of CD4 and CD8 memory T-cell subsets were associated with response to anti–CTLA-4.[115] Overall, biomarkers of response to ICT are a highly active area of investigation, and further understanding of mechanisms, genetic backgrounds and interactions of host and tumor immunity will inform future development to enable improved patient selection.

Other Inhibitory Checkpoints

Beyond CTLA-4 and PD-1/PD-L1, a range of other inhibitory checkpoints are under active investigation and are briefly discussed here. Lymphocyte activation gene 3 (LAG-3) is expressed on T-cell subsets, B cells, DCs, and natural killer (NK) cells and is co-expressed with PD-1 on activated T-cells, providing a potential rational for combination with PD-1–directed therapy. LAG-3 shares homology with CD4, and it is hypothesized that it interacts with MHC class I to regulate T-cell responses.[116] Early clinical studies of the anti–LAG-3 mAb relatlimab (BMS-986016) in combination with nivolumab in patients with melanoma previously treated with immunotherapy demonstrated encouraging responses and is currently being investigated in a phase III clinical trial (NCT03470922).[117] Anti–LAG-3 mAbs are currently being studied in a range of tumor types.[118]

V-domain Ig suppressor of T-cell activation (VISTA) is an immune checkpoint highly expressed on myeloid cells (eg, macrophages, DCs, monocytes, neutrophils) and moderately expressed on regulatory T-cells (Tregs).[119] VISTA suppresses T-cell activation, and in preclinical models, VISTA blockade has been shown to improve antitumor immunity.[120] Upregulation of VISTA on macrophages in response to anti–CTLA-4 therapy with ipilimumab has been identified as a possible mechanism of resistance to immunotherapy in prostate cancer.[121] Anti-VISTA mAbs are currently under clinical development, with early-phase trials underway.[122] T-cell Ig and mucin domain–containing-3 (TIM-3) is another inhibitory receptor expressed on T-cell subsets and DCs—TIM3+ T-cells have been shown to display an exhausted phenotype, and targeting TIM-3 can restore the activated T-cell phenotype.[123] In a phase I study of the anti–TIM-3 antibody LY3321367 with or without anti–PD-L1 therapy, drug activity was observed, including one patient with SCLC after PD-1 treatment who achieved a PR.[124] Anti–TIM-3 mAbs under active clinical development. B7-H3 (CD276) is an immune checkpoint expressed on APCs whose receptor has yet to be defined and was initially thought to be a co-stimulatory checkpoint, though recent findings have pointed to its co-inhibitory functions.[125] Expression of B7-H3 on tumor cells has been identified as a possible mechanism of resistance to PD-1 blockade, and anti–B7-H3 antibodies are being tested in early-phase clinical trials.[126] Other inhibitory checkpoints under active investigation include TIGIT (T-cell immunoglobulin and ITIM domain) and BTLA (B- and T-lymphocyte attenuator).[127,128] In a phase I study of the anti-TIGIT mAb tiragolumab with or without atezolizumab, clinical activity was observed with the combination.[129] A phase II study of patients with newly diagnosed locally advanced or metastatic NSCLC with 1% or greater PD-L1 tumor expression (without *EGFR* or *ALK* alterations) reported an ORR of 37% and median PFS of 5.6 months with the combination versus 21% and 3.9 months with atezolizumab alone.[130] This combination is now being tested in a phase III study in patients with PD-L1–selected NSCLC (NCT04294810).

Co-stimulatory Checkpoints

As described earlier, T-cell activation requires two signals: (1) TCR engagement on T-cells with MHC molecules and (2) binding of co-stimulatory molecules on T-cells (eg, CD28) to B7 proteins (eg, CD80/CD86) on APCs. Thus, co-stimulatory agonism has also been explored as a potential therapeutic avenue. Initially, however, in a phase I trial of the anti-CD28 mAb TGN142, six healthy young patients experienced massive cytokine storm and multiorgan failure secondary to uncontrolled T-cell activation.[131] Since then, more precise targeting of T-cell activation has been sought,

specifically seeking to target co-stimulatory receptors that are expressed when T-cells are activated rather than constitutively expressed.

4-1BB/CD137 is an inducible co-stimulatory receptor that is expressed on activated T- and NK cells, promotes upregulation of antiapoptotic genes and protection from activation-induced cell death, and demonstrated promising preclinical efficacy.[132] In phase I trials, whereas the anti-CD137 antibody urelumab was associated with significant transaminitis, another anti-CD137 antibody, utomilumab, demonstrated a well-tolerated safety profile but an overall ORR of 3.8% across solid tumors.[133,134] Whereas OX40 is a late co-stimulatory receptor expressed transiently on activated CD4 and CD8 T-cells, the ligand OX40L is expressed on activated DCs, B cells, macrophages, activated T-cells, and endothelial cells.[135] OX40 functions to regulate T-cell survival, prevent T-cell tolerance, and inhibit regulatory T-cells. An antimouse OX40 demonstrated promising preclinical efficacy, and a phase Ib dose-escalation study of an OX40 agonist in combination with atezolizumab demonstrated acceptably safety but limited efficacy.[136,137] CD27 is expressed constitutively on naïve T-cells and has also been described on NK and B cells; its ligand is CD70.[138] The role of the CD27–CD70 axis in antitumor immunity has been identified—approximately one third of patients with germline deficiencies in CD27 or CD70 present with Hodgkin lymphoma or diffuse large B-cell lymphoma (DLBCL), and somatic alteration in CD27 or CD70 are often observed in patients with DLBCL or Burkitt lymphoma.[138] Varlilumab is an antihuman CD27 mAb that induced CD8 T-cell–dependent tumor rejection in human-CD27 transgenic mice and has demonstrated activity in a phase I clinical trial.[138] Glucocorticoid-induced tumor necrosis factor receptor (TNFR) (GITR) is constitutively expressed at high levels on Tregs and low levels on naïve and memory T-cells; T-cell activation leads to increased GITR expression on both regulatory and effector T-cells.[139] The GITR ligand is predominantly expressed by APCs, including DCs, macrophages, and activated B cells.[139] A phase I trial of a GITR agonist (TRX518) demonstrated limited efficacy as monotherapy, although it was found to reduce circulating and intratumoral Treg cells and increase effector T cell (Teff)-to-Treg ratio, prompting a subsequent study in combination with PD-1 inhibition.[140,141]

Finally, ICOS is a member of the CD28 and CTLA-4 family expressed on activated T-cells. ICOS interacts with its ligand (ICOSL) on APCs to provide a co-stimulatory signal for proliferation and activation.[142] In murine models of melanoma and prostate cancer, concomitant CTLA-4 blockade and ICOS engagement enhanced antitumor immune resposnes.[143] Anti–CTLA-4 therapy was shown to result in higher frequency of ICOS expressing CD4 T-cells in nonmalignant and malignant prostate tissue.[144] Moreover, in ipilimumab-treated patients with melanoma, persistent ICOS upregulation on CD4 T-cells was associated with improved clinical outcomes.[145] Multiple clinical trials are currently testing ICOS agonist alone and in combination with anti–CTLA-4 or anti–PD-1 therapy.[146,147] Overall, targeting co-stimulatory checkpoints represents a promising avenue in cancer immunotherapy, which will require careful patient selection and biomarker development.

Response Assessment with Immune Checkpoint Therapy

The distinct mechanisms of action of ICT compared with chemotherapy have required evolution in assessment of tumor responses. In the initial trials of ICT, patterns of response were observed that resembled traditional tumor flare but then subsequently developed deep and durable responses, a phenomenon deemed pseudoprogression.[148] These observations have led to the development of modified criteria for response assessment, such as immune-related response criteria (irRC),[149] immune-modified Response Evaluation Criteria in Solid Tumours (imRECIST)[150] and immune response evaluation criteria in solid tumors (iRECIST).[148] A pooled FDA analysis of lesion measurements for 7920 patients receiving ICT or chemotherapy from 14 randomized controlled trials demonstrated that patients with initial progressive disease per standard RECIST v1.1 can have prolonged stability or reduction in tumor burden per iRECIST, which can be associated with improved OS.[151] Similarly, a retrospective evaluation of atezolizumab data from clinical trials of NSCLC, RCC, melanoma, and urothelial carcinoma demonstrated that imRECIST captured a 1% to 2% greater best overall response, 8% to 13% greater disease control rate, and 0.5- to 1.5-month longer median PFS versus RECIST v.1.1.[150] Emerging techniques in imaging for immunotherapy include volumetric imaging, dynamic contrast imaging, and quantitative imaging biomarkers that may be able to identify T-cell infiltration of tumors.[152]

Immune-Related Adverse Events

Although ICT induces T-cell–mediated antitumor responses, they also carry the risk of breach of immune self-tolerance mechanisms, leading to inflammation of normal tissue, termed *immune-related adverse events (irAEs)*. These irAEs can affect a wide spectrum of organs, most commonly the skin, GI tract, lungs, and endocrine system (thyroid, adrenal, pituitary), but can also have musculoskeletal, renal, ocular, cardiovascular, neurologic, and hematologic effects (Fig. 56–2). These effects can range from sufficiently mild that ICT can be continued, to severe, requiring hospitalization,

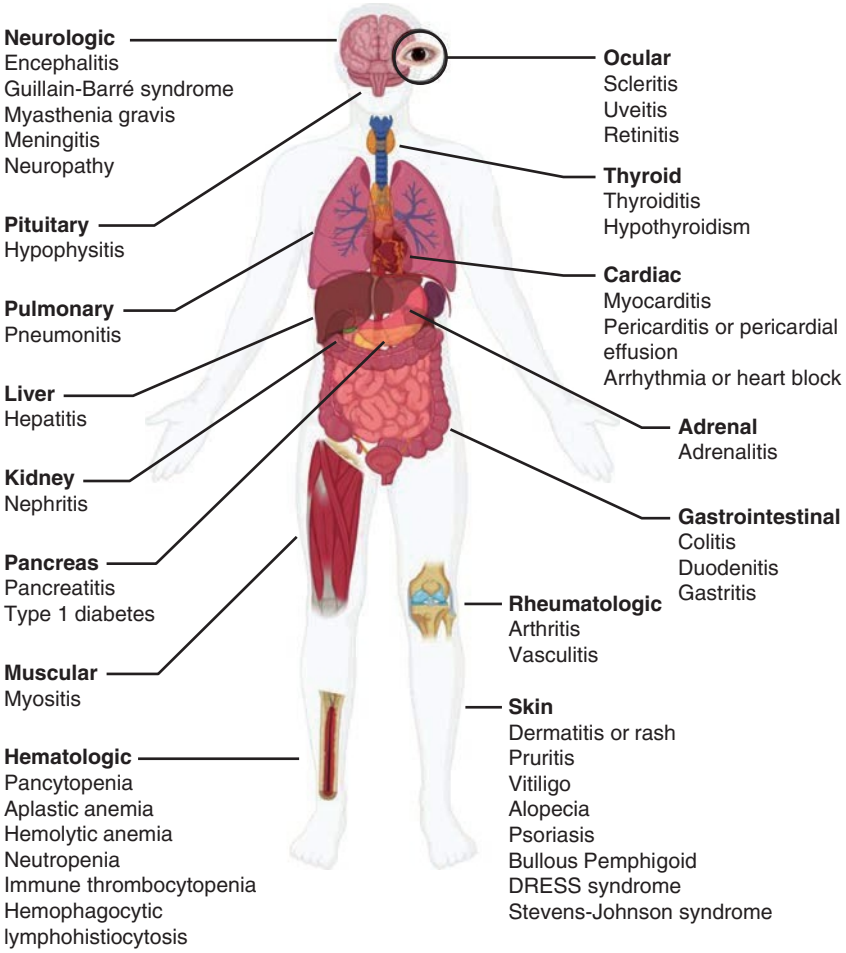


FIGURE 56–2 **Distribution of immune-related adverse events. DRESS, drug rash with eosinophilia and systemic symptoms.**

and even fatal. Prompt recognition and early intervention for irAEs, with close multidisciplinary collaboration is essential. Management of irAEs is an active area of investigation, with a number of studies underway investigating ICT rechallenge, identification of biomarkers to predict toxicity, and determining immunological mechanisms of irAEs, including the possibility of decoupling antitumor immunity from autoimmune toxicity.[153,154]

General principles of irAE management and an overview of selected toxicities are outlined here; detailed clinical guidelines for each toxicity are reviewed elsewhere.[155] Overall, a high index of suspicion is key in recognizing the emergence of irAEs. For most grade 1 events (as defined by the Common Terminology Criteria for Adverse Events v. 5.0), ICT is able to be continued, with the exception of certain cardiac, neurologic, and hematologic toxicities.[155] Grade 2 toxicities usually warrant interrupting ICTs and treatment with corticosteroids (at an initial dosage of 0.5–1 mg/kg/day of prednisone or equivalent), with resumption of ICT when the toxicity returns to grade 1 or greater.[155] Grade 3 toxicities warrant high-dose corticosteroids in addition to withholding ICT and often involve specific therapies (briefly described later). Although many guidelines advocate for prolonged steroid taper over 4 to 6 weeks, prolonged corticosteroids are associated with iatrogenic side effects, including myopathy, hyperglycemia, and infection risk; therefore, steroid-sparing approaches are under active investigation. Grade 4 toxicities usually warrant permanent cessation of ICT, with the exception of certain endocrinopathies that are controlled with hormone replacement.[155] Intriguingly, in a retrospective study of 346 patients at MD Anderson Cancer Center (MDACC) with metastatic melanoma, the occurrence of any grade GI irAEs was associated with improved OS, independent of immunosuppression, highlighting the careful balance between immune activation and tolerance inherent in ICT.[156]

ICT-associated enterocolitis most commonly presents as watery diarrhea, associated with abdominal pain, blood or mucous in stool, distension, nausea, vomiting, and fever, with a spectrum of severity that can range from self-limited, nonbloody diarrhea to perforation and even death.[157] Although the typical presentation of enterocolitis occurs approximately 5 to 10 weeks after initiation of ICT, the range is wide and can occur after the first dose or more than 6 months after cessation of ICT and can be acute or gradual.[157,158] Treatment of patients with ICT-associated enterocolitis generally matches the principles outlined earlier, with interruption of ICT for grade 2 or greater toxicity and introduction of corticosteroids. In more severe cases, adjunctive treatments in addition to corticosteroids have been studied, including the anti–tumor necrosis factor-α (TNF-α) mAb infliximab and the anti-$\alpha_4\beta_7$ integrin mAb vedolizumab; early introduction of targeted immunosuppression has been associated with favorable clinical outcomes compared to those who received targeted therapy more than 10 days after onset of toxicity, including fewer hospitalizations, shorter course of steroids, lower rate of steroid taper failure, and shorter duration of symptoms.[159] For refractory cases, fecal microbiota transplantation is emerging as a promising therapeutic approach.[160]

ICT-associated myocarditis is a feared complication of therapy that can result in fulminant cardiomyopathy, hemodynamic instability, and cardiac arrest.[161] The reported incidence of ICT-associated myocarditis is less than 1%; however, this may be an underestimation because of the possibility of subclinical cases of myocarditis.[162] A safety database report of 20,594 patients who received ipilimumab, nivolumab, or both reported an incidence of severe myocarditis in 0.09% of patients, with a rate of 0.27% in patients who received combination therapy.[161] The median time to developing myocarditis after the first treatment has been reported at 17 days but may range from 2 to 32 weeks after initiation of threatment.[162] The clinical spectrum of cardiotoxicity includes myocarditis and frank cardiomyopathy but also pericarditis and pericardial effusion, QTc prolongation and advanced heart block, and hypertension.[162] Notably, case series have identified an overlap syndrome of cardiac and neuromuscular toxicities encompassing myositis and myasthenia gravis in addition to myocarditis.[163–165] Guidelines for the management of myocarditis currently recommend holding ICT for grade 1 toxicity and permanent discontinuation if greater than grade 1, given the high risk of progression to fulminant toxicity and death.[155] Initial management remains high-dose corticosteroids.[162] In refractory cases, addition of adjunct immunosuppression has been explored, including infliximab.[162] Additionally, case reports have demonstrated success in refractory cases with the CTLA-4 Ig fusion protein abatacept as well as anti-CD52, alemtuzumab.[166,167]

CELLULAR THERAPY

Because immune effector cells, such as CD8 T-cells, are some of the primary mechanisms of tumor killing, cellular therapy seeks to directly harness these cells to recognize and eliminate tumor cells. This section briefly reviews adoptive cellular therapy with tumor-infiltrating lymphocytes and CAR T-cells, as well as highlighting emerging areas of research, including CAR NK cells.

Adoptive T-Cell Therapy

Adoptive T-cell therapy (ACT) involves transfer of autologous TILs to the tumor-bearing host.[168,169] Preparation of cells involves isolation and ex vivo rapid expansion of TILs from tumor followed by infusion of large numbers of expanded autologous TILs as depicted in Figure 56–3. TIL therapy has demonstrated objective response rates ranging from 40% to 70%, with durable CRs reported in certain heavily pretreated patients with metastatic melanoma.[169,170] The efficacy of TIL therapy is boosted through combination with interleukin-2 (IL-2) and through the development of preconditioning chemotherapy regimens, such as those incorporating cyclophosphamide and fludarabine. ACT has encountered challenges in clinical practice, including factors relating to difficulties in generating appropriate products for adoptive transfer, factors relating to host or tumor resistance to transferred populations, and off-tumor toxicity with associated treatment-related morbidity and mortality. Furthermore, TIL therapy has been shown to be particularly beneficial in patients pretreated with other immunotherapy agents such as IL-2 or checkpoint blockade such as anti–CTLA-4.[169]

Chimeric Antigen Receptor T-Cells

CAR T-cells are engineered to increase the affinity of T-cell to the tumor antigen and contain a synthetic antigen receptor with specificity to a tumor cell marker coupled with T-cell signaling domain, resulting in high-affinity recognition of the tumor antigen.[171] Therefore, CAR T-cells are particularly effective against tumors in which the tumor antigen is well-defined. The manufacturing process for CAR T-cells involves leukapheresis for collection and enrichment of CD3 T-cells, transduction with viral CAR construct and ex vivo CAR T-cell expansion, conditioning chemotherapy (most

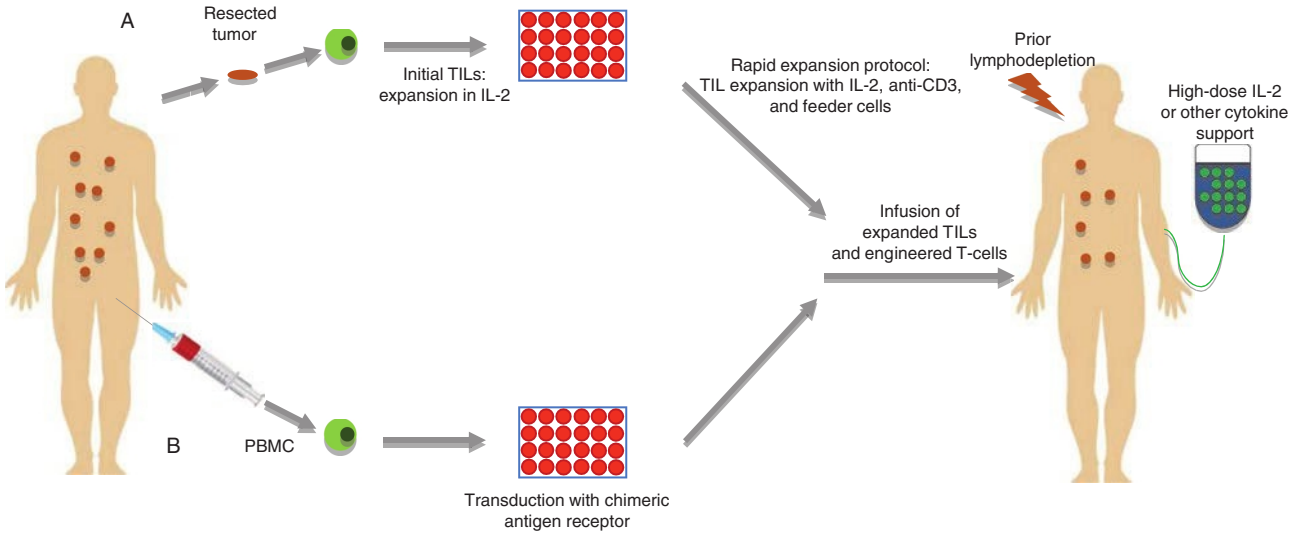


FIGURE 56–3 Adoptive T-cell therapy. There are currently two major sources of T-cells used in adoptive cell therapy for melanoma and other cancers. A. The first form of therapy uses tumor-infiltrating lymphocytes (TILs) expanded ex vivo from surgically resected metastatic tumors. The TILs are initially expanded ex vivo using anti-CD3 activation in the presence of irradiated peripheral blood mononuclear cell (PBMC) feeder cells and interleukin-2 (IL-2). The final product is infused into the patient. B. The second major approach for adoptive T-cell therapy uses T-cells expanded from autologous PBMCs that undergo one of three possible manipulations to enrich the cells for tumor antigen-specific T-cells.

commonly with cyclophosphamide and fludarabine), and finally infusion into the patient. CAR T-cells have had particularly respect in hematologic malignancies, with approvals of three CD19-directed CAR T-cell therapies, axicabtagene ciloleucel, tisagenlecleucel, and brexucabtagene autoleucel.

Axicabtagene ciloleucel is a CD19-directed autologous CAR T-cell composed of a murine single-chain antibody fragment recognizing CD19, fused with the co-stimulatory domain CD28 and the signaling domain CD3-zeta. This agent is approved by the FDA for relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy. In the phase II trial that led to its approval, 111 patients with DLBCL, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma with refractory disease experienced an ORR of 82% with a CR rate of 54%.[172] At a 2-year follow-up, the duration of response was 11.1 months, and the median OS was not reached.[173]

Tisagenlecleucel is a CD19-directed autologous CAR T-cell transduced with a lentivirus encoding a murine single-chain antibody fragment recognizing CD19 fused to the co-stimulatory domain 41-BB (CD137) and signaling domain CD3 zeta. This CAR T product is FDA approved for B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse in patients younger than the age of 25 years and for relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy. In a multicenter phase II study of pediatric and young adult patients with CD19+ relapsed or refractory B-cell ALL, the overall remission rate within 3 months was 81%.[174] In a phase II trial of adults with relapsed or refractory DLBCL, tisagenlecleucel achieved an ORR of 52%.[175]

Brexucabtagene autoleucel is a CD19-directed CAR T-cell therapy, recently approved for the treatment of relapsed or refractory mantle cell lymphoma (MCL). In a single-arm, open-label, multicenter phase II study of 74 patients with relapsed or refractory MCL who had previously been treated with chemotherapy (anthracycline or bendamustine-based), CD20-directed treatment, and Bruton's tyrosine inhibitor, patients were treated with a single infusion of brexucabtagene autoleucel.[176] Of 60 patients in the primary efficacy analysis, the ORR was 93% (95% CI, 53–78), with a 67% CR rate.[176] In the intention-to-treat analysis of all 74 patients, the ORR was 85%.[176] Grade 3 or high cytokine release syndrome (CRS) occurred in 15% and neurologic events in 31%, with two grade 5 infectious adverse events reported.[176]

CAR T-cell approaches are currently being explored in a wide array of tumors, including solid cancers, although this has been challenging, in part because of the multiplicity of tumor-associated antigens. Finally, additional cell populations are being explored, such as NK cells, which offer the possibility of allogeneic cell transfer. In a phase I/II study of HLA-mismatched, cord blood–derived anti-CD19 CAR NK cells, 11 patients with relapsed or refractory CD19-positive cancers (non-Hodgkin lymphoma or chronic lymphocytic leukemia) achieved a 73% response rate.[177]

Chimeric Antigen Receptor T-Cell Toxicity

CAR T-cell therapy is associated with unique toxicities arising from its mechanism of action: CRS and immune effector cell–associated neurotoxicity syndrome (ICANS). These toxicities are reversible. Less common toxicities include B-cell aplasia, tumor lysis syndrome, hemophagocytic lymphohistiocytosis, and anaphylaxis.[178] CRS is a common inflammatory syndrome associated with massive cytokine release (eg, IFN-γ, TNF-α, and IL-6, among others), triggering an inflammatory cascade, which can manifest with fever, hypotension, rigors, tachycardia, hypoxia, and in severe cases, multiorgan failure.[178] These symptoms occur earlier in CAR T-cells transduced with CD28 co-stimulatory domains (median time to onset with axicabtagene ciloleucel, 2 days) compared with those with 4-1BB domains (median time to onset with tisagenlecleucel, 3 days).[178] The reported incidences of CRS were 93% with axicabtagene ciloleucel (with grade ≥3 in 13%) and 58% with tisagenlecleucel (with grade ≥3 in 22%).[173,175]

Management of patients with CRS requires prompt recognition and multidisciplinary evaluation; consensus guidelines have been developed for standardized grading of toxicities.[179] Patients with grade 1 CRS may be managed supportively with antipyretics, fluids, and empiric antibiotics as indicated.[178] For grade 2 CRS, defined as fever with temperature 38°C or greater, hypotension not requiring vasopressors, or hypoxia requiring low-flow nasal cannula, treatment involves IL-6 blockade.[178] Tocilizumab, a humanized mAb against IL-6 is FDA approved for this indication. Siltuximab, a chimeric mAb, has also been used off-label in the management of patients with CRS. For cases refractory to IL-6 blockade, corticosteroids are used, with dexamethasone 10 to 20 mg every 6 hours in grade 3 toxicity and methylprednisolone up to 1000 mg/day for grade 4 toxicity.[178] The median time to resolution is 7 to 8 days.[178]

ICANS was reported in 64% (grade ≥3 in 32%) of patients with axicabtagene ciloleucel and in 39% (grade ≥3 in 12%) of patients with tisagenlecleucel.[172,175] The early manifestations of ICANS can be subtle and include decreased attention or impaired handwriting and can subsequently progress to confusion, agitation, somnolence, tremors, or aphasia, with the most severe cases associated with seizure, obtundation, weakness, increased intracranial pressure, and cerebral edema.[178] ICANS can clinically progress in two phases, with a first phase concurrently with CRS and a second phase without CRS.[178] Similar to CRS, management involves aggressive supportive care, IL-6 blockade, and corticosteroids in a closely monitored multidisciplinary setting.

Overall, cellular therapy continues to evolve, with significant efforts underway to optimize the CAR structure, develop suicide switches to abort toxicity, and develop allogeneic cells such as CAR NK described above.

CANCER VACCINES

Because tumors express a variety of antigens, cancer vaccines have been studied as a means of activating a tumor antigen-specific lymphocyte population, leading to eradication of cell expressing this antigen. This is in contrast to preventative cancer vaccines, such as the recombinant human papillomavirus vaccine. Although therapeutic cancer vaccines demonstrated significant antitumor activity in animal models and early-phase clinical trials, the clinical impact has been minimal.[180]

To date, only one therapeutic cancer vaccine has been approved for human use, sipuleucel-T, for metastatic, castration-resistant prostate cancer. Sipuleucel-T is an autologous DC vaccine prepared from a patient's peripheral blood mononuclear cells pulsed with a fusion protein of granulocyte-macrophage colony-stimulating factor (GM-CSF) and the prostate cancer antigen prostatic acid phosphatase. Sipuleucel-T was FDA approved on the basis of a phase III clinical trial that demonstrated a 4.1-month improvement in OS compared with placebo.[181] Notably, no effect on time to disease progression was observed.[181] A similarly promising vaccine in prostate cancer was (PROSTVAC) or PSA-TRICOM, composed of vaccinia and fowlpox vectors containing transgenes for prostate-specific antigen and three co-stimulatory molecules, B7.1, leukocyte function-associated antigen 3, and intercellular adhesion molecule 1, known as TRICOM. Despite early signals of benefit, a phase III clinical trial did not demonstrate an OS benefit.[182]

In light of the proof of principle demonstrated by sipuleucel-T, investigation continues into the design of cancer vaccines, including combinatorial approaches with ICT to boost immunogenicity.

OTHER IMMUNOTHERAPIES

Cytokine-Based Therapies

Cytokine-based therapies have a long history in the treatment of certain cancers, particularly melanoma and RCC. The use of high-dose IL-2 was approved for metastatic RCC by the FDA in 1992, with studies from the NCI showing a 20% objective response rate and durable response observed in certain patients.[183] High-dose IL-2 is associated with cytokine-related

toxicities, including capillary leak and hypotension, and with the growth of treatment options for these disease, notably ICT, high-dose IL-2 has been reserved for highly selected situations. Novel cytokine approaches are under investigation, including a pegylated form of IL-2 that is being studied in combination with ICT.

Oncolytic Viruses

Oncolytic viruses function through selective tumor killing as well as induction of antitumor immunity. Talimogene laherparepvec (T-VEC) is a genetically modified attenuated herpes simplex 1 virus that has been FDA approved for local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with recurrent melanoma after initial surgery. In a phase III clinical trial of intratumoral T-VEC versus subcutaneous GM-CSF, the median OS was 23.3 months with T-VEC versus 18.9 months with GM-CSF, although these analyses were descriptive.[184] The objective response rate was 31.5%.[184] Oncolytic viruses are being studied for use in the neoadjuvant setting and as part of combination therapy in melanoma as well as other tumor types.

Bispecific Antibodies

Bispecific antibodies are antibody constructs that ligate an anti-CD3 domain to a tumor-associated antigen-recognizing domain and have been postulated to promoted redirected T-cell killing of tumor cells. Currently, the only FDA-approved bispecific antibody is blinatumomab, a CD19-directed agent approved for relapsed or refractory B-cell precursor ALL and treatment of B-cell precursor ALL in first or second complete remission with minimal residual disease 0.1% or greater. In a study of 405 pretreated patients with relapsed or refractory Philadelphia chromosome positive B-cell ALL versus chemotherapy, an OS benefit of 7.7 versus 4.0 months as well as complete remission with full hematologic recovery of 34% versus 12%.[185] Bispecific antibodies are now being explored in solid tumors as well as other hematologic malignancies.

Dendritic Cell–Based Immunostimulatory Agents

DCs are professional APCs that are critical for effective T-cell stimulation. Both DCs and T-cells possess an array of stimulatory molecules that are necessary for sustained and durable immune response, making them potential therapeutic targets.

Toll-like receptors (TLRs) are a group of 13 receptors present in DCs that have distinct ligands, and the receptor–ligand interaction leads to the activation of DCs, inducing the expression of type I IFNs, cytokines (eg, IL-12), and co-stimulatory molecules (eg, CD80, CD86, and CD40) that are critical for T-cell activation.[186,187] Clinical trials with TLR agonists have shown promise, particularly in combination with other therapeutic modalities. The imidazoquinoline imiquimod ligates TLR7; in several clinical trials, topical application resulted in an 80% to 90% clearance rate for superficial basal cell carcinoma.[188,189] Systemic administration of TLR7 and TLR9 agonist as monotherapy in melanoma and RCC had a strong immune response but failed to demonstrate objective clinical response.[190,191]

Another attractive target for enhancing DC function is CD40, which is present on APCs, including DCs, and ligation of CD40 with its ligand CD40L present on T-cells is critical for T-cell priming.[192] CD40 targeting agents as monotherapy showed modest clinical benefit in non-Hodgkin lymphoma and melanoma.[193] To increase its efficacy, one approach used electroporation to introduce mRNA encoding CD40 ligand, constitutively active TLR4, CD70, and multiple melanoma tumor antigens into autologous DCs (TriMix-DC). Tumor regressions were observed in 6 of 17 patients who had received IFN-α-2b in combination with TriMix-DC.[194] Furthermore, combination of anti-CD40 antibody and the chemotherapy agent gemcitabine showed tumor regression in both humans and mice.[195]

FUTURE DIRECTIONS

Immunotherapy is firmly established as a mainstay of cancer treatment. Current areas of active research include (among many others) the discovery and validation of additional checkpoints as rational targets, refinement of CAR T-cell therapies and the emergence of allogeneic cellular therapies, testing of immunotherapy earlier in the disease state (eg, neoadjuvant), continuing exploration of combination treatments (including chemotherapy and radiation therapy), improved understanding of immune-related adverse events, and development of predictive biomarkers for toxicities and response. As the field of cancer immunotherapy continues to develop, continued focus will be toward improving patient selection to minimize toxicities and maximize efficacy.

MD ANDERSON PRACTICE TIPS

- ICT has transformed the care of many cancers, providing subsets of patients with durable responses and survival benefit, but many patients do not respond. To increase ORR, multiple clinical trials are ongoing with combinatorial strategies. At MDACC, we advise patients to be treated on clinical trials when possible.
- ICT can have unique patterns of response resembling traditional tumor flare that subsequently develops into deep and durable responses, termed *pseudoprogression*. For this reason, modified criteria for response assessment have been developed, including immune-related response criteria irRC, imRECIST, and iRECIST.
- irAEs require prompt recognition and early intervention because these events can be fatal. Although corticosteroids are the mainstay of management, prolonged steroid courses carry morbidity, and there is growing evidence for the use of selective immunosuppression. At MDACC, patients with irAEs are managed with close multidisciplinary collaboration with expertise in advanced immunosuppression, and patients should be managed in specialized centers when feasible.
- The most commonly used biomarkers for ICT are tissue PD-L1 expression, TMB, and dMMR and MSI-H. These have utility in specific circumstances (and are required for certain indications), but they have limitations, and development of more sophisticated biomarkers is an active area of investigation.
- CAR T-cell therapy is associated with unique toxicities: CRS and ICANS. These toxicities are reversible and can be managed supportively (fluids, antipyretics, vasopressors) or with IL-6 blockade and corticosteroids in severe cases. Consensus guidelines have been developed for standardized toxicity grading. A high index of suspicion is warranted, and patients should be treated in experienced centers with expertise in these therapies.

REFERENCES

1. Gresser I. A. Chekhov, M.D., and Coley's toxins. *N Engl J Med*. 1987;317:457.
2. Coley WB. The treatment of inoperable sarcoma with the mixed toxins of erysipelas and bacillus prodigiosus: immediate and final results in one hundred and forty cases. *JAMA*. 1898;XXXI:456-465.
3. Lamm DL, Blumenstein BA, Crawford ED, et al. A randomized trial of intravesical doxorubicin and immunotherapy with bacille Calmette-Guérin for transitional-cell carcinoma of the bladder. *N Engl J Med*. 1991;325:1205-1209.
4. Bjorkman PJ, Saper MA, Samraoui B, et al. Structure of the human class I histocompatibility antigen, HLA-A2. *Nature*. 1987;329:506-512.
5. Allison JP, McIntyre BW, Bloch D. Tumor-specific antigen of murine T-lymphoma defined with monoclonal antibody. *J Immunol*. 1982;129:2293-300.
6. Mittal D, Gubin MM, Schreiber RD, Smyth MJ. New insights into cancer immunoediting and its three component phases—elimination, equilibrium and escape. *Curr Opin Immunol*. 2014;27:16-25.
7. van der Bruggen P, Traversari C, Chomez P, et al. A gene encoding an antigen recognized by cytolytic T lymphocytes on a human melanoma. *Science*. 1991;254:1643-1647.
8. Peggs KS, Quezada SA, Allison JP. Cancer immunotherapy: co-stimulatory agonists and co-inhibitory antagonists. *Clin Exp Immunol*. 2009;157:9-19.
9. Smith-Garvin JE, Koretzk GA, Jordan MS. T cell activation. *Annu Rev Immunol*. 2009;27:591-619.
10. Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. *Science*. 1996;271:1734-1736.
11. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363:711-723.
12. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med*. 2011;364:2517-2526.
13. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2015;16522-530.
14. Schadendorf D, Hodi FS, Robert C, et al. Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma. *J Clin Oncol*.2015;33:1889-1894.
15. Ribas A, Kefford R, Marshall MA, et al. Phase III randomized clinical trial comparing tremelimumab with standard-of-care chemotherapy in patients with advanced melanoma. *J Clin Oncol*. 2013;31:616-622.
16. Keir ME, Butte MJ, Freeman GJ, Sharpe A. H. PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol*. 2008;26677-26704.
17. Iwai Y, Terawaki S, Honjo T. PD-1 blockade inhibits hematogenous spread of poorly immunogenic tumor cells by enhanced recruitment of effector T cells. *Int Immunol*. 2005;17:133-144.
18. Nomi T, Sho M, Akahori T, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. *Clin Cancer Res*. 2007;13:2151-2157.
19. Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2015;16375-16384.
20. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med*. 2015;372:320-330.
21. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. *N Engl J Med*. 2017;377:1824-1835.
22. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med*. 2015;372:2521-2532.
23. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. *N Engl J Med*. 2018;378:1789-1801.
24. Nghiem PT, Bhatia S, Lipson EJ, et al. PD-1 blockade with pembrolizumab in advanced merkel-cell carcinoma. *N Engl J Med*. 2016;374:2542-2552.
25. Nghiem P, Bhatia S, Lipson EJ, et al. Durable tumor regression and overall survival in patients with advanced Merkel cell carcinoma receiving pembrolizumab as first-line therapy. *J Clin Oncol*. 2019;37:693-702.
26. D'Angelo SP, Russell J, Lebbé C, et al. Efficacy and safety of first-line avelumab treatment in patients with stage IV metastatic Merkel cell carcinoma a preplanned interim analysis of a clinical trial. *JAMA Oncol*. 2018;4:1-5.
27. Migden MR, Rischin D, Schmults CD, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. *N Engl J Med*. 2018;379:341-351.
28. Migden MR, Khushalani NI, Chang ALS, et al. Cemiplimab in locally advanced cutaneous squamous cell carcinoma: results from an open-label, phase 2, single-arm trial. *Lancet Oncol*. 2020;21:294-305.
29. Grob JJ, Gonzalez R, Basset-Seguin N,et al. KEYNOTE-629: phase 2 study of pembrolizumab for recurrent/metastatic or locally advanced unresectable cutaneous squamous cell carcinoma (cSCC). *J Clin Oncol*. 2019;37(15 suppl):TPS9598-TPS9598.
30. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373:1803-1813.
31. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med*. 376(11):1015-1026.
32. Vuky J, Balar AV, Castellano DE, et al. Updated efficacy and safety of KEYNOTE-052: a single-arm phase 2 study investigating first-line pembrolizumab (pembro) in cisplatin-ineligible advanced urothelial cancer (UC). *J Clin Oncol*. 2018;364524.
33. Balar AV, Castellano DE, O'Donnell PH, al. Pembrolizumab as first-line therapy in cisplatin-ineligible advanced urothelial cancer: results from the total KEYNOTE-052 study population. *J Clin Oncol*. 2017;35:284.
34. Balar AV, Castellano D, O'Donnell PH, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. *Lancet. Oncol*. 2017;18:1483-1492.
35. Balar AV, Kulkarni GS, Uchio EM, et al. Keynote 057: phase II trial of pembrolizumab (pembro) for patients (pts) with high-risk (HR) nonmuscle invasive bladder cancer (NMIBC) unresponsive to bacillus Calmette-Guérin (BCG). *J Clin Oncol*. 2019;37:350.
36. Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2017;18:312-322.
37. Powles T, Durán I, van der Heijden MS, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. *Lancet*. 2018;391:748-757.
38. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet*. 2016;387:1909-1920.

39. Patel MR, Ellerton J, Infante JR, et al. Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial. *Lancet Oncol*. 2018;19:51-64.
40. Powles T, O'Donnell PH, Massard C, et al. Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: updated results from a phase 1/2 open-label study. *JAMA Oncol*. 2017;3:1-10.
41. Powles T, Park SE, Voog E, et al. Maintenance avelumab + best supportive care (BSC) versus BSC alone after platinum-based first-line (1L) chemotherapy in advanced urothelial carcinoma (UC): JAVELIN Bladder 100 phase III interim analysis. *J Clin Oncol*. 2020;38:LBA1-LBA1.
42. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. 2015;373:123-135.
43. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015;373:1627-1639.
44. Carbone DP, Reck M, Paz-Ares L, et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. *N Engl J Med*. 2017;3762415-2426.
45. Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol*. 2016;17:883-895.
46. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016;387:1540-1550.
47. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Updated analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. *J Clin Oncol*. 2019;37:537-546.
48. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet*. 2019;393:1819-1830.
49. Chung HC, Piha-Paul SA, Lopez-Martin J, et al. Pembrolizumab after two or more lines of previous therapy in patients with recurrent or metastatic SCLC: results From the KEYNOTE-028 and KEYNOTE-158 studies. *J Thorac Oncol*. 2020;15:618-627.
50. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet*. 2017;389:255-265.
51. Fehrenbacher L, von Pawel J, Park K, et al. Updated efficacy analysis including secondary population results for OAK: a randomized phase III study of atezolizumab versus docetaxel in patients with previously treated advanced non-small cell lung cancer. *J Thorac Oncol*. 2018;13:1156-1170.
52. Spigel D, de Marinis F, Giaccone G, et al. IMpower110: interim overall survival (OS) analysis of a phase III study of atezolizumab (atezo) vs platinum-based chemotherapy (chemo) as first-line (1L) treatment (tx) in PD-L1–selected NSCLC. *Ann Oncol*. 2019;30:v915.
53. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med*. 2017;377:1919-1929.
54. Seiwert TY, Burtness B, Mehra R, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. *Lancet Oncol*. 2016;17:956-965.
55. Mehra R, Seiwert TY, Gupta S, et al. Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma: pooled analyses after long-term follow-up in KEYNOTE-012. *Br J Cancer*. 2018;119:153-159.
56. Burtness B, Harrington KJ, Greil R, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *Lancet*. 2019;394:1915-1928.
57. Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2016;375:1856-1867.
58. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet*. 2017;389:2492-2502.
59. Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. *Lancet Oncol*. 2018;19:940-952.
60. Finn RS, Ryoo BY, Merle P, et al. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: a randomized, double-blind, phase III trial. *J Clin Oncol*. 2020;38:193-202.
61. Fuchs CS, Doi T, Jang RW, et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial. *JAMA Oncol*. 2018;4:1-8.
62. Tabernero J, Van Cutsem E, Bang Y-J, et al. Pembrolizumab with or without chemotherapy versus chemotherapy for advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma: the phase III KEYNOTE-062 study. *J Clin Oncol*. 2019;37:LBA4007-LBA4007.
63. Shah MA, Kojima T, Hochhauser D, et al. Efficacy and safety of pembrolizumab for heavily pretreated patients with advanced, metastatic adenocarcinoma or squamous cell carcinoma of the esophagus: the phase 2 KEYNOTE-180 study. *JAMA Oncol*. 2019;5:546-550.
64. Kojima T, Muro K, Francois E, et al. Pembrolizumab versus chemotherapy as second-line therapy for advanced esophageal cancer: phase III KEYNOTE-181 study. *J Clin Oncol*. 2019;37:2.
65. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol*. 2017;18:1182-1191.
66. Le DT, Kim TW, Van Cutsem E, et al. Phase II open-label study of pembrolizumab in treatment-refractory, microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: KEYNOTE-164. *J Clin Oncol*. 2020;38:11-19.
67. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med*. 2015;372:311-319.
68. Chen R, Zinzani PL, Lee HJ, et al. Pembrolizumab in relapsed or refractory Hodgkin lymphoma: 2-year follow-up of KEYNOTE-087. *Blood*. 2019;134:1144-1153.
69. Armand P, Rodig S, Melnichenko V, et al. Pembrolizumab in relapsed or refractory primary mediastinal large b-cell lymphoma. *J Clin Oncol*. 2019;37:3291-3299.
70. Chung HC, Ros W, Delord JP, et al. Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: results from the phase II KEYNOTE-158 study. *J Clin Oncol*. 2019;37:1470-1478.
71. Asaoka Y, Ijichi H, Koike K. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med*. 2015;372:2509-2520.
72. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science*. 2017;357:409-413.
73. Marabelle A, Fakih M, Lopez J, et al. Association of tumor mutational burden with outcomes in patients with select

advanced solid tumors treated with pembrolizumab in KEYNOTE-158. *Ann Oncol*. 2019;30:v475-v532.
74. Curran MA, Montalvo W, Yagita H, Allison J P. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. *Proc Natl Acad Sci U S A*. 2010;107:4275-80.
75. Wei SC, Levine JH, Cogdill AP, et al. Distinct cellular mechanisms underlie anti-CTLA-4 and anti-PD-1 checkpoint blockade. *Cell*. 2017;170:1120-1133.e17.
76. Wei SC, Sharma R, Anang NAS, et al. Negative co-stimulation constrains T cell differentiation by imposing boundaries on possible cell states. *Immunity*. 2019;50:1084-1098.e10.
77. Larkin J, Hodi FS, Wolchok JD. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373:23-34.
78. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med*. 2019;381:1535-1546.
79. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med*. 2018;378:1277-1290.
80. Motzer RJ, Rini BI, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2019;20:1370-1385.
81. El-Khoueiry AB, Yau T, Kang Y-K, et al. Nivolumab (NIVO) + ipilimumab (IPI) combination therapy in patients (pts) with advanced hepatocellular carcinoma (aHCC): results from CheckMate 040. *J Clin Oncol*. 2019;37:4012.
82. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N Engl J Med*. 2019;381:2020-2031.
83. Overman MJ, Lonardi S, Wong KYM, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. *J Clin Oncol*. 2018;36(8):773-779.
84. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378:2078-2092.
85. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med*. 2018;379:2040-2051.
86. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med*. 2018;378:2288-2301.
87. West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20:924-937.
88. Horn L, Mansfield AS, Szczęsna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med*. 2018;379:2220-2229.
89. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2019;394:1929-1939.
90. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *N Engl J Med*. 2018;379:2108-2121.
91. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2019;380:1116-1127.
92. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2019;380:1103-1115.
93. Gutzmer R, Stroyakovskiy D, Gogas H, et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced BRAFV600 mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2020;395:1835-1844.
94. Makker V, Rasco D, Vogelzang NJ, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: an interim analysis of a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol*. 2019;20:711-718.
95. Ganesan S, Mehnert J. Biomarkers for response to immune checkpoint blockade. *Annu. Rev. Cancer Biol*. 2020;4:331-351.
96. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 2012;3662443-3662454.
97. Balar AV, Galsky MD, Rosenberg JE, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. *Lancet*. 2017;389:67-76.
98. Liakou CI, Kamat A, Tang DN, et al. CTLA-4 blockade increases IFNgamma-producing CD4+ICOShi cells to shift the ratio of effector to regulatory T cells in cancer patients. *Proc Natl Acad Sci U S A*. 2008;105:14987-14992.
99. Chan TA, Wolchok JD, Snyder A. Genetic basis for clinical response to CTLA-4 blockade in melanoma. *N Engl J Med*. 2014;371:2189-2199.
100. Hellmann MD, Nathanson T, Rizvi H, et al. Genomic features of response to combination immunotherapy in patients with advanced non-small-cell lung cancer. *Cancer Cell*. 2018;33:843-852.e4.
101. Yarchoan M, Hopkins A, Jaffee EM. Tumor mutational burden and response rate to PD-1 inhibition. *N Engl J Med*. 2017;377:2500-2501.
102. Manogue C, Cotogno P, Ledet E, et al. Biomarkers for programmed death-1 inhibition in prostate cancer. *Oncologist*. 2018;119:6226-6233.
103. Lee L, Ali S, Genega E, et al. Aggressive-variant microsatellite-stable POLE mutant prostate cancer with high mutation burden and durable response to immune checkpoint inhibitor therapy. *JCO Precis Oncol*. 2018;1-8.
104. Sen T, Rodriguez BL, Chen L, et al. Targeting DNA damage response promotes antitumor immunity through STING-mediated T-cell activation in small cell lung cancer. *Cancer Discov*. 2019;9:646-661.
105. Parkes EE, Walker SM, Taggart LE, et al. Activation of STING-dependent innate immune signaling by s-phase-specific DNA damage in breast cancer. *J Natl Cancer Inst*. 2017;109:1-10.
106. Härtlova A, Erttmann SF, Raffi FA, et al. DNA damage primes the type I interferon system via the cytosolic DNA sensor STING to promote anti-microbial innate immunity. *Immunity*. 2015;42:332-343.
107. Tumeh PC, Harview CL, Yearley JH, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature*. 2014;515:568-571.
108. Loi S, Drubay D, Adams S, et al. Tumor-infiltrating lymphocytes and prognosis: a pooled individual patient analysis of early-stage triple-negative breast cancers. *J Clin Oncol*. 2019;37:559-569.
109. Zhang Y, Chen L. Classification of advanced human cancers based on tumor immunity in the microenvironment (TIME) for cancer immunotherapy. *JAMA Oncol*. 2016;2:1403-1404.
110. Helmink BA, Reddy SM, Gao J, et al. B cells and tertiary lymphoid structures promote immunotherapy response. *Nature*. 2020;577(7791):549-555.
111. Cristescu R, Mogg R, Ayers M, et al. Pan-tumor genomic biomarkers for PD-1 checkpoint blockade-based immunotherapy. *Science*. 2018;362(6411). Erratum in: *Science*. 2019;363(6430).
112. Ayers M, Lunceford J, Nebozhyn M, et al. IFN-γ-related mRNA profile predicts clinical response to PD-1 blockade. *J Clin Invest*. 2017;127(8):2930-2940.

113. Matson V, Fessler J, Bao R, et al. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. *Science*. 2018;359(6371):104-108.
114. Gopalakrishnan V, Spencer CN, Nezi L, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. *Science*. 2018;359(6371):97-103.
115. Subrahmanyam PB, Dong Z, Gusenleitner D, et al. Distinct predictive biomarker candidates for response to anti-CTLA-4 and anti-PD-1 immunotherapy in melanoma patients. *J Immunother Cancer*. 2018;6(1):18.
116. Grosso JF, Goldberg MV, Getnet D, et al. Functionally distinct LAG-3 and PD-1 subsets on activated and chronically stimulated CD8 T cells. *J Immunol*. 2009;182:6659-6669.
117. Ascierto PA, Melero I, Bhatia S, et al. Initial efficacy of anti-lymphocyte activation gene-3 (anti-LAG-3; BMS-986016) in combination with nivolumab (nivo) in pts with melanoma (MEL) previously treated with anti-PD-1/PD-L1 therapy. *J Clin Oncol*. 2017;35:9520.
118. Puhr HC, Ilhan-Mutlu A. New emerging targets in cancer immunotherapy: the role of LAG3. *ESMO Open*. 2019;4:1-6.
119. Lines JL, Pantazi E, Mak J, et al. VISTA is an immune checkpoint molecule for human T cells. *Cancer Res*. 2014;74:1924-1932.
120. Le Mercier I, Chen W, Lines JL, et al. VISTA regulates the development of protective antitumor immunity. *Cancer Res*. 2014;74:1933-1944.
121. Gao J, Ward JF, Pettaway CA, et al. VISTA is an inhibitory immune checkpoint that is increased after ipilimumab therapy in patients with prostate cancer. *Nat Med*. 2017;23:551-555.
122. Marin-Acevedo JA, Dholaria B, Soyano AE, et al. Next generation of immune checkpoint therapy in cancer: new developments and challenges. *J. Hematol Oncol*. 2018;11:1-20.
123. Sakuishi K, Apetoh L, Sullivan JM, et al. Targeting Tim-3 and PD-1 pathways to reverse T cell exhaustion and restore anti-tumor immunity. *J Exp Med*. 2010;207:2187-2194.
124. Harding JJ, Patnaik A, Moreno V, et al. A phase Ia/Ib study of an anti-TIM-3 antibody (LY3321367) monotherapy or in combination with an anti-PD-L1 antibody (LY3300054): interim safety, efficacy, and pharmacokinetic findings in advanced cancers. *J Clin Oncol*. 2019;37:12.
125. Castellanos JR, Purvis IJ, Labak CM, et al. B7-H3 role in the immune landscape of cancer. *Am J Clin Exp Immunol*. 2017;666-675.
126. Cai D, Li J, Liu D, et al. Tumor-expressed B7-H3 mediates the inhibition of antitumor T-cell functions in ovarian cancer insensitive to PD-1 blockade therapy. *Cell Mol Immunol*. 2020;17:227-236.
127. Harjunpää H, Guillerey C. TIGIT as an emerging immune checkpoint. *Clin Exp Immunol*. 2019;200(2):108-119.
128. Chen YL, Lin HW, Chien CL, et al. BTLA blockade enhances Cancer therapy by inhibiting IL-6/IL-10-induced CD19high B lymphocytes. *J Immunother Cancer*. 2019;7:1-14.
129. Bendell JC, Bedard P, Bang Yu-J, et al. CT302—phase Ia/Ib dose-escalation study of the anti-TIGIT antibody tiragolumab as a single agent and in combination with atezolizumab in patients with advanced solid tumors. Presented at: American Association of Cancer Research. Virtual Meeting II; 2020.
130. Rodríguez-Abreu D, Johnson ML, Hussein MA, et al. Primary analysis of a randomized, double-blind, phase II study of the anti-TIGIT antibody tiragolumab (tira) plus atezolizumab (atezo) versus placebo plus atezo as first-line (1L) treatment in patients with PD-L1-selected NSCLC (CITYSCAPE). *J Clin Oncol*. 2020;38:9503.
131. Suntharalingam G, Perry MR, Ward S, et al. Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. *N Engl J Med*. 2006;355:1018-1028.
132. Chester C, Sanmamed MF, Wang J, Melero I. Immunotherapy targeting 4-1BB: mechanistic rationale, clinical results, and future strategies. *Blood*. 2018;131:49-57.
133. Segal NH, Logan TF, Hodi FS, et al. Results from an integrated safety analysis of urelumab, an agonist anti-CD137 monoclonal antibody. *Clin Cancer Res*. 2017;23:1929-1936.
134. Segal NH, He AR, Doi T, et al. Phase I study of single-agent utomilumab (PF-05082566), a 4-1bb/cd137 agonist, in patients with advanced cancer. *Clin Cancer Res*. 2018;24:1816-1823.
135. Croft M, So T, Duan W, Soroosh P. The significance of OX40 and OX40L to T-cell biology and immune disease. *Immunol Rev*. 2009;229:173-191.
136. Kim JM. Abstract DDT01-02: unleashing anti-tumor immunity through anti-OX40 monotherapy and in combination with anti-PD-L1. *Cancer Res*. 2015;75:DDT01-02 LP-DDT01-02.
137. Infante JR, Hansen AR, Pishvaian MJ, et al. A phase Ib dose escalation study of the OX40 agonist MOXR0916 and the PD-L1 inhibitor atezolizumab in patients with advanced solid tumors. *J Clin Oncol*. 2016;34:101.
138. Buchan SL, Rogel A, Al-Shamkhani A. The immunobiology of CD27 and OX40 and their potential as targets for cancer immunotherapy. *Blood*. 2018;131:39-48.
139. Knee DA, Hewes B, Brogdon JL. Rationale for anti-GITR cancer immunotherapy. *Eur J Cancer*. 2016;67:1-10.
140. Koon HB, Shepard DR, Merghoub T, et al. First-in-human phase 1 single-dose study of TRX-518:an anti-human glucocorticoid-induced tumor necrosis factor receptor (GITR) monoclonal antibody in adults with advanced solid tumors. *J Clin Oncol*. 2016;34:3017.
141. Zappasodi R, Sirard C, Li Y, et al. Rational design of anti-GITR-based combination immunotherapy. *Nat Med*. 2019;25:759-766.
142. Dong C, Juedes AE, Temann UA, et al. ICOS co-stimulatory receptor is essential for T-cell activation and function. *Nature*. 2001;409:97-101.
143. Fan X, Quezada SA, Sepulveda MA, et al. Engagement of the ICOS pathway markedly enhances efficacy of CTLA-4 blockade in cancer immunotherapy. *J Exp Med*. 2014;211:715-725.
144. Chen H, Liakou CI, Kamat A, et al. Anti-CTLA-4 therapy results in higher CD4 +ICOS hi T cell frequency and IFN-γ levels in both nonmalignant and malignant prostate tissues. *Proc Natl Acad Sci U S A*. 2009;1062729-1062734.
145. Carthon BC, Wolchok JD, Yuan J, et al. Preoperative CTLA-4 blockade: tolerability and immune monitoring in the setting of a presurgical clinical trial. *Clin Cancer Res*. 2010;162861-162871.
146. Yap TA, Burris HA, Kummar S, et al. ICONIC: biologic and clinical activity of first in class ICOS agonist antibody JTX-2011 +/- nivolumab (nivo) in patients (pts) with advanced cancers. *J Clin Oncol*. 2018;363000.
147. Rischin D, Groenland SL, Lim AML, et al. Inducible T cell costimulatory (ICOS) receptor agonist, GSK3359609 (GSK609) alone and in combination with pembrolizumab (pembro): preliminary results from INDUCE-1 expansion cohorts (EC) in head and neck squamous cell carcinoma (HNSCC). *Ann Oncol*. 2019;30:v449-v474.
148. Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol*. 2017;18:e143-e152.
149. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res*. 2009;15:7412-7420.
150. Hodi FS, Ballinger M, Lyons B, et al. Immune-modified response evaluation criteria in solid tumors (imrecist): refining guidelines to assess the clinical benefit of cancer immunotherapy. *J Clin Oncol*. 2018;36850-36858.
151. Mulkey F Theoret MR, Keegan P, et al. Comparison of iRECIST versus RECIST V.1.1 in patients treated with an anti-PD-1 or PD-L1 antibody: pooled FDA analysis. *J Immunother Cancer*. 2020;8:1-7.
152. Ayoub M, Eleneen Y, Colen RR. Cancer imaging in immunotherapy. In: Naing A, Hajjar J, eds. *Immunotherapy*. Springer; 2020:309-324.

153. Dolladille C, Ederhy S, Sassier M, et al. Immune checkpoint inhibitor rechallenge after immune-related adverse events in patients with cancer. *JAMA Oncol*. 2020;6(6):865-871.
154. Abou Alaiwi S, Xie W, Nassar AH, et al. Safety and efficacy of restarting immune checkpoint inhibitors after clinically significant immune-related adverse events in metastatic renal cell carcinoma. *J Immunother Cancer*. 2020;8:1-11.
155. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2018;361714-1768.
156. Abu-Sbeih H, Ali FS, Qiao W, et al. Immune checkpoint inhibitor-induced colitis as a predictor of survival in metastatic melanoma. *Cancer Immunol Immunother*. 2019;68:553-561.
157. Abu-Sbeih H, Wang Y. Gastrointestinal tract adverse events. In: Naing A, Hajjar J, eds. *Immunotherapy*. Springer; 2020:247-253.
158. Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol*. 2012;30:2691-2697.
159. Abu-Sbeih H, Ali FS, Wang X, et al. Early introduction of selective immunosuppressive therapy associated with favorable clinical outcomes in patients with immune checkpoint inhibitor-induced colitis. *J Immunother Cancer*. 2019;7:1-11.
160. Wang Y, Wiesnoski DH, Helmink BA, et al. Fecal microbiota transplantation for refractory immune checkpoint inhibitor-associated colitis. *Nat Med*. 2018;24:1804-1808.
161. Johnson DB, Balko JM, Compton ML, et al. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med*. 2016;375(18):1749-1755.
162. Zarifa A, Lopez-Mattei, Juan Palaskas, Nicolas, et al. Immune checkpoint inhibitors (ICIs)-related cardiotoxicity. In: Naing A, Hajjar J, eds. *Immunotherapy*. Springer; 2020:277-284.
163. Rota E, Varese P, Agosti S, et al. Concomitant myasthenia gravis, myositis, myocarditis and polyneuropathy, induced by immune-checkpoint inhibitors: a life-threatening continuum of neuromuscular and cardiac toxicity. *eNeurologicalSci*. 2018;14.
164. Valenti-Azcarate R, Esparragosa Vazquez I, Toledano Illan C, et al. Nivolumab and Ipilimumab-induced myositis and myocarditis mimicking a myasthenia gravis presentation. *Neuromuscul. Disord*. 2019;10-12.
165. Fazel M, Jedlowski PM. Severe myositis, myocarditis, and myasthenia gravis with elevated anti-striated muscle antibody following single dose of ipilimumab-nivolumab therapy in a patient with metastatic melanoma. *Case Reports Immunol*. 2019;2019:1-3.
166. Esfahani K, Buhlaiga N, Thébault P, et al. Alemtuzumab for immune-related myocarditis due to PD-1 therapy. *N Engl J Med*. 2019;380:2375-2376.
167. Salem JE, Allenbach Y, Vozy A, et al. Abatacept for severe immune checkpoint inhibitor-associated myocarditis. *N Engl J Med*. 2019;380:2377-2379.
168. Dudley ME, Wunderlich JR, Robbins PF, et al. Cancer regression and autoimmunity in patients after clonal repopulation with antitumor lymphocytes. *Science*. 2002;298:850-854.
169. Rosenberg SA, Yang JC, Sherry RM, et al. Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy. *Clin Cancer Res*. 2011;17:4550-4557.
170. Dudley ME, Wunderlich JR, Yang JC, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. *J Clin Oncol*. 2005;23:2346-2357.
171. Yun CO, Nolan KF, Beecham EJ, et al. Targeting of T lymphocytes to melanoma cells through chimeric anti-GD3 immunoglobulin T-cell receptors. *Neoplasia*. 2000;2:449-459.
172. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-Cell lymphoma. *N Engl J Med*. 2017;377:2531-2544.
173. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. *Lancet Oncol*. 2019;20:31-42.
174. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med*. 2018;378:439-448.
175. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med*. 2019;380:45-56.
176. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. *N Engl J Med*. 2020;382:1331-1342.
177. Liu E, Marin D, Banerjee P, et al. Use of CAR-transduced natural killer cells in CD19-positive lymphoid tumors. *N Engl J Med*. 2020;382:545-553.
178. Nair R, Westin J. CAR T-cells. In: Naing A, Hajjar J, eds. *Immunotherapy*. Springer; 2020:215-233.
179. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2019;25:625-638.
180. Rosenberg SA, Yang JC, Restifo NP. Cancer immunotherapy: moving beyond current vaccines. *Nat Med*. 2004;10:909-915.
181. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. 2010;363:411-422.
182. Gulley JL, Borre M, Vogelzang NJ, et al. Phase III trial of PROSTVAC in asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer. *J Clin Oncol*. 2019;37:1051-1061.
183. Rosenberg SA. Interleukin 2 for patients with renal cancer. *Nat Clin Pract Oncol*. 2007;4:497.
184. Andtbacka RHI, Collichio F, Harrington KJ, et al. Final analyses of OPTiM: a randomized phase III trial of talimogene laherparepvec versus granulocyte-macrophage colony-stimulating factor in unresectable stage III-IV melanoma. *J Immunother Cancer*. 2019;7:1-11.
185. Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. *N Engl J Med*. 2017;376836-376847.
186. Iwasaki A, Medzhitov R. Regulation of adaptive immunity by the innate immune system. *Science*. 2010;327:291-295.
187. Banchereau J, Steinman RM. Dendritic cells and the control of immunity. *Nature*. 391998;2:245-252.
188. Geisse J, Caro I, Lindholm J, et al. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from two phase III, randomized, vehicle-controlled studies. *J Am Acad Dermatol*. 2004;50:722-733.
189. Schulze HJ, Cribier B, Requena L, et al. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from a randomized vehicle-controlled phase III study in Europe. *Br J Dermatol*. 2005;152:939-47.
190. Pashenkov M, Goëss G, Wagner C, et al. Phase II trial of a toll-like receptor 9-activating oligonucleotide in patients with metastatic melanoma. *J Clin Oncol*. 2006;24:5716-5724.
191. Thompson JA, Kuzel T, Drucker BJ, et al. Safety and efficacy of PF-3512676 for the treatment of stage IV renal cell carcinoma: an open-label, multicenter phase I/II study. *Clin. Genitourin. Cancer*. 2009;7:E58-E65.
192. Vonderheide RH. Prospect of targeting the CD40 pathway for cancer therapy. *Clin Cancer Res*. 2007;13:1083-1088.
193. Advani R, Forero-Torres A, Furman RR, et al. Phase I study of the humanized anti-CD40 monoclonal antibody dacetuzumab

in refractory or recurrent non-Hodgkin's lymphoma. *J Clin Oncol*. 2009;27:4371-4377.
194. Wilgenhof S, Van Nuffel AM, Corthals J, et al. Therapeutic vaccination with an autologous mRNA electroporated dendritic cell vaccine in patients with advanced melanoma. *J Immunother*. 2011;34:448-456.
195. Beatty GL, Chiorean EG, Fishman MP, et al. CD40 agonists alter tumor stroma and show efficacy against pancreatic carcinoma in mice and humans. *Science*. 2011;331:1612-1616.
196. Kato K, Cho BC, Takahashi M, et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20:1506-1517.
197. Andre T, Amonkar M, Norquist JM, et al. Pembrolizumab versus chemotherapy for microsatellite instability-high/mismatch repair deficient metastatic colorectal cancer: the phase 3 KEYNOTE-177 Study. *J Clin Oncol*. 2020;38:LBA4-LBA4.
198. Robert C, Ribas A, Schachter J, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. *Lancet Oncol*. 2019;20:1239-1251.
199. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382:1894-1905.

This page intentionally left blank

57 Targeted Therapy in Cancer

Rabih Said
Apostolia-Maria Tsimberidou

KEY CONCEPTS

- The therapeutic approach for patients with metastatic cancer includes multigene tissue genomic analysis and assessment of immune markers that include programmed cell death-ligand 1, microsatellite instability (MSI) status, tumor mutational burden, neurotrophic tyrosine kinase receptor (NTRK) fusion, human *epidermal growth factor* receptor 2 (HER2) amplification, and cell-free DNA analysis to identify drivers of carcinogenesis. The use of targeted therapy against molecular alterations in individual patients has been associated with improved clinical outcomes.
- Patients with advanced cancer may have tumor molecular alterations in one or more of the following genes and pathways: RAS-RAF-MEK, PI3K-AKT-mTOR, EGFR, HER-2, BRCA, HER2, RET, ROS-1, KIT, CDK4/6, PDGFR, VEGFR1/2/3, PDGFRα, NTRK, METex1h4, FGF, Trop-2 CSF1R, AR, ER, and other genes. (See text for abbreviations.)
- Larotrectinib and entractinib are novel NTRK inhibitors indicated for patients whose tumor has a NTRK fusion, irrespective of tumor type.
- Treatment with pembrolizumab (a programmed cell death protein 1 inhibitor) is indicated for patients with MSI-H mismatch repair deficient tumors irrespective of tumor type.
- The combination of targeted therapy with either chemotherapy or immunotherapy has shown promising results in various tumors. Prospective trials are warranted to provide biomarkers associated with response or resistance to immunotherapeutic agents.
- Novel drug development, complete understanding of mechanisms of carcinogenesis, innovative clinical trials, and harmonization of policy and practice will accelerate the implementation of personalized medicine.

The Human Genome Project has enabled sequencing of human DNA and led to advancements in technologies that detect genomic, transcriptional, proteomic, and epigenetic changes. The application of these technologies and novel drug development have accelerated the implementation of personalized medicine. Personalized medicine uses concepts of the genetic and environmental bases of disease to individualize prevention, diagnosis, and treatment.[1,2] Optimization of treatment by incorporating targeted therapy—the use of molecules that target specific enzymes, growth factor receptors, and signal transducers to interfere with a variety of oncogenic cellular processes—and other strategies made possible by advancements in the field of translational medicine hold the promise of improving patient care.[3] In recent years, immunotherapy has revolutionized the field of personalized medicine, and many drugs have been approved for the treatment of patients with specific tumor types and for patients whose tumors express specific immune markers. These drugs are now included in the targeted therapy arsenal.

This chapter focuses on the evolution of targeted therapy in cancer therapeutics and is organized according to the key drivers of carcinogenesis in humans, focusing on the novel agents designed to target those drivers. It also summarizes the current state-of-the-art applications of personalized medicine.

RAS-RAF-MEK PATHWAY INHIBITORS

The mitogen-activated protein kinase (MAPK) cascades contribute to carcinogenesis with upregulation of the MAPK cascades rapidly accelerated fibrosarcoma (RAF) and MAPK/extracellular signal-regulated kinase

(ERK) (MEK). Cell-surface molecules activate the RAS family (KRAS, NRAS, and HRAS), which are GTPases that activate downstream RAF protein kinases [rapidly accelerated fibrosarcoma homolog B (BRAF); rapidly accelerated fibrosarcoma homolog C (CRAF); rapidly accelerated fibrosarcoma homolog A (ARAF)]. The most important substrates of RAF kinases are MEK1 and MEK2, the MAPK/ERK kinases. MEK kinases have one main substrate, ERK. Activation of ERK leads to gene expression modifications, mediated by transcription factors that control cell cycle progression, differentiation, metabolism, survival, migration, and invasion. This pathway regulates apoptosis through the posttranslational phosphorylation of apoptotic regulatory molecules, including Bad, Bim, Mcl-1, and caspase 9. RAS is a downstream effector of epidermal growth factor receptor (EGFR). ERK activation promotes upregulated expression of EGFR ligands and an autocrine loop critical for tumor growth.

BRAF mutations are found in 62% to 72% of patients with metastatic melanoma[4] and are less frequent in radial growth phase (10%) and in situ (5.6%) melanomas. *NRAS* mutations occur in 5.2% of melanomas.[5] In conjunctival melanoma, *BRAF* and *NRAS* mutations were identified in 29% and 18% of patients, respectively. KIT alterations were found in 36% and 39% of patients with acral and mucosal melanoma, respectively. GNAQ and GNA11 alterations were found in 45% and 32% of patients with uveal melanoma, respectively. The Food and Drug Administration (FDA)–approved drugs by molecular target are listed in Table 57–1 and Figure 57–1.

BRAF Inhibitors

Vemurafenib

Vemurafenib was the first FDA-approved inhibitor of BRAF for metastatic melanoma with a *BRAF* V600E mutation (Table 57–2). A phase III trial demonstrated a 3.7-month improvement in progression-free survival (PFS) in the vemurafenib arm compared with the dacarbazine arm (median, 5.3 months and 1.6 months, respectively).[6] A 5-year follow-up analysis demonstrated the superiority of vemurafenib in prolonging overall survival OS; 13.6 vs 9.7 months; hazard ratio [HR], -.81; $P = .03$).[7]

Dabrafenib

Dabrafenib is indicated for patients with unresectable or metastatic melanoma with a *BRAF* V600E mutation. A phase III study demonstrated longer PFS in the dabrafenib arm compared with the dacarbazine arm (median, 5.1 vs 2.7 months, respectively).[8] Both vemurafenib[9] and dabrafenib[10] have antitumor activity in patients with melanoma and brain metastases. However, adjuvant treatment with vemurafenib for 1 year did not increase disease-free survival (DFS) compared with observation in patients with stage IIC to IIIC melanoma with *BRAF* V600E and V600K mutation.[11]

Encorafenib

Encorafenib is an adenosine triphosphate (ATP)–competitive RAF kinase inhibitor that leads to the decrease of ERK phosphorylation and the down-regulation of cyclin D1, ultimately arresting the cell cycle at phase G1 and causing cell senescence.[12] Encorafenib in combination with binimetinib is indicated for the treatment of patients with advanced melanoma with *BRAF* V600E and V600K mutations on the basis of a phase III study in this setting that compared encorafenib versus vemurafenib versus encorafenib plus the MEK inhibitor binimetinib and demonstrated longer PFS in the combination arm.[13] The median PFSs were 9.6 months, 14.9 months, and 7.3 months, respectively.[13]

MEK Inhibitors

Trametinib

Trametinib, a MEK1/MEK2 kinase inhibitor, is indicated as monotherapy or in combination with dabrafenib for unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation. The FDA approval of trametinib was based on the results of a randomized trial, which demonstrated longer PFS with trametinib than with chemotherapy consisting of either dacarbazine or paclitaxel in patients with stage IIIc to IV melanoma and a *BRAF* V600E or V600K mutation.[14] The median PFS durations were 4.8 and 1.5 months in the trametinib and chemotherapy arms, respectively (HR, 0.47; $P < .0001$). The 6-month OS rates were 81% and 67%, respectively.[14] A long-term follow-up analysis of the patients who received trametinib plus dabrafenib demonstrated that the OS rate was 37% at 4 years and 34% at 5 years.[15] Of 563 patients, 109 (19%) had a complete response (CR) and improved long-term outcomes, and the 5-year OS rate was 71%.[15] Cutaneous squamous cell carcinoma (SCC), an adverse event noted in patients treated with BRAF inhibitors, was less common in the dabrafenib plus trametinib group than in the dabrafenib monotherapy group (7% vs 19%, respectively).

Cobimetinib

Cobimetinib, an oral highly selective inhibitor of MEK, is indicated in combination with vemurafenib for the treatment of unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation on the basis of improvement in PFS with this combination compared with vemurafenib monotherapy (9.9 months vs 6.2 months; $P < .001$).[16] Binimetinib is another orally bioavailable selective inhibitor of MEK1/2.[17] As

TABLE 57–1 Food and Drug Administration–Approved Drugs by Molecular Target

Target	Drug	Target	Drug
BRAF	Dabrafenib	ALK	Ceritinib
	Vemurafenib		Crizotinib
	Encorafenib		Alectinib
			Lorlatinib
MEK	Dabrafenib		Brigatinib
	Vemurafenib		
	Encorafenib	NTRK	Larotrectinib
	Trametinib		Entrectinib
	Cobimetinib		
	Selumetinib	ROS-1	Crizotinib
	Binimetinib		Entrectinib
mTOR	Everolimus	KIT, PDGFR, ABL	Imatinib
	Temsirolimus		Dasatinib
			Ponatinib
PI3K	Alpelisib		Bosutinib
	Duvelisib		Ripretinib
	Idelalisib		
	Copanlisib	KIT, PDGFRβ, RAF, RET, VEGFR1/2/3	Regorafenib Sorafenib
		PDGFRα	Avapritinib
BRCA	Olaparib		
	Talazoparib	MET^{ex14}	Capmatinib
	Niraparib		
	Rucaparib		
		RET	Selpercatinib
EGFR	Osimertinib		
	Erlotinib	VEGF	Bevacizumab
	Afatinib		Sunitinib
	Panitumumab		
	Cetuximab	c-MET, VEGFR2, AXL, RET	Cabozantinib
EGFR, RET, VEGFR2	Vandetanib	FGF	Erdafitinib
			Pemigatinib
HER2	Pertuzumab		
	Trastuzumab	Trop-2	Sacituzumab Govitecan-hziy
	Trastuzumab emtansine		
	Fam-trastuzumab deruxtecan-nxki	CSF1R	Pexidartinib
	Neratinib		
		Checkpoint Blockade	
HER2, EGFR	Lapatinib	CTLA-4	Ipilimumab
		PD-1	Pembrolizumab

(*Continued*)

TABLE 57–1 Food and Drug Administration–Approved Drugs by Molecular Target (*Cont.*)

Target	Drug	Target	Drug
CDK4/6	Palbociclib	PD-1	Nivolumab
	Ribociclib	PD-L1	Avelumab
	Abemaciclib	PD-1	Cemiplimab
		PD-1/PD-L1	Durvalumab
AR	Enzalutamide	PD-L1	Atezolizumab
	Apalutamide		
	Abiraterone		

ABL, Abelson murine leukemia virus tyrosine kinase; ALK, anaplastic lymphoma kinase; AR, androgen receptor; AXL, anexelekto; BRAF, rapidly accelerated fibrosarcoma homolog B; BRCA, breast cancer type 1; CDK4/6, cyclin-dependent kinase 4 and 6; CSFR-1, colony-stimulating factor receptor-1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EGFR, epidermal growth factor receptor; FGF, fibroblast growth factor; HER2, human epidermal growth factor receptor 2; KIT, tyrosine-protein kinase of CD117 (cluster of differentiation 117); MEK, mitogen-activated protein kinase; MET^{ex14}, mesenchymal-epithelial transition exon 14 deletion; mTOR, mammalian target of rapamycin; NTRK, neurotrophin receptor kinase; PDGFR, platelets derived growth factor receptor; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; PDGFR, platelet-derived growth factor receptor; PI3K, phosphoinositide 3-kinases; RAF, rapidly accelerated fibrosarcoma; RET, receptor tyrosine kinase; ROS-1, c-ros oncogene 1; Trop-2, trophoblast antigen 2; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

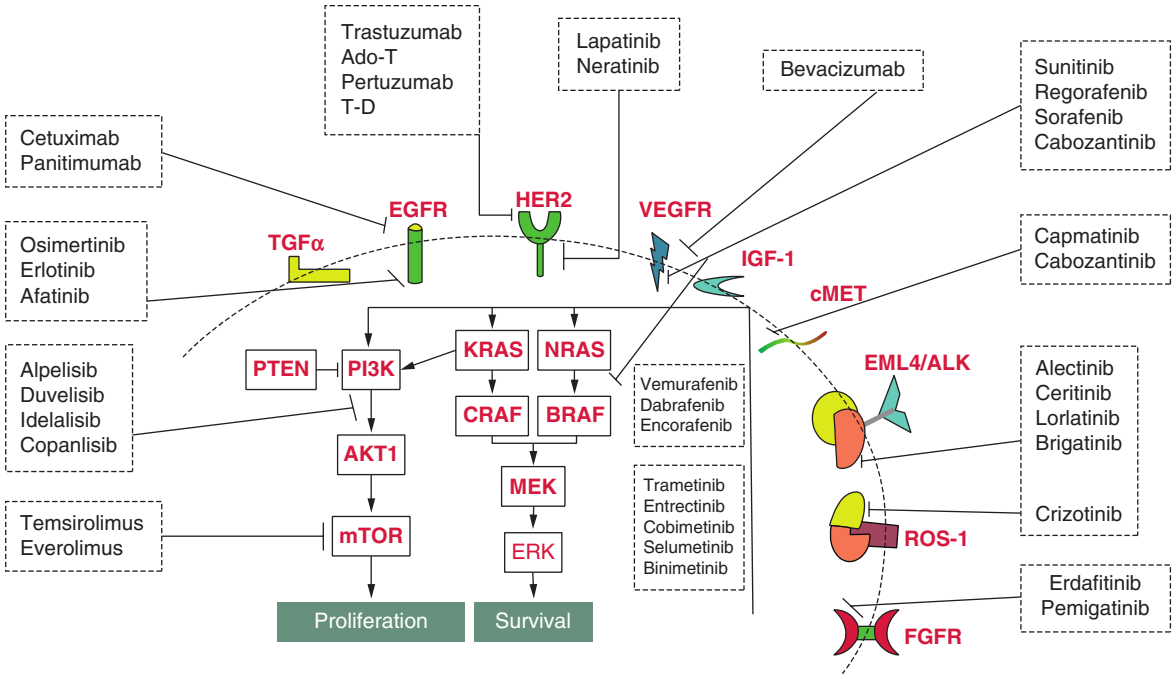


FIGURE 57–1 Common intracellular cancer pathways and associated approved targeted agents. AKT, protein kinase B; BRAF, v-raf murine sarcoma viral oncogene homolog B1; c-MET, hepatocyte growth factor receptor; CRAF, Raf-1 proto-oncogene; EGFR, epidermal growth factor receptor; EML4/ALK, echinoderm microtubule-associated protein-like 4/anaplastic lymphoma kinase; ERK, extracellular signal-regulated kinase; FGFR, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor 2; IGF-1, insulinlike growth factor-1; MEK, mitogen-activated extracellular signal-regulated kinase; mTOR, mammalian target of rapamycin; NRAS, neuroblastoma RAS viral oncogene homolog; PTEN, phosphatase and tensin homolog; PI3K, phosphoinositide 3-kinase; RAS, Kirsten rat sarcoma viral oncogene homolog; ROS-1, ROS proto-oncogene 1; TGF-α, transforming growth factor α; VEGFR, vascular endothelial growth factor receptor.

mentioned earlier, the combination of binimetinib and encorafenib was approved by the FDA for the treatment of patients with melanoma harboring *BRAF* V600E and V600K mutations.[13]

Up to 4% of patients with non–small cell lung cancer (NSCLC) have *BRAF* mutations. Molecular alterations in *EGFR*, *ALK*, *ROS1*, *NRAS*, and *KRAS* also contribute to the pathogenesis of lung cancer. In phase II trials, vemurafenib or dabrafenib monotherapy has demonstrated efficacy in *BRAF*-mutant NSCLC, with response rates of 42% and 33%, respectively.[18,19] However, two subsequent phase II trials demonstrated higher response rates (63% and 64%) with the combination of dabrafenib and trametinib.[20,21] Thus,

TABLE 57–2 Targets of Food and Drug Administration–Approved and Investigational Therapy in Selected Tumor Types

Tumor Type	FDA-Approved Therapy Targets	Investigational Therapy Targets
NSCLC	EGFR, ALK, ROS-1, BRAF, MET^{ex14}, PD-1/PDL-1, CTLA-4, NTRK	RET, HER-2
Breast	ER, HER-2, PI3K, PD-1/PDL-1, NTRK, BRCA, DDR	AKT, mTOR
Colorectal carcinoma	RAS, BRAF, MMR/MSI, NTRK	HER-2
Gastroesophageal carcinoma	HER-2, MSI, PDL-1, NTRK	
Melanoma	BRAF, MEK, PD-1, NTRK, MSI	RAS, KIT, ALK, ROS-1
Ovarian carcinoma	VEGF, BRCA, DDR, ER, MSI/MMR, NTRK	MEK
Prostate adenocarcinoma	AR, MSI/MMR, NTRK	PD-1/PDL-1, BRCA
Bladder cancer	PDL-1, FGFR, NTRK	VEGF, Nectin-4

ALK, anaplastic lymphoma kinase; AR, androgen receptor; AXL, anexelekto; BRAF, rapidly accelerated fibrosarcoma homolog B; BRCA, breast cancer type 1; CDK4/6, cyclin-dependent kinase 4 and 6; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EGFR, epidermal growth factor receptor; FGF, fibroblast growth factor; DDR, DNA damage repair; HER2, human epidermal growth factor receptor 2; KIT, tyrosine-protein kinase of CD117 (cluster of differentiation 117); MEK, mitogen-activated protein kinase; MET^{ex14}, mesenchymal-epithelial transition exon 14 deletion; mTOR, mammalian target of rapamycin; NTRK, neurotrophin receptor kinase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand; PDGFR, platelet-derived growth factor receptor; PI3K, phosphoinositide 3-kinases; RAF, rapidly accelerated fibrosarcoma; RET, receptor tyrosine kinase; ROS-1, c-ros oncogene 1; Trop-2, trophoblast antigen 2; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

the combination of dabrafenib and trametinib was approved by the FDA for patients with advanced or metastatic NSCLC with *BRAF* V600E mutation. *KRAS* mutations are more common in smokers, and in metastatic NSCLC, they are associated with a worse prognosis than *EGFR* mutations.[22]

PI3K-AKT-mTOR PATHWAY INHIBITORS

The phosphatidylinositol 3-kinase (PI3K) signaling pathway is among the most critical in cancer, affecting the survival, growth, metabolism, motility, and progression of cancer.[23] Of the proteins in the PI3K family, only class IA signaling aberrations are involved in human cancers. The class IA PI3Ks are composed of heterodimers of regulatory subunits (p85α, p85β, p50α, p55α, and p55γ) and catalytic subunits (p110α, p110β, and p110δ). Three genes encode the regulatory subunits: *PIK3R1* encodes p85α, and *PIK3R2* and *PIK3R3* encode the p85β and p55γ isoforms of the p85 regulatory subunit, respectively. *PIK3CA*, *PIK3CB*, and *PIK3CD* encode the highly homologous p110 catalytic subunit isoforms p110α, p110β, and p110δ and share a similar five-domain structure. At the amino (N) terminus, there is an adaptor-binding domain that interacts with the p85 regulatory subunit followed by a RAS-binding domain that mediates interaction with RAS. The class I PI3Ks can phosphorylate the 3¢ position of the phosphatidylinositols PI-4-P and PI-4,5-P_2, through PI-4,5-P_2, to generate phosphatidylinositol (3,4,5) triphosphate (PIP_3). Cytosolic proteins, such as the AKT family of protein-serine/threonine kinases, bind to PIP_3 and localize to the plasma membrane in response to PI3K activation. In the absence of stimulated growth conditions, PIP_3 levels in the plasma membrane are undetectable in mammals and regulated by the tumor suppressor phosphatase and tensin homolog (PTEN), whose lipid phosphatase activity converts PIP_3 back to PI-4,5-P_2. The loss of PTEN function—owing to inactivating mutations, deletion, chromosomal translocation, or epigenetic silencing—is second only to p53 mutation as a driver of cancer initiation.

Mutations or amplifications of the PI3K catalytic subunits p110α (*PIK3CA*) and p110β (*PIK3CB*), the PI3K regulatory subunits p85α (*PIK3R1*) and p85β (*PIK3R2*), and AKT (*AKT1*) can activate the PI3K pathway. Mutations, deletions, or epigenetic changes in negative regulators of the PI3K axis (PTEN and inositol polyphosphate-4-phosphatase, type II) may modify tumor cell sensitivity to chemotherapy or targeted therapies.[24] AKT is the main effector of PI3K activation and has three isoforms: AKT1, AKT2, and AKT3. AKT signaling plays a significant role in cell hypertrophy, survival, hyperplasia, and metabolism. The mammalian target of rapamycin (mTOR) is the catalytic subunit of mTOR complex 1 (mTORC1) and mTORC2, which are distinguished by their respective accessory proteins, regulatory-associated protein of mTOR and rapamycin-insensitive companion of mTOR.

Several studies focus on targeting the PI3K-AKT-mTOR pathway. Rapamycin analogs (rapalogs) have antitumor activity in several tumor types and are frequently combined with other anticancer agents.[25] Everolimus is approved for the treatment of subependymal giant cell astrocytoma; hormone receptor (HR)–positive, human epidermal growth factor

receptor 2 (HER2)–negative breast cancer (in combination with exemestane); neuroendocrine pancreatic tumors; tuberous sclerosis-associated subependymal giant cell astrocytoma; and renal cell carcinoma (sunitinib- or sorafenib-refractory). Temsirolimus is approved for patients with renal cell carcinoma.

PI3K Inhibitors

The first generation of class I pan-PI3K inhibitors, including Wortmannin and LY294002, targeted PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ but had limited activity. New pan-PI3K inhibitors that have improved pharmacokinetic profiles and target specificity are being evaluated in ongoing studies. The antitumor activity of these inhibitors is primarily cytostatic. Novel agents that inhibit both PI3K and mTOR may result in greater antitumor activity than either agent alone.

Pictilisib

Pictilisib is a selective, oral, class I PI3K inhibitor; it is also an mTOR inhibitor at high concentrations. Several studies were unsuccessful owing to lack of efficacy or neuropsychiatric and gastrointestinal (GI) toxicity.

Buparlisib

Several clinical studies of buparlisib, an oral pyrimidine-derived pan-PI3K inhibitor with activity against all class I PI3K isoforms, demonstrated limited antitumor activity in phase I studies in patients with various tumor types and in phase II/III studies in patients with postmenopausal, HR-positive, HER2-negative, advanced breast cancer.[26] The use of buparlisib was associated with hyperglycemia, rash, nausea, fatigue, and mood alterations.

Idelalisib

Idelalisib, a highly selective inhibitor of PI3Kδ is indicated for the treatment of patients with relapsed follicular B-cell non-Hodgkin lymphoma or relapsed small lymphocytic lymphoma (SLL) previously treated with two or more prior systemic therapies. In a phase 2 study in this setting, idelalisib was associated with an objective response rate (ORR) of 57%, the median duration of response (DOR) was 12.5 months, and the median PFS was 11 months. The most common grade 3 to 4 adverse events were neutropenia, increase in liver enzymes, and diarrhea.[27]

Duvelisib

Duvelisib, an oral dual PI3Kδγ inhibitor, is indicated for adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or SLL after two or more prior therapies. In a phase 3 trial in patients with relapsed or refractory CLL or SLL, duvelisib was associated with longer PFS than ofatumumab. The median PFS durations were 13.3 and 9.9 months for duvelisib and ofatumumab, respectively (HR, 0.52; P <.0001).[28] Similar benefit was noted in patients with high-risk chromosome 17p13.1 deletion or TP53 mutations (HR, 0.40; P = .0002). The ORR was significantly higher in the duvelisib arm compared with the ofatumumab arm (74% vs 45%, respectively; P <.0001) regardless of del(17p) status.[28]

Copanlisib

Copanlisib, a pan-class I PI3K inhibitor with activity against PI3Kα, PI3Kβ, PI3Kδ, and PI3Kγ, is indicated for the treatment of adult patients with relapsed follicular lymphoma treated with two or more prior systemic therapies. In a phase II trial, the use of copanlisib was associated with an ORR of 43.7% and 27.1% in indolent and aggressive lymphoma, respectively. The median PFS and DOR in indolent lymphoma were 9.8 and 13 months, respectively. Common adverse events included hyperglycemia, hypertension, and diarrhea.[29]

Dactolisib

Dactolisib an oral, selective inhibitor of PI3K and TORC1/2, was investigated in phase I/II clinical trials in patients with advanced solid malignancies alone or combined with other agents, in metastatic breast cancer with PI3K/PTEN alterations, in patients with advanced pancreatic neuroendocrine tumors, and in prostate cancer. The development of dactolisib was terminated because of limited antitumor activity and poor safety profile that included nausea, diarrhea, and elevated transaminases.

Alpelisib

Alpelisib, a p110a isoform-specific inhibitor, is indicated in combination with fulvestrant for postmenopausal women and men with HR-positive, HER2-negative, *PI3KCA*-mutated advanced or metastatic breast cancer after progression on or after an endocrine-based therapy. The FDA approval of alpelisib was based on results of a phase III trial; alpelisib combined with fulvestrant was compared with placebo with fulvestrant in patients with HR-positive, HER2-negative breast cancer previously treated with endocrine therapy and stratified on the basis of their *PIK3CA* mutational status. In the *PIK3C*-mutated cohort, the median PFSs were 11.0 months with alpelisib treatment and 5.7 months in the placebo groups (P <.001). No difference in PFS was noted in the wild-type *PIK3CA* cohort.[30]

AKT Inhibitors

AKT inhibitors may induce the PI3K-stimulating receptor tyrosine kinase HER3 in breast cancer cell lines and may increase insulinlike growth factor (IGF) 1R and the insulin receptor, thereby leading to the development of escape pathways and resistance mechanisms. Combination therapies that block the feedback response may overcome resistance to AKT inhibitors. Various AKT inhibitors were investigated in clinical trials, including MK2206, GSK2141795, and BAY1125976, as single agents or in combination with other agents, but their clinical efficacy was limited. A clinical trial with MSC2363318A, a dual p70S6K/AKT inhibitor, has been completed (NCT01971515).

In summary, molecular alterations in the PI3K/AKT/mTOR pathway have been identified in several different tumor types, emphasizing the critical role of this pathway in tumorigenesis and disease progression. Resistance to PI3K/AKT/mTOR inhibitors occurs via several escape mechanisms, and to overcome these mechanisms, PI3K, AKT, or mTOR inhibitors in combination with other targeted or cytotoxic agents are being investigated in clinical trials. In our experience, among patients referred for phase I clinical trials who were treated with targeted therapies, those with molecular alterations in the PI3K/AKT/mTOR pathway had shorter OS than patients with alterations in the RAS/RAF/MEK or EGFR/HER/other pathways.[31] This difference may be attributed at least partially to limited efficacy of targeted agents against tumors driven by PI3K/AKT/mTOR pathway alterations.

Carefully designed clinical trials with novel effective drugs, and the elucidation of mechanisms of response and resistance to PI3K/AKT/mTOR pathway inhibitors, including protein and phosphoprotein expression with signatures of sensitivity or resistance, may improve clinical outcomes.

EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS

EGFR (ErbB1; HER1) is a cell-surface transmembrane receptor that belongs to the EGF family of extracellular protein ligands. It is a member of the ErbB receptor family, which consists of four receptor tyrosine kinases: EGFR, HER2 (ErbB2), HER3 (ErbB3), and HER4 (ErbB4). EGF binds to EGFR, stimulating ligand-induced dimerization, receptor dimerization, and signaling through tyrosine kinase activity, leading to activation of multiple pathways involved in cell proliferation, survival, metastases, and neoangiogenesis. EGFR-targeted therapies include tyrosine kinase inhibitors (TKIs) and monoclonal antibodies.

Erlotinib

Erlotinib targets the EGFR tyrosine kinase and is indicated for first-line treatment of patients with metastatic NSCLC with tumor *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations, maintenance therapy of patients with NSCLC and no evidence of disease progression after four cycles of platinum-based first-line chemotherapy, treatment of patients with NSCLC after one or more failed chemotherapy regimens, and first-line treatment of patients with locally advanced or metastatic pancreatic cancer in combination with gemcitabine.

In NSCLC, erlotinib demonstrated a significant improvement in median PFS and OS compared with placebo.[32] *EGFR* kinase domain mutations predicted response to EGFR-TKIs.[33,34] In patients with *EGFR* alterations, the response rate to EGFR-TKIs ranges from 48% to 90%.[35,36] Randomized trials demonstrated that the use of gefitinib or erlotinib is associated with longer PFS compared with platinum doublets in patients with lung adenocarcinoma and activating *EGFR* mutations. No OS benefit was noted,[37–41] perhaps partially because of crossover after disease progression. In a randomized study of erlotinib versus placebo as maintenance therapy in patients with advanced NSCLC who had an objective response or stable disease after four cycles of a platinum-based doublet, erlotinib was associated with superior PFS in patients with adenocarcinoma or SCC. Survival benefit was noted only in SCC.[42]

Gefitinib

Gefitinib, an EGFR inhibitor, is indicated as first-line treatment in patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. It selectively binds to its tyrosine kinase domain, which prevents the binding and blocking of ATP to subsequent receptor autophosphorylation and results in inhibition of signal transduction. Gefitinib was the first FDA-approved selective EGFR inhibitor in 2003 for NSCLC, but in 2005, the FDA withdrew this approval for use in new patients because it did not improve OS compared with placebo in previously treated patients.[43] In a phase III trial, patients with metastatic NSCLC and *EGFR* mutations were randomized to receive either gefitinib or carboplatin plus paclitaxel.[39] In the interim analysis, PFS (primary endpoint) was longer in the gefitinib group than in the chemotherapy group (median, 10.8 months vs 5.4 months, respectively; HR, 0.30; $P < .001$). No difference in OS was noted between the two arms.[39]

Afatinib

Afatinib, a selective, oral inhibitor of EGFR/ErbB1, HER2, and HER4, is indicated for patients with

metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. In a phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations, afatinib was associated with longer PFS compared with standard doublet chemotherapy (11.1 months vs 6.9 months, respectively; $P = .001$).[44] In patients with exon 19 deletions or L858R mutations, the median PFS with afatinib was 13.6 months. Development of resistance to afatinib was attributed to additional *EGFR* (T790M on exon 20, 50% of patients)[45] or *PIK3CA* mutations, *MET* or *HER2* amplification, epithelial-to-mesenchymal transformation, or transformation to small cell lung cancer.

Dacomitinib

Dacomitinib, a second-generation pan-EGFR inhibitor, is indicated for the first-line treatment of patients with metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations. In a phase III study, in treatment-naïve patients with advanced NSCLC and *EGFR* mutation, the median PFS durations (primary endpoint) were 14.7 months and 9.2 months in the dacomitinib and the gefitinib arms, respectively (HR, 0.59; $P < .0001$). Grade 3 and 4 adverse events were more frequent with dacomitinib than with gefitinib and included dermatitis acneiform, diarrhea, and increase in alanine aminotransferase (ALT) levels. The median OS durations were 34.1 months and 26.8 months in the dacomitinib and the gefitinib arms, respectively (HR, 0.76; $P = .044$).[46]

Osimertinib

Osimertinib, an oral, third-generation EGFR inhibitor, is indicated for the treatment of patients with metastatic EGFR-T790M mutation-positive NSCLC whose disease has progressed on or after EGFR-TKI therapy and for the first-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations. Osimertinib covalently binds to and inhibits the activity of mutant forms of EGFR, including the acquired EGFR resistance mutation T790M, thereby preventing EGFR-mediated signaling that ultimately both induces cell death and inhibits tumor growth.[47] In a phase III study, patients with T790M-positive advanced NSCLC whose disease progressed after first-line EGFR-TKI therapy were randomized to receive osimertinib or pemetrexed plus either carboplatin or cisplatin.[48] PFS was longer in the osimertinib arm compared with the chemotherapy arm (median, 10.1 months vs 4.4 months; HR, 0.30; $P < .001$), and it was also longer in patients with central nervous system (CNS) metastases (8.5 months vs 4.2 months, respectively; HR, 0.32). Grade 3 and 4 adverse events were less frequent with osimertinib arm (23%) compared with chemotherapy (47%).[48] In a phase III study, previously untreated patients with advanced NSCLC and an EGFR deletion in exon 19 or L858R mutation, PFS was longer in the osimertinib arm compared with the standard EGFR-TKI (gefitinib or erlotinib) arm (median, 18.9 months vs 10.2 months, respectively; HR, 0.46; $P < .001$). At 18 months, the OS rates were 83% and 71%, respectively (HR, 0.63; $P = .007$), and osimertinib was better tolerated than the standard EGFR-TKIs (grade 3–4 adverse events, 34% vs 45%, respectively).[49]

Cetuximab

Cetuximab is a chimeric mouse–human immunoglobulin (Ig) 1 monoclonal antibody (mAb) against EGFR. It is indicated for the treatment of patients with advanced SCC of the head and neck combined with radiation therapy, recurrent or metastatic SCC of the head and neck combined with platinum-based therapy with 5-fluorouracil (5-FU), and recurrent or metastatic SCC of the head and neck that progresses after platinum-based therapy. Cetuximab with FOLFIRI (infusional fluorouracil, leucovorin, and irinotecan) is indicated for the first-line treatment of patients with *KRAS* wild-type, EGFR-positive metastatic colorectal cancer (CRC); cetuximab with irinotecan is indicated for irinotecan-refractory patients. Cetuximab monotherapy is also indicated for patients with oxaliplatin- and irinotecan-refractory CRC or patients with irinotecan intolerance.

Because EGFR mutations and overexpression are frequent in patients with CRC, in patients with irinotecan-refractory CRC, cetuximab demonstrated antitumor activity as monotherapy (ORR, 10.8%; median time to progression [TTP], 1.5 months; median OS, 6.9 months) or combined with irinotecan (ORR, 22.9%; median TTP, 4.1 months; median OS, 8.6 months).[50] In a phase III study, cetuximab was associated with improved OS compared with best supportive care in patients with refractory metastatic CRC (6.1 months vs 4.6 months).[51] In another phase III study, first-line treatment with cetuximab plus FOLFIRI reduced the risk of progression compared with FOLFIRI alone in patients with metastatic CRC, but the benefit of cetuximab was limited to patients with *KRAS* wild-type tumors.[52] In patients with previously untreated metastatic CRC, cetuximab plus FOLFOX-4 (oxaliplatin, leucovorin, and FU) was associated with a higher ORR compared with FOLFOX-4 alone (43% vs 36%).[53] In patients with KRAS wild-type CRC, cetuximab plus FOLFOX-4 compared with FOLFOX-4 alone was associated with a higher ORR (61% vs 37%; $P = .01$) and a lower risk of disease progression (HR, 0.57; $P = .02$). This study established KRAS mutational status as

a selection criterion for the addition of cetuximab to FOLFOX-4 in this setting.[53]

Panitumumab

Panitumumab, a fully humanized IgG2 anti-hEGFR antibody, is indicated for the treatment of patients with wild-type *KRAS* (exon 2 in codons 12 or 13) metastatic CRC as first-line therapy in combination with FOLFOX or monotherapy in fluoropyrimidine-, oxaliplatin-, and irinotecan-refractory patients. In a phase III study of panitumumab with FOLFOX4 versus FOLFOX4 alone as first-line therapy in patients with wild-type *KRAS* metastatic CRC, the addition of panitumumab to FOLFOX4 resulted in higher ORR (57% vs 48%; $P = .02$), PFS (10 months vs 8.6 months; $P = .01$), and OS (HR, 0.83; $P = .03$).[54] In a randomized study of panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type *KRAS* exon 2 metastatic CRC, panitumumab was not inferior to cetuximab, and the OS benefit was similar (median OS, 10.4 months vs 10 months, respectively; HR, 0.97).[55]

Necitumumab

Necitumumab, a second-generation, recombinant, human IgG1 EGFR mAb, is indicated in combination with gemcitabine and cisplatin for the first-line treatment of patients with locally advanced or metastatic squamous NSCLC.[56] Necitumumab binds to EGFR with high affinity, competing with ligands leading to the inhibition of receptor activation and downstream signaling. In a phase III study in patients with previously untreated stage IV squamous NSCLC, the use of necitumumab plus gemcitabine and cisplatin was associated with longer OS compared with gemcitabine and cisplatin (median, 11.5 months vs 9.9 months; HR, 0.84; $P = .01$]). Grade 3 and 4 adverse events were more frequent in the necitumumab arm (72% vs 62%).[56]

c-KIT PATHWAY INHIBITORS

The receptor tyrosine kinase protein KIT (c-Kit or CD117) is encoded by the *KIT* gene. KIT regulates cell differentiation and proliferation, resists cell apoptosis, and plays an important role in tumorigenesis and migration by activating downstream signaling molecules following interaction with stem cell factor (SCF). Complete loss of KIT activity results in in utero or perinatal death; KIT "loss of function" leads to failure of particular stem cell populations to migrate and survive.

Activating mutations of *KIT* occur in almost all patients with systemic mastocytosis. In gastrointestinal stromal tumors (GISTs), activating mutations of KIT occur in more than 80% of patients; two thirds of *KIT* mutations occur in exon 11, resulting in dysfunction of the intracellular autoinhibitory juxtamembrane domain. The majority of these mutations are indels. Deletion of exon 11 is associated with shorter PFS and OS in patients with GIST. Approximately 10% to 15% of *KIT* mutations in GIST occur in the extracellular region encoded by exon 9 (primarily in intestinal GIST). KIT mutations occur in core binding factor leukemias (17% of acute myeloid leukemia), in up to 26% of patients with testicular seminomas, and in 30% of patients with unilateral ovarian dysgerminomas. Activating *KIT* mutations and amplifications have been reported in 5% of patients with melanoma. In melanoma, more than 90% of these mutations are missense mutations and their distribution is as follows: exon 9 (5%), exon 11 (45%), exon 13 (25%), exon 17 (10%), and exon 18 (15%). KIT inhibition is an effective therapeutic strategy in patients with tumor aberrations of the SCF/c-KIT signaling pathway.

In the pre-imatinib era, the median survival time of patients with advanced GIST was less than 1.5 years. The use of imatinib in patients with advanced GIST is associated with a median survival period of approximately 5 years.[57] Imatinib binds directly to the ATP-binding site within KIT, competitively inhibiting ATP binding and stabilizing the kinase in the inactive conformation. In the adjuvant setting, imatinib was associated with decreased risk of relapse after surgery with curative intent.[58] The reintroduction of imatinib after disease relapse is associated with results inferior to those for continued imatinib therapy, suggesting that imatinib treatment should not be interrupted.[57] Primary resistance to imatinib is noted in 10% of patients with GIST and is attributed to the type of KIT mutation (threefold higher risk of resistance with exon 9 mutations than with exon 11 mutations) or to suboptimal dose in patients with *KIT* exon 9 mutations.[59] Secondary resistance is attributed to acquired mutations in the ATP-binding site (exons 13/14) that interfere with imatinib binding or in the activation loop (exons 17/18) that stabilize the active conformation of KIT.[60]

In patients with imatinib-resistant GIST tumors, sunitinib (anti–vascular endothelial growth factor [VEGF] TKI) demonstrated significant improvement in the median TTP compared with placebo, leading to FDA approval for this indication.[61] The efficacy of sunitinib in patients with imatinib-secondary resistance is attributed to its structural and enzymatic characteristics and to targeting additional tyrosine kinases.[62] Regorafenib is also indicated for patients with TKI-resistant GIST. In a phase III study, regorafenib was associated with longer PFS than placebo (median PFS, 4.8 months vs 0.9 months, respectively; $P < .0001$).[63]

Ripretinib

Ripretinib, a synthetic kinase inhibitor that targets a wide range of KIT mutants, is for the treatment of adults with GIST who have received therapy with three or more kinase inhibitors, including imatinib. DP-5439, the active metabolite of ripretinib, is a type II inhibitor of KIT and platelet-derived growth factor receptor (PDGFR) A.[64] In a phase III study in patients with GIST previously treated with imatinib, sunitinib, and regorafenib, the ORR was 9% with ripretinib versus 0% with placebo; the median PFS was 6.3 months versus 1.0 month, respectively (HR, 0.15; P <.0001); and the median OS was 15.1 months versus 6.6 months, respectively (HR, 0.36). The most common adverse events were GI symptoms, alopecia, fatigue, myalgia, and palmar-plantar erythrodysesthesia. KIT inhibitors have been combined with other targeted agents in the hope of improving the outcomes of patients with KIT alterations and overcoming resistance.

Avapritinib

Avapritinib, a selective kinase inhibitor with broad activity against oncogenic KIT/PDGFRA mutants, is indicated for the treatment of adults with unresectable or metastatic GIST harboring PDGFRA exon 18 mutations, including D842V mutations. In a phase II study in 43 patients with advanced GIST harboring PDGFRA mutations in exon 18, the ORR was 86%.[65]

HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 PATHWAY INHIBITORS

HER2 is involved in the regulation of proliferation and survival of epithelial cells. HER1, HER3, and HER4 receptors have ligands and form homodimers or heterodimers upon ligand binding. HER2 can heterodimerize with any of the other receptors and is the preferred dimerization partner, leading to autophosphorylation of tyrosine residues within the cytoplasmic domain of the receptors and initiating signal transduction via the PI3K/AKT and RAS/MAPK pathways. In breast cancer, amplification and overexpression of the HER2 oncogene occurs in approximately 15% to 20% of patients. HER2 is overexpressed in various tumor types, including gastroesophageal junction adenocarcinoma and colorectal, gallbladder, and lung tumors.

Trastuzumab

Trastuzumab is a recombinant DNA-derived humanized mAb that selectively binds with high affinity to the extracellular domain of HER2 protein. The antibody is an IgG1κ that contains human framework regions with the complementarity-determining regions of a murine antibody that binds to HER2. Trastuzumab is indicated as monotherapy for patients with metastatic breast cancer whose tumors overexpress HER2 protein and who have had one or more chemotherapy regimen and combined with paclitaxel for patients with metastatic breast cancer whose tumors overexpress HER2 protein and who have not received chemotherapy for their metastatic disease. Approximately 15% of patients develop disease recurrence after trastuzumab therapy. Resistance to trastuzumab has been attributed to altered receptor–antibody interaction, activation of the downstream pathways by increased signaling from other members of the HER family or other receptors, or constitutive activation of downstream elements.

Lapatinib

Lapatinib, a dual TKI of EGFR and HER2, is indicated in combination with capecitabine for patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy, including anthracycline, taxane, and trastuzumab therapy; it is also indicated in combination with letrozole for postmenopausal women with HR-positive metastatic breast cancer that overexpresses the HER2 receptor and for whom hormonal therapy is also indicated.

Ado-Trastuzumab Emtansine

Trastuzumab emtansine (ado-trastuzumab emtansine, T-DM1), an antibody–drug conjugate consisting of trastuzumab linked to the cytotoxic agent mertansine, is indicated as monotherapy for patients with HER2-positive, metastatic breast cancer previously treated with trastuzumab with or without a taxane. Trastuzumab binds to HER2, and mertansine enters and destroys cells by binding to tubulin. In patients with HER2-positive, trastuzumab-resistant breast cancer, trastuzumab emtansine improved survival by 5.8 months compared with lapatinib and capecitabine combination therapy.[66] Trastuzumab emtansine is also indicated for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.[67] In a phase III study in this setting, the rates of invasive disease or death were 12.2% with trastuzumab emtansine versus 22.2% with trastuzumab. Invasive DFS was significantly higher in the trastuzumab emtansine group (HR, 0.5; P <.001).[67]

Pertuzumab

Pertuzumab, a humanized mAb that binds to the HER2 receptor and inhibits the interaction between HER2 and HER1, HER3, and HER4, is indicated in combination with trastuzumab and docetaxel as a neoadjuvant treatment for patients with HER2-positive breast cancer and as a treatment for patients with HER2-positive metastatic breast cancer. In a phase III trial, patients with node-positive or high-risk node-negative HER2-positive, operable breast cancer were randomized to receive pertuzumab or placebo added to standard adjuvant chemotherapy plus 1 year of treatment with trastuzumab.[68] The rates of disease recurrence were 7.1% versus 8.7% in the pertuzumab and the placebo groups, respectively (HR, 0.81; $P = .045$), and the 3-year rate of invasive DFS was lower in the node-positive group treated with pertuzumab compared with placebo (HR, 0.77; $P = .02$).[68]

Neratinib

Neratinib, an irreversible small-molecule TKI of HER1, HER2, and HER4, is indicated for the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed or amplified breast cancer to follow adjuvant trastuzumab-based therapy. In a phase III trial in patients with stage 1-3c HER2-positive, operable breast cancer who had completed neoadjuvant and adjuvant chemotherapy plus trastuzumab with no evidence of disease recurrence or metastatic disease at study entry, the events of invasive DFS were lower with 1 year of neratinib compared with placebo (116 vs 163 events; HR, 0.73; $P = .0083$).[69] The most common adverse events were GI, mainly diarrhea. Neratinib is also indicated in combination with capecitabine for adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.[70] In a phase III study in this setting, PFS was longer with neratinib and capecitabine than with lapatinib and capecitabine (at 1-year, 37.8% vs 14.8%, respectively), and the 1-year OS rates were 87.5% and 66.7%, respectively (HR, 0.88; $P = .21$).[70]

Fam-Trastuzumab Deruxtecan-Xki

Trastuzumab deruxtecan, is an antibody–drug conjugate of a humanized mAb that targets HER2, a cleavable tetrapeptide-based linker, and topoisomerase I inhibitor (cytotoxic drug). It is indicated for the treatment of patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.[71] In a phase 2 study in 184 patients with HER2-positive metastatic breast cancer who had previously received trastuzumab emtansine, trastuzumab deruxtecan was associated with response duration of 14.8 months and PFS of 16.4 months. The most common adverse events grade 3 or greater were neutropenia, anemia, and nausea.[72]

CDK 4/6 INHIBITORS

The cell cycle progression from G1 to mitosis is controlled by many proteins, including CDKs, cyclins, and the retinoblastoma (Rb)-E2F signaling pathway. These cyclins are the downstream effectors of many upstream activating complex networks, including ER/PR/androgen receptor (AR), nuclear factor κB (NF-κB), MAPKs, signal transducers and activators of transcription (STATs), WNT/β-catenin, and PI3K/AKT/mTOR.[73] In many cancer cells, CDK4 and CDK6 mediate cell cycle control. CDK inhibitors include the first-generation inhibitors (eg, flavopiridol) and the newer, more selective inhibitors (eg, palbociclib, ribociclib, and abemaciclib) (Fig. 57–2).

Flavopiridol

Flavopiridol is a pan-CDK inhibitor that targets CDK 1, 2, 4, 6, 7, and 9, has modest antitumor activity in patients with CLL.

Palbociclib

Palbociclib, an oral selective CDK4/6 inhibitor, is indicated in combination with an aromatase inhibitor for the initial endocrine-based therapy of postmenopausal women with HR-positive, HER2-negative, advanced or metastatic breast cancer. This indication was expanded to include men based on data from electronic health records. In a phase III trial in postmenopausal women with ER-positive, HER2-negative, previously untreated breast cancer, the median PFS was 24.8 versus 14.5 months in the palbociclib plus letrozole arm and in the placebo plus letrozole arm, respectively (HR, 0.58; $P < .001$). Grade 3 and 4 adverse events were more frequent in the combination arm (neutropenia, 66.4% vs 1.4%; leukopenia, 24.8% vs 0%).[74]

Palbociclib is also indicated in combination with fulvestrant for the treatment of patients with HR-positive, HER2-negative advanced or metastatic breast cancer in women with disease progression after endocrine therapy on the basis of results of a phase III study in this setting that demonstrated longer OS with palbociclib plus fulvestrant group than with placebo plus fulvestrant (median, 34.9 vs 28 months, respectively; HR, 0.81; $P = .09$). The median time to initiation of subsequent chemotherapy at the time of disease progression was 17.6 versus 8.8 months in the palbociclib

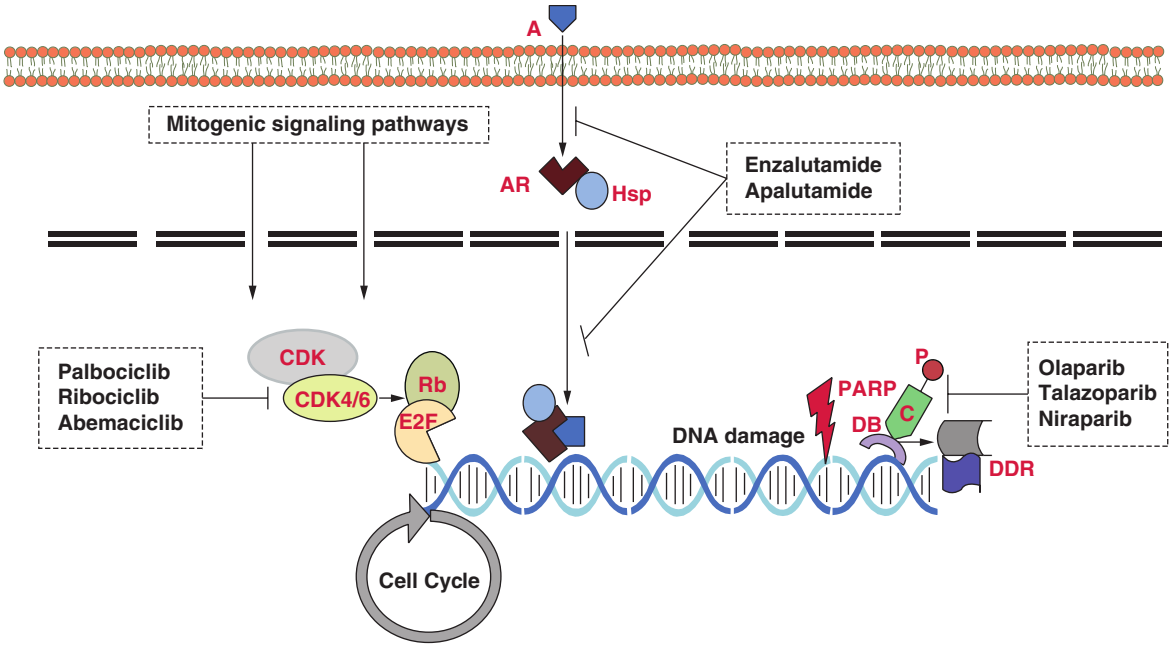


FIGURE 57–2 Major targeted intranuclear cancer pathways and associated approved targeted agents. A, androgen; AR, androgen receptor; CDK, cyclin-dependent kinase; DB, DNA binding domain; DDR, DNA damage response; E2F, eukaryote factor 2; Hsp, heat shock protein; PARP, poly (ADP-ribose) polymerase; P, phosphorylated; C, catalytic domain, Rb, retinoblastoma protein.

plus fulvestrant group and the placebo plus fulvestrant group, respectively (HR, 0.58; P <.001).[75]

Ribociclib

Ribociclib, an oral CDK4/6 inhibitor that blocks the phosphorylation of the Rb protein that leads to the inhibition of cell cycle progression and induces G1 phase arrest, is indicated in combination with an aromatase inhibitor as initial endocrine-based therapy for treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer. In a phase III study in postmenopausal women with HR-positive, HER2-negative recurrent or metastatic breast cancer with no previous systemic therapy, PFS (primary endpoint) was longer with ribociclib plus letrozole than with placebo plus letrozole (HR, 0.56; $P = 3.29 \times 10^{-6}$). At 18 months, the PFS rate was 63.0% vs 42.2% in the ribociclib versus the placebo group, respectively. Grade 3/4 neutropenia occurred in 59.3% of patients in the ribociclib arm and 0.9% in the placebo arm.[76] In another phase III trial in premenopausal or perimenopausal women with HR-positive, HER2-negative advanced breast cancer, the addition of ribociclib to endocrine therapy (goserelin adose and either a nonsteroidal aromatase inhibitor or tamoxifen) was associated with a longer OS than endocrine therapy alone (3.5-year OS rates, 70.2% vs 46.0% in the ribociclib vs placebo groups, respectively, HR, 0.71; P = .0097).[77] Therefore, the FDA expanded the approval of ribociclib to include pre- and perimenopausal women. In another phase III study, men and postmenopausal women with HR-positive, HER2-negative advanced breast cancer (metastatic or locoregionally recurrent disease not amenable to curative treatment) were randomized to receive ribociclib plus fulvestrant or placebo plus fulvestrant.[78] The 3.5-year OS (primary endpoint) rates were 57.8% vs 45.9% in the ribociclib and the placebo groups, respectively (relative risk of death, 28%; HR, 0.72; P = .0045).[78]

Abemaciclib

Abemaciclib is a selective inhibitor of CDK4/6 with higher potency against CDK4/cyclin D1 than CDK6/cyclin D6 and a lower IC_{50} compared with other available CDK4/6 inhibitors. Abemaciclib is indicated as monotherapy for women and men with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting and in combination with fulvestrant for women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression after endocrine therapy. In a phase III study in women with HR-positive, HER2-negative advanced breast cancer whose disease had progressed while receiving prior endocrine therapy, abemaciclib plus fulvestrant significantly extended PFS (primary endpoint) versus fulvestrant alone (median, 16.4 vs 9.3 months; HR, 0.55; P

<.001). The most common adverse events in the abemaciclib versus placebo arms were diarrhea (86.4% vs 24.7%), neutropenia (46.0% vs 4.0%), nausea (45.1% vs 22.9%), and fatigue (39.9% vs 26.9%).[79]

In another phase III study in postmenopausal women with HR-positive, HER2-negative advanced breast cancer with no prior systemic therapy in the advanced setting of abemaciclib or placebo plus a nonsteroidal aromatase inhibitor, the median PFS (primary objective) was significantly prolonged in the abemaciclib arm (HR, 0.54; $P = .000021$).[80] Adverse events were more common in the abemaciclib arm and included diarrhea (all grades, 81.3%; grade 1, 44.6%), neutropenia (grades 3–4, 21.1% vs 1.2%) and leukopenia (grades 3–4, 7.6% vs 0.6%).[80]

ANDROGEN RECEPTOR PATHWAY INHIBITORS

The AR, a member of the nuclear receptor superfamily, shares similar structure with estrogen receptor (ER), progesterone receptor (PR), and the thyroid hormone and glucocorticoid receptors. The gene that encodes for AR consists of eight exons and is located on chromosome X. Testing of AR by immunohistochemistry in normal prostate results in strong staining of luminal cells, fibromuscular stromal cells, and endothelial cells but not basal cells. In normal prostate tissue, AR plays a major role in protein secretion and prostate growth, and the functions of AR in prostate cancer include prostate-specific antigen synthesis and lipid metabolism regulation. Androgen deprivation is a key treatment option for patients with prostate cancer. Some patients develop castration-resistant prostate cancer (CRPC) status via various mechanisms that include AR point mutation, amplification, variants or cofactor variations, and androgen biosynthesis variations.

Enzalutamide

Older antiandrogens (bicalutamide and flutamide) bind to the ligand-binding domain (LBD) of AR and result in the inhibition of androgen binding to LBD, leading to growth inhibition of prostate cancer cells. Second-generation nonsteroidal antiandrogens, such as enzalutamide, have greater affinity for the LBD of AR.[81] Enzalutamide is indicated for the treatment of patients with metastatic or nonmetastatic CRPC as first-line therapy and for patients with metastatic castration-sensitive prostate cancer.

Abiraterone

Abiraterone is a selective inhibitor of androgen biosynthesis mainly via blocking cytochrome P450 c17 (CYP17), a critical enzyme in testosterone synthesis, and blocking androgen synthesis in the adrenal glands, testes, and the prostate tumor. Abiraterone is indicated in combination with prednisone for the treatment of patients with metastatic CRPC and for metastatic high-risk castration-sensitive prostate cancer. Adverse events include mineralocorticoid excess, adrenocortical insufficiency, and hepatotoxicity.

Apalutamide

Apalutamide, a nonsteroidal antiandrogen agent, binds directly to the LBD of the AR, leading to the inhibition of AR translocation to DNA binding and subsequently blocking AR-mediated transcription and inhibition of prostate cancer cell growth. Apalutamide is indicated for the treatment of patients with nonmetastatic CRPC and for metastatic castration-sensitive prostate cancer.

PARP INHIBITORS

BRCA1 and BRCA2 are key proteins in DNA damage response (DDR). Hereditary BRCA1/2 mutations, by leading to impaired double-strand DNA repair, are associated with an increased risk of breast and ovarian cancer. Poly (ADP-ribose) polymerase (PARP) is a family of proteins that play a key role in various cellular processes that include DNA repair, chromatin modulation, and replication stress response. PARP1 and PARP2, through multiple DDR pathways, play critical roles in DNA strand break repair that help maintain cell survival. Thus, the use of PARP inhibitors in tumors with deleterious BRCA1/2 mutations or other DDR alterations renders the cells unable to efficiently repair DNA and makes them vulnerable to apoptosis.

PARP inhibitors in clinical testing include olaparib, talazoparib, niraparib, rucaparib, and velaparib as single agents or in combination with other agents.

Olaparib

Olaparib, an oral PARP inhibitor, that induces synthetic lethality in BRCA-deficient cells, is indicated for the treatment of patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), HER2-negative metastatic breast cancer previously treated with chemotherapy either in the neoadjuvant, adjuvant, or metastatic setting. In a phase II trial, maintenance treatment with olaparib in patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer who had received two or more platinum-based regimens significantly improved PFS but not OS.[82] In a phase III trial in patients with a gBRCAm and HER2–negative metastatic breast cancer with two or fewer previous chemotherapy regimens for metastatic disease,

olaparib was associated with longer PFS than single-agent chemotherapy per physician's choice (median, 7.0 months vs 4.2 months; HR, 0.58; P <.001).[83]

Another indication of olaparib is for the treatment of adult patients with deleterious or suspected deleterious gBRCAm or somatic BRCA-mutated (sBRCAm) advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR after first-line platinum-based chemotherapy as maintenance treatment. This approval was based on results of a phase III trial in this setting that demonstrated that after a median follow-up period of 41 months, the risk of disease progression was 70% lower in the olaparib arm compared with the placebo arm (60% vs 27%, HR, 0.3; P <.0001).[84]

Olaparib is also indicated for the maintenance treatment of adult patients with deleterious or suspected deleterious gBRCA-mutated metastatic pancreatic adenocarcinoma whose disease has not progressed on 16 weeks or longer of a first-line platinum-based chemotherapy regimen, on the basis of a phase III study that demonstrated longer PFS in this setting in patients treated with olaparib compared with placebo (median, 7.4 vs 3.8 months, respectively; HR, 0.53; P = .004).[85]

Talazoparib

Talazoparib a PARP inhibitor with strong catalytic inhibition of TRAP in addition to potential for PARP trapping, is indicated for patients with deleterious or suspected deleterious gBRCAm, HER2-negative locally advanced or metastatic breast cancer. In a phase III study in this setting, talazoparib was associated with longer PFS compared with the standard of care (SOC) (capecitabine, eribulin, gemcitabine, or vinorelbine) physician's choice (8.6 vs 5.6 months, respectively, HR, 0.54; P <.001). The most common grade 3 and 4 adverse event was anemia (55%).

Niraparib

Niraparib, a selective inhibitor of PARP 1/2, is indicated for patients with advanced ovarian, fallopian tube, or primary peritoneal cancer treated with three or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD)–positive status, defined as a deleterious or suspected deleterious BRCA mutation or genomic instability in patients with disease progression for longer than 6 months after response to the last platinum-based chemotherapy. In a phase III trial in patients with platinum-sensitive, recurrent ovarian cancer, niraparib was associated with longer PFS compared with placebo (21.0 vs 5.5 months in the gBRCA mutation cohort; HR, 0.27; and 9.3 months vs 3.9 months in the overall non-gBRCA cohort; HR, 0.45; P <.001 for both comparisons).[86] In another phase III trial, in patients with newly diagnosed advanced ovarian cancer, in the HRD group, the median PFS was 21.9 months versus 10.4 months in the niraparib versus the placebo arms, respectively (HR, 0.43; P <.001); and in the overall population, the median PFS was 13.8 months versus 8.2 months (HR, 0.62; P <.001).[87]

Rucaparib

Rucaparib is indicated for the treatment of patients with deleterious gBRCAm mutation or somatic BRCAm-associated advanced ovarian cancer who have been treated with two or more chemotherapies, on the basis of results of two multicenter, single-arm clinical trials that demonstrated an ORR of 54% (CR, 9%) and response duration of 9.2 months in this setting.

c-MET PATHWAY INHIBITORS

c-MET (or MET) is a receptor tyrosine kinase with specificity for a single ligand, the hepatocyte growth factor (HGF). HGF binding to MET leads to receptor dimerization and autophosphorylation of MET on its intracellular kinase domain and subsequent phosphorylation of its C-terminal docking site and juxtamembrane domain. These phosphorylation events enable activation of multiple downstream effector proteins such as the adaptor proteins Grb2 and Gab1, leading to activation of the PI3K, RAS/RAF/MEK/ERK, PLC-γ, STATs, and FAK signaling pathways. c-MET plays a role in promoting the proliferation, survival, motility, and invasion of normal and tumor cells. c-MET and phospho-c-MET have been associated with poor clinical outcomes in various tumors. c-MET mutations are usually a result of sporadic somatic alterations acquired during cancer development.

Cabozantinib

Cabozantinib, a small-molecule inhibitor that inhibits c-MET, VEGFR2, AXL, and RET (receptor tyrosine kinase), is indicated for medullary thyroid cancer,[88] for renal cell carcinoma as first- and second-line therapy after TKI treatment and as second-line therapy after sorafenib in advanced hepatocellular carcinoma.

Capmatinib

Capmatinib, a selective MET inhibitor is indicated for the treatment of adult patients with metastatic NSCLC whose tumors have a mutation that leads to $MET\Delta^{ex14}$ as detected by an FDA-approved test on the basis of an ORR of 68%, response duration of 9.7 months, and manageable toxicity in this subset of patients.[89] Phase

II/III studies of other c-MET inhibitors (rilotumumab, ficlatuzumab, onartuzumab, tivantinib) were discontinued owing to the lack of clinical efficacy.[90] Clinical trials of selective c-MET inhibitors are ongoing. Most clinical trials with MET inhibitors were inconclusive, likely owing to differences in function of MET alterations, suboptimal validation of biomarker analysis, and limited antitumor activity of most inhibitors.[91]

ANAPLASTIC LYMPHOMA KINASE PATHWAY INHIBITORS

Crizotinib

ALK gene rearrangements occur in 2% to 7% of patients with NSCLC. Crizotinib, a small-molecule inhibitor of ALK, ROS1, and c-MET, is indicated for the treatment of patients with ALK-positive NSCLC. In these patients, crizotinib as first-line therapy was associated with longer PFS and less toxicity compared with chemotherapy.[92,93] Novel ALK inhibitors were developed to overcome resistance to crizotinib, which is attributed to secondary mutations within the ALK-TK domain; EML4-ALK amplification; bypass activation of the alternative signaling pathways EGFR, c-KIT, KRAS, and IGF-1 receptor; and progression or occurrence of CNS metastases.

Ceritinib

Ceritinib, an ATP-competitive ALK inhibitor, is indicated for the treatment of patients with ALK-positive metastatic NSCLC who have shown disease progression on or are intolerant to crizotinib. In a phase III study, patients with stage IIIB/IV ALK-rearranged nonsquamous NSCLC who were randomized to receive ceritinib had longer PFS than those randomized to receive platinum-based chemotherapy (16.6 vs 8.1 months, respectively; HR, 0.55, P <.00001). GI toxicity was commonly reported in the ceritinib group.[94]

Alectinib

Alectinib, another second-generation ALK inhibitor, is indicated for the treatment of patients with metastatic ALK-positive NSCLC. In a phase III study in patients with previously untreated, advanced ALK-positive NSCLC, alectinib was associated with longer PFS compared with crizotinib (HR, 0.47; P <.001).[95] After a median follow-up period of 1.5 years, disease progression or death occurred in 41% versus 68% of the alectinib and crizotinib groups, respectively. CNS progression was noted in 12% versus 45% of the alectinib and crizotinib groups, respectively (HR, 0.16; P<.001). Grade 3 to 5 adverse events were less frequent with alectinib compared with crizotinib (41% vs 50%).[95]

Brigatinib

Brigatinib, an inhibitor of ALK and mutant EGFR, is indicated for the treatment of patients with metastatic ALK-positive NSCLC who have progressed on or are intolerant to crizotinib. In a phase III study in patients with advanced ALK-positive NSCLC who had not previously received ALK inhibitors, PFS was longer with brigatinib than with crizotinib (1-year PFS, 67% vs 43%; HR, 0.49; P <.001).[96] The ORR and intracranial response rates both favored brigatinib over crizotinib.[96]

Lorlatinib

Lorlatinib is a new, reversible, ATP-competitive, small-molecule, third-generation, highly selective inhibitor of ALK and the ROS1, that retains potency against all known ALK-resistant mutants.[97] Lorlatinib is indicated for patients with ALK-positive metastatic NSCLC whose disease has progressed on crizotinib and one or more other ALK inhibitor for metastatic disease or whose disease has progressed on alectinib or ceritinib as the first ALK inhibitor therapy for metastatic disease. In a phase II study, patients with ALK-positive or ROS1-positive, advanced NSCLC, with or without CNS metastases, were treated with lorlatinib.[98] The primary endpoints were ORR and intracranial tumor response. The treatment groups were as follows: ALK positive and treatment naive (EXP1); ALK positive and prior crizotinib without chemotherapy (EXP2); ALK positive and prior crizotinib with chemotherapy (EXP3A); ALK positive, one prior non-crizotinib ALK inhibitor with or without chemotherapy (EXP3B); ALK positive, two prior ALK inhibitors with or without chemotherapy (EXP4); ALK positive, three prior ALK inhibitors with or without chemotherapy (EXP5); and ROS1 positive with any previous treatment (EXP6). In treatment-naïve patients (EXP1), the ORR was 90%, and the objective intracranial response rate was 67%. In ALK-positive patients with one or more previous ALK TKI (EXP2–5), the ORR was 47%, and the objective intracranial response rate was 63%. The ORR rates were 69.5% in patients previously treated with crizotinib (EXP2–3A), 32.1% in patients previously treated with a non-crizotinib ALK TKI (EXP3B), and 38.7% in patients with two or more previous ALK TKI treatments (EXP4–5). The objective intracranial response rates were 87% in EXP2–3A, 55.6% in EXP3B, and 53% in EXP 4–5.[98]

NTRK PATHWAY INHIBITORS

The neurotrophic tyrosine kinase receptor (NTKR) genes encode for a family of kinase membrane-bound receptors that, upon neurotrophin binding,

phosphorylate themselves (autophosphorylation) and members of the MAPK pathway. Gene fusions of NTRK1, NTRK2, or NTRK3 that encode the neurotrophin receptors TRKA, TRKB, and TRKC, respectively, are oncogenic drivers of various adult and pediatric tumor types. NTRK fusions are rarely identified in head and neck (0.5%), lung (0.1%–3.3%), colon (0.2%–2.7%), or thyroid (2.4%) cancers; glioblastoma (0.6%–1.2%); and sarcoma (0.2%–1.0%). Their frequency is higher in pediatric high-grade glioma (7%), papillary thyroid cancer (25.9%), and infantile fibrosarcoma and mammary analogue secretory carcinoma of the salivary gland (> 90%). The treatment of patients with NTRK fusion-positive cancers with larotrectinib or entrectinib, the first-generation TRK inhibitors, is associated with high response rates (>75%), regardless of tumor histology. Development of resistance to these inhibitors is attributed to the acquisition of NTRK kinase domain mutations. Second-generation NTRK inhibitors, such as LOXO-195 and TPX-0005, are currently being explored in clinical trials.

Larotrectinib

Larotrectinib, a potent and highly selective small-molecule inhibitor of NTRK1, NTRK2, and NTRK3 proteins, is FDA approved for adult and pediatric patients with solid tumors that have a NTRK gene fusion without a known acquired resistance mutation, that are either metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed after treatment. In patients aged 4 months to 76 years with 17 different tumor types and a TRK fusion, the ORR was 75%.[99] The PFS rate at 1 year was 55%. Drug-related grade 3 or 4 adverse events were reported in fewer than 5% of patients.[99] In patients with TRK fusion-positive cancer treated included in phase I and II trials of larotrectinib, the ORR rate was 79% (CR, 16%) and grade 3 or 4 adverse events were increased ALT (3%), anemia (2%), and neutropenia (2%).[100]

Entrectinib

Entrectinib, a potent inhibitor of TRKA, TRKB, TRKC, ROS1, and ALK, is specifically designed to cross the blood brain barrier (BBB) in addition to its systemic activity. It is indicated for the treatment of adults and patients 12 years of age or older with solid tumors with NTRK gene fusions without a known acquired resistance mutation, with metastatic disease or when surgical resection is contraindicated, and with progression after treatment or without satisfactory standard therapy. In three phase I to II trials in adults with advanced, metastatic NTRK fusion-positive solid tumors, the ORR was 57% (CR, 7%), and the median response duration was 10 months.[101] Grade 3 and 4 adverse events were increased weight (10%), anemia (12%), and nervous system disorders (4%).[101]

ROS PROTO-ONCOGENE 1 RECEPTOR TYROSINE KINASE PATHWAY INHIBITORS

ROS1 is a pivotal transmembrane receptor protein tyrosine kinase that regulates apoptosis, survival, differentiation, proliferation, cell migration, and transformation. ROS1 rearrangements were reported in 1% to 2% of patients with NSCLC and, is involved in various malignancies, including glioblastoma, colorectal cancer, gastric adenocarcinoma, inflammatory myofibroblastic tumor, ovarian cancer, and angiosarcoma. ROS1 and ALK share 49% sequence homology in their primary structures.

Crizotinib is indicated for the treatment of patients with metastatic NSCLC whose tumors are ROS1 positive. Crizotinib was superior to standard chemotherapy in patients with advanced NSCLC with *ALK* rearrangement in a phase III study.[92] In a phase II study in advanced NSCLC with *ROS1* rearrangement, crizotinib was associated with an ORR of 72% (CR, 6%), and the median DOR and PFS were 17.6 months and 19.2 months, respectively.[102]

NOTCH PATHWAY INHIBITORS

Notch was first identified as an oncogene in T-cell acute lymphoblastic leukemia (T-ALL) in which the t(7;9) chromosomal translocation fuses the N-terminal region of the T-cell receptor β (TCR-β) to the C-terminus of Notch1. The truncated Notch1 protein lacks the extracellular subunit and is constitutively active. The intracellular forms of all four Notch proteins are capable of transforming normal cells. Deregulated expression of Notch proteins, ligands, and targets has been described in various solid tumors and hematologic malignancies. Notch contributes to carcinogenesis by inhibiting differentiation, inhibiting apoptosis, or promoting proliferation. The intracellular forms of Notch induce transformation when it is expressed with oncoproteins that disable the G1-S checkpoint, such as adenovirus E1A, human papillomavirus E6 and E7, RAS, Myc, or SV40 large T-antigen. Notch also can activate the expression of several oncogenic pathways via induction of cyclins D1 and D3, cyclin A, SKP2, or c-Myc or via activation of PI3K-AKT-mTOR, NF-κB and NF-κB2, β-catenin,

or signal transducer and activator of transcription-3 (STAT3); it cooperates with oncogenic pathways such as WNT or HER2/Neu. In addition, it is involved in tumor–stroma interactions and has a tumor suppressor effect in the epidermis. Notch activity has been reported in cancer stem–like cells, a small subset of self-sustaining cancer cells that enhance resistance to chemotherapy and radiotherapy.

Neutralizing monoclonal antibodies directed against Notch 1–3 have been used in clinical trials. The development of the humanized mAb tarextumab was terminated due to lack of efficacy. Clinical trials of novel inhibitors are ongoing (eg, AL101, CB-103). Nonselective γ-secretase inhibitors (GSIs) are also known as "Notch inhibitors." Nirogacestat, an oral GSI, demonstrated encouraging results in phase I and II studies in patients with desmoid tumors with most common adverse events diarrhea, skin disorders, and hypophosphatemia. A grade 3 or 4 3 trial comparing nirogacestat with placebo in adults with progressing desmoid tumors is ongoing.

FIBROBLAST GROWTH FACTOR RECEPTOR PATHWAY INHIBITOR

The fibroblast growth factor receptor (FGFR) family comprises four main members (*FGFR1-FGFR4*) and encodes membrane tyrosine kinase receptors involved in signaling by interacting with fibroblast growth factors.[103] *FGFR3*- and *FGFR4*-activating mutations exist,[104,105] but amplification of *FGFR3* and *FGFR4* has been described rarely in cancer. *FGFR1* amplification occurred in 3.4% of 10,648 patients found in found in lung cancer, SCC of the head and neck, esophageal SCC, breast cancer, and pancreatic cancer. *FGFR2* amplification occurred in 0.9% of 8,352 patients[106] and were found in gastric and breast cancer and NSCLC.

In a phase II study of brivanib, an oral, multitargeted TKI with activity against VEGF and FGFR, in recurrent or persistent endometrial cancer, the ORR was 18.6%.[107] Dovitinib, a TKI that inhibits FGFR, VEGFR, and PDGFR, had limited antitumor activity in metastatic renal cell carcinoma and breast cancer.

Erdafitinib

Erdafitinib, an oral potent TKI of FGFR1–4, is indicated for patients with locally advanced or metastatic urothelial carcinoma, with susceptible FGFR3 or FGFR2 genetic alterations, that has progressed during or after platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. In a phase II study, in this patient setting, the ORR was 40% (CR, 3%).[108] In patients with prior immunotherapy, the ORR was 59%. The median duration of PFS and OS were 5.5 months and 13.8 months, respectively.[108]

Pemigatinib

Pemigatinib is another oral inhibitor of FGFR1-3 that is indicated for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or other rearrangement based. The FDA approval was based on favorable results of a phase II study that demonstrated an ORR rate of 35.5% in patients with this disease. Grade 3 and 4 adverse events occurred in 64% of patients and included hypophosphatemia and arthralgia.[109]

Other FGFR inhibitors that are being investigated in clinical trials.

P53 MDM2 PATHWAY/INHIBITORS

The P53-MDM2 interaction has a major role in maintaining the cellular normal function.[110] Direct interaction between P53 and MDM2 blocks the activity of P53 through diverse mechanisms. Inhibition of the P53-MDM2 pathway are an interesting target in cancer drug development. Ongoing clinical trials that include MDM-2 inhibitors are evaluating their safety and efficacy.

SACITUZUMAB GOVITECAN-HZIY

Sacituzumab govitecan-hziy is an antibody drug–conjugate that includes the topoisomerase I inhibitor SN-38 (irinotecan active metabolite), the humanized antitrophoblast cell-surface antigen 2 (Trop-2) mAb hRS7 IgG1κ, and the cleavable CL2A linker. The transmembrane calcium signal transducer Trop-2 is overexpressed in up to 85% in various carcinomas and has a stimulatory growth impact. When bound to Trop-2, hRS7 is internalized and delivers SN-38 into the tumor cell. SN-38, because of the characteristics of the cleavable linker, is released in the microenvironment with therapeutic concentrations in the bystander cells, enabling tumor cell death by extracellular release of SN-38. Sacituzumab govitecan-hziy is indicated for adult patients with metastatic triple-negative breast cancer with two or more prior therapies for metastatic disease. In a phase I/II trial, in patients with these characteristics treated with sacituzumab govitecan-hziy the ORR was 33.3%, and the median response duration was 7.7 months.[111] Grade 3 and 4 adverse events, noted in more than 10% of the patients, included severe neutropenia and diarrhea.[111]

RET PATHWAY INHIBITORS

Selpercatinib, a RET inhibitor, is indicated for the treatment of NSCLC, medullary thyroid cancer, and other types of thyroid cancers in patients whose tumors have a RET mutation or fusion. This is the first therapy approved specifically for patients with cancer and RET gene alterations. The approval was based on favorable ORR and response duration in patients with NSCLC with RET fusion, RET mutated medullary thyroid cancer, and other solid tumors with RET alterations treated with selpercatinib in a phase I/II study.

COLONY-STIMULATING FACTOR 1 RECEPTOR INHIBITOR

Pexidartinib

Pexidartinib, an oral small-molecule TKI of CSF1R, KIT, and FLT3-internal tandem duplication, is indicated for the treatment of adult patients with symptomatic tenosynovial giant cell tumor associated with severe morbidity or functional limitations and not amenable to improvement with surgery.[112] In a phase III trial in patients with advanced tenosynovial giant cell tumor, the ORR was 39% in patients (n = 61) randomized to receive pexidartinib compared with 0% in those randomized to the placebo arm (n = 59; P <.0001). Common adverse events included hair color changes, fatigue, and hepatotoxicity.

CHECKPOINT BLOCKADE PATHWAY INHIBITORS

A large family of costimulatory molecules (eg, programmed cell death protein 1 [PD-1] and PDL-1 and CTLA-4) modulate TCR signaling via phosphorylation cascades, leading to a crucial role in the regulation of the immune response (Table 57–3). These molecules represent remarkable targets for drug development and opened the era of antitumoral immunotherapy since 2011. Currently, there are seven FDA-approved checkpoint inhibitors in various tumors and indications: ipilimumab, pembrolizumab, nivolumab, avelumab, cemiplimab, durvalumab, and atezolizumab. The approval of these molecules is based on their favorable ORR and durable CRs in selected patients. Immunooncology (IO) drugs are associated with unique patterns of response and toxicity.[113]

Multiple trials have been or are being conducted to evaluate IO therapies and biomarkers that may be associated with response or toxicity to immunotherapy. High microsatellite instability (MSI-H) and PDL-1 expression are used to select patients who may benefit from immunotherapy.[114–118] Ongoing IO trials evaluate the association of high tumor mutational burden and other biomarkers with patient outcomes.

FUTURE PERSPECTIVES

Breakthroughs in technology and the discovery of effective drugs have led to epic advances in the war against cancer. We first demonstrated that in early-phase clinical trials across tumor types, tumor molecular profiling, and selection of matched targeted therapy were associated with high rates of response, PFS, and survival in patients with one targetable molecular alteration.[1,3,31,119,120] Progress in next-generation sequencing to identify alterations in tumor and cell-free DNA, profiling of immune markers, proteomics, and transcriptomics optimize treatment selection as standard of care or for selection of clinical trials. Current research focuses on understanding complex mechanisms of tumorigenesis, their dynamic changes and tumor plasticity, and the role of the immune system and microenvironment for identification of clinically significant biomarkers and effective drug discovery (Fig. 57–3). Optimization of bioinformatic analyses and use of artificial intelligence and overcoming regulatory and financial challenges will improve patient access to promising drugs and will improve patient outcomes.

TABLE 57–3 Tissue-agnostic approved targeted agents in cancer

Drug	Targeted Biomarker	Patient Population	Year	Trials
embrolizumab (Keytruda)	MSI-H/dMMR	Adults, children	2017	NCT01876511 (phase 2)
Larotrectinib (Vitrakvi)	NTRK	Adults, children	2018	NCT02122913 (phase 1) NCT02637687 (phase 1/2) NCT02576431 (phase 2)
Entrectinib (Rozlytrek)	NTRK	12 years or older	2019	NCT02097810 (phase 1) NCT02097810 (phase 1) NCT02568267 (phase 2)

dMMR, mismatch repair deficient; high MSI-H, microsatellite instability; NTRK, neurotrophic tyrosine receptor kinase.

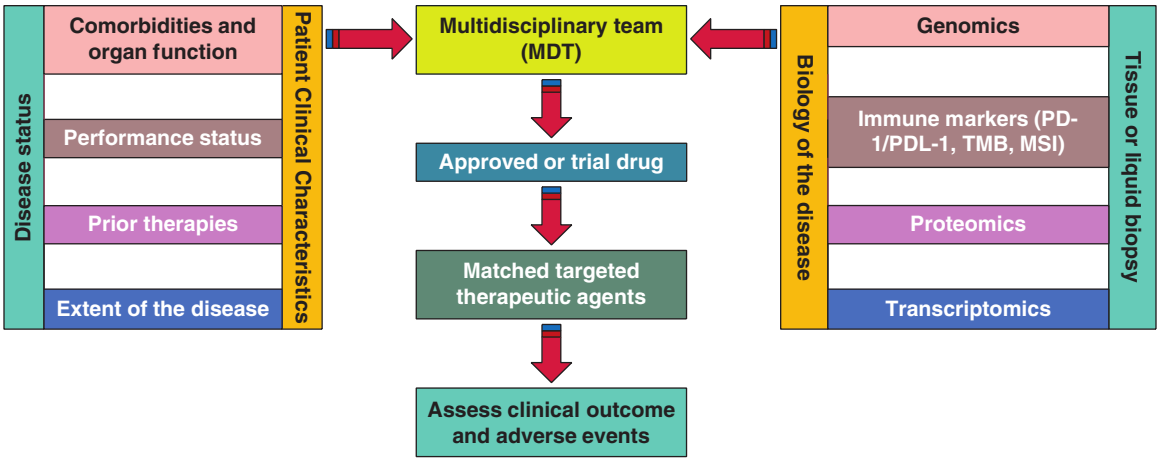


FIGURE 57–3 **Algorithm for investigational therapy. MSI, microsatellite instability; PD-1, programmed cell death protein 1; PD-LI, programmed cell death-ligand 1; TMB, tumor mutational burden.**

As the number of FDA-approved drugs continues to increase, ongoing clinical trials with adaptive design such as Initiative for Molecular Profiling and Advanced Cancer Therapy 2 (IMPACT2), Investigation of Serial Studies to Predict Your Therapeutic Response through Imaging and Molecular Analysis 2 (I-SPY 2), National Cancer Institute Molecular Analysis for Therapy Choice (NCI MATCH), and Targeted Agent and Profiling Utilization Registry (TAPUR) hold the promise of accelerating the implementation of precision medicine using targeted anticancer therapy. Innovative clinical trials with immunotherapy and adoptive cell therapy that include tumor-infiltrating lymphocytes, chimeric antigen receptor T-cells, engineered TCRs, and natural killer cells have improved the clinical outcomes of selected patients and will elucidate the role of immunotherapy in the therapeutic approach of patients with cancer.

MD ANDERSON PRACTICE TIPS

- Early-phase clinical trials of investigational agents in patients with advanced, metastatic cancer and various tumor types have shown that matched therapy based on patients' molecular profiling is associated with higher rates of response, PFS, and OS compared with nonmatched targeted therapy.
- Improvement in bioinformatic analysis, tumor boards, and multidisciplinary conferences help optimize the selection of targeted therapies.
- Current research focuses on understanding complex mechanisms of tumorigenesis, their dynamic changes and tumor plasticity, and the role of the immune system and microenvironment for identification of clinically significant biomarkers of response or resistance to drugs and associated toxicity.
- Circulating tumor DNA analysis emerged as a useful molecular diagnostic approach for patients whose tumor is not accessible to tumor biopsies, tumor biopsies are deemed unsafe, or for monitoring of molecular signatures.
- Adaptive trial design, such as the design of the IMPACT 2 study and American Society of Clinical Oncology (ASCO) TAPUR, hold the promise to accelerate the implementation of precision medicine using targeted anticancer therapy.
- Innovative clinical trials with immunotherapy and adoptive cell therapy have improved the clinical outcomes of selected patients and will elucidate the role of immunotherapy in the therapeutic approach of patients with cancer.

REFERENCES

1. Tsimberidou AM, Iskander NG, Hong DS, et al. Personalized medicine in a phase I clinical trials program: the MD Anderson Cancer Center initiative. *Clin Cancer Res*. 2012;18(22):6373-6383.
2. Von Hoff DD, Stephenson JJ Jr, Rosen P, et al. Pilot study using molecular profiling of patients' tumors to find potential targets and select treatments for their refractory cancers. *J Clin Oncol*. 2010;28(33):4877-4883.
3. Tsimberidou AM, Eggermont AM, Schilsky RL. Precision cancer medicine: the future is now, only better. *Am Soc Clin Oncol Educ Book*. 2014;34:61-69.
4. Dong J, Phelps RG, Qiao R, et al. BRAF oncogenic mutations correlate with progression rather than initiation of human melanoma. *Cancer Res*. 2003;63(14):3883-3885.
5. Poynter JN, Elder JT, Fullen DR, et al. BRAF and NRAS mutations in melanoma and melanocytic nevi. *Melanoma Res*. 2006;16(4):267-273.
6. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med*. 2011;364(26):2507-2516.
7. Chapman PB, Robert C, Larkin J, et al. Vemurafenib in patients with BRAFV600 mutation-positive metastatic melanoma: final overall survival results of the randomized BRIM-3 study. *Ann Oncol*. 2017;28(10):2581-2587.
8. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet*. 2012;380(9839):358-365.
9. Rochet NM, Kottschade LA, Markovic SN. Vemurafenib for melanoma metastases to the brain. *N Engl J Med*. 2011;365(25):2439-2441.
10. Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2012;13(11):1087-1095.
11. Maio M, Lewis K, Demidov L, et al. Adjuvant vemurafenib in resected, BRAF(V600) mutation-positive melanoma: a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. *Lancet Oncol*. 2018;19(4):510-520.
12. Li Z, Jiang K, Zhu X, et al. Encorafenib, a potent BRAF inhibitor, induces senescence accompanied by autophagy in BRAFV600E melanoma cells. *Cancer Lett*. 2016;370(2):332-344.
13. Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma: a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2018;19(5):603-615.
14. Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. *N Engl J Med*. 2012;367(2):107-114.
15. Robert C, Grob JJ, Stroyakovskiy D, et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. *N Engl J Med*. 2019;381(7):626-636.
16. Larkin J, Ascierto PA, Dreno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med*. 2014;371(20):1867-1876.
17. Koelblinger P, Dornbierer J, Dummer R. A review of binimetinib for the treatment of mutant cutaneous melanoma. *Future Oncol*. 2017;13(20):1755-1766.
18. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. *N Engl J Med*. 2015;373(8):726-736.
19. Planchard D, Kim TM, Mazieres J, et al. Dabrafenib in patients with BRAF(V600E)-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2016;17(5):642-650.
20. Planchard D, Besse B, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. *Lancet Oncol*. 2016;17(7):984-993.
21. Planchard D, Smit EF, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously untreated BRAF(V600E)-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. *Lancet Oncol*. 2017;18(10):1307-1316.
22. Johnson ML, Sima CS, Chaft J, et al. Association of KRAS and EGFR mutations with survival in patients with advanced lung adenocarcinomas. *Cancer*. 15 2013;119(2):356-362.
23. Cantley LC. The phosphoinositide 3-kinase pathway. *Science*. 2002;296(5573):1655-1657.
24. Hollander MC, Blumenthal GM, Dennis PA. PTEN loss in the continuum of common cancers, rare syndromes and mouse models. *Nat Rev Cancer*. 2011;11(4):289-301.
25. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell*. 2000;100(1):57-70.
26. Martin M, Chan A, Dirix L, et al. A randomized adaptive phase II/III study of buparlisib, a pan-class I PI3K inhibitor, combined with paclitaxel for the treatment of HER2- advanced breast cancer. *Ann Oncol*. 2017;28(2):313-320.
27. Gopal AK, Kahl BS, de Vos S, et al. PI3Kdelta inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med*. 2014;370(11):1008-1018.
28. Flinn IW, Hillmen P, Montillo M, et al. The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. *Blood*. 2018;132(23):2446-2455.
29. Dreyling M, Morschhauser F, Bouabdallah K, et al. Phase II study of copanlisib, a PI3K inhibitor, in relapsed or refractory, indolent or aggressive lymphoma. *Ann Oncol*. 2017;28(9):2169-2178.
30. Andre F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. *N Engl J Med*. 2019;380(20):1929-1940.
31. Tsimberidou AM, Hong DS, Wheler JJ, et al. Long-term overall survival and prognostic score predicting survival: the IMPACT study in precision medicine. *J Hematol Oncol*. 2019;12(1):145.
32. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med*. 2005;353(2):123-132.
33. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2004;350(21):2129-2139.
34. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science*. 2004;304(5676):1497-1500.
35. Sequist LV, Martins RG, Spigel D, et al. First-line gefitinib in patients with advanced non-small-cell lung cancer harboring somatic EGFR mutations. *J Clin Oncol*. 2008;26(15):2442-2449.
36. Cappuzzo F, Ligorio C, Janne PA, et al. Prospective study of gefitinib in epidermal growth factor receptor fluorescence in situ hybridization-positive/phospho-Akt-positive or never smoker patients with advanced non-small-cell lung cancer: the ONCOBELL trial. *J Clin Oncol*. 2007;25(16):2248-2255.
37. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009;361(10):947-957.
38. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor: an open label, randomised phase 3 trial. *Lancet Oncol*. 2010;11(2):121-128.
39. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med*. 2010;362(25):2380-2388.
40. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer: a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol*. 2011;12(8):735-742.

41. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer: a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2012;13(3):239-246.
42. Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomized, placebo-controlled phase 3 study. *Lancet Oncol*. 2010;11(6):521-529.
43. Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study. *Lancet*. 2005;366(9496):1527-1537.
44. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol*. 2013;31(27):3327-3334.
45. Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med*. 2011;3(75):75ra26.
46. Mok TS, Cheng Y, Zhou X, et al. Improvement in overall survival in a randomized study that compared dacomitinib with gefitinib in patients with advanced non-small-cell lung cancer and EGFR-activating mutations. *J Clin Oncol*. 2018;36(22):2244-2250.
47. Cross DA, Ashton SE, Ghiorghiu S, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. *Cancer Discov*. 2014;4(9):1046-1061.
48. Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med*. 2017;376(7):629-640.
49. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med*. 2018;378(2):113-125.
50. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med*. 2004;351(4):337-345.
51. Jonker DJ, O'Callaghan CJ, Karapetis CS, et al. Cetuximab for the treatment of colorectal cancer. *N Engl J Med*. 2007;357(20):2040-2048.
52. Licitra L, Storkel S, Kerr KM, et al. Predictive value of epidermal growth factor receptor expression for first-line chemotherapy plus cetuximab in patients with head and neck and colorectal cancer: analysis of data from the EXTREME and CRYSTAL studies. *Eur J Cancer*. 2013;49(6):1161-1168.
53. Bokemeyer C, Bondarenko I, Makhson A, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol*. 2009;27(5):663-671.
54. Douillard JY, Siena S, Cassidy J, et al. Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. *Ann Oncol*. 2014;25(7):1346-1355.
55. Price TJ, Peeters M, Kim TW, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer: a randomised, multicentre, open-label, non-inferiority phase 3 study. *Lancet Oncol*. 2014;15(6):569-579.
56. Thatcher N, Hirsch FR, Luft AV, et al. Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer: an open-label, randomised, controlled phase 3 trial. *Lancet Oncol*. 2015;16(7):763-774.
57. Patel S. Long-term efficacy of imatinib for treatment of metastatic GIST. *Cancer Chemother Pharmacol*. 2013;72(2):277-286.
58. Bednarski BK, Araujo DM, Yi M, et al. Analysis of prognostic factors impacting oncologic outcomes after neoadjuvant tyrosine kinase inhibitor therapy for gastrointestinal stromal tumors. *Ann Surg Oncol*. 2014;21(8):2499-2505.
59. Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. *J Clin Oncol*. 2003;21(23):4342-4349.
60. Corless CL, Barnett CM, Heinrich MC. Gastrointestinal stromal tumours: origin and molecular oncology. *Nat Rev Cancer*. Dec 2011;11(12):865-878.
61. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet*. 2006;368(9544):1329-1338.
62. Gajiwala KS, Wu JC, Christensen J, et al. KIT kinase mutants show unique mechanisms of drug resistance to imatinib and sunitinib in gastrointestinal stromal tumor patients. *Proc Natl Acad Sci U S A*. 2009;106(5):1542-1547.
63. Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib: an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381(9863):295-302.
64. Smith BD, Kaufman MD, Lu WP, et al. Ripretinib (DCC-2618) is a switch control kinase inhibitor of a broad spectrum of oncogenic and drug-resistant KIT and PDGFRA variants. *Cancer Cell*. 2019;35(5):738-751 e739.
65. Heinrich MC, Jones RL, von Mehren M, et al. Clinical activity of avapritinib in ≥ fourth-line and PDGFRA Exon 18 gastrointestinal stromal tumors (GIST). *J Clin Oncol*. 2019;37(15 suppl):11022.
66. Mustacchi G, Biganzoli L, Pronzato P, et al. HER2-positive metastatic breast cancer: a changing scenario. *Crit Rev Oncol Hematol*. 2015.
67. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med*. 2019;380(7):617-628.
68. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med*. 2017;377(2):122-131.
69. Martin M, Holmes FA, Ejlertsen B, et al. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer: 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2017;18(12):1688-1700.
70. Saura C, Oliveira M, Feng Y-H, et al. Neratinib plus capecitabine versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer previously treated with ≥ 2 HER2-directed regimens: findings from the multinational, randomized, phase III NALA trial. *J Clin Oncol*. 2019;37(15 suppl):1002.
71. Doi T, Shitara K, Naito Y, et al. Safety, pharmacokinetics, and antitumour activity of trastuzumab deruxtecan, a HER2-targeting antibody-drug conjugate, in patients with advanced breast and gastric or gastro-oesophageal tumours: a phase 1 dose-escalation study. *Lancet Oncol*. 2017;18(11):1512-1522.
72. Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med*. 2020;382(7):610-621.
73. VanArsdale T, Boshoff C, Arndt KT, Abraham RT. Molecular pathways: targeting the cyclin D-CDK4/6 axis for cancer treatment. *Clin Cancer Res*. 2015;21(13):2905-2910.
74. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med*. 2016;375(20):1925-1936.
75. Turner NC, Slamon DJ, Ro J, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. *N Engl J Med*. 2018;379(20):1926-1936.
76. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for hr-positive, advanced breast cancer. *N Engl J Med*. 2016;375(18):1738-1748.
77. Im SA, Lu YS, Bardia A, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. *N Engl J Med*. 2019;381(4):307-316.
78. Slamon DJ, Neven P, Chia S, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. *N Engl J Med*. 2020;382(6):514-524.

79. Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol*. 2017;35(25):2875-2884.
80. Goetz MP, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol*. 2017;35(32):3638-3646.
81. Tran C, Ouk S, Clegg NJ, et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. *Science*. 2009;324(5928):787-790.
82. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med*. 2012;366(15):1382-1392.
83. Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *N Engl J Med*. 2017;377(6):523-533.
84. Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med*. 2018;379(26):2495-2505.
85. Golan T, Hammel P, Reni M, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. *N Engl J Med*. 2019;381(4):317-327.
86. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *N Engl J Med*. 2016;375(22):2154-2164.
87. Gonzalez-Martin A, Pothuri B, Vergote I, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med*. 2019;381(25):2391-2402.
88. Bentzien F, Zuzow M, Heald N, et al. In vitro and in vivo activity of cabozantinib, an inhibitor of RET, MET, and VEGFR2, in a model of medullary thyroid cancer. *Thyroid*. 2013;23(12):1569-1577.
89. Wolf J, Seto T, Han JY, et al. Capmatinib in METΔex14-mutated advanced non-small cell lung cancer: efficacy data from the phase II GEOMETRY mono-1 study. *J Clin Oncol*. 2019;37(15 suppl):9004.
90. Otsuka T, Takayama H, Sharp R, et al. c-MET autocrine activation induces development of malignant melanoma and acquisition of the metastatic phenotype. *Cancer Res*. 1998;58(22):5157-5167.
91. Rehman S, Dy GK. MET inhibition in non-small cell lung cancer. *Eur Med J*. 2018;4[1]:100-111.
92. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med*. 2013;368(25):2385-2394.
93. Shaw AT, Yeap BY, Solomon BJ, et al. Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring ALK gene rearrangement: a retrospective analysis. *Lancet Oncol*. 2011;12(11):1004-1012.
94. Soria JC, Tan DSW, Chiari R, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer: a randomised, open-label, phase 3 study. *Lancet*. 2017;389(10072):917-929.
95. Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med*. 2017;377(9):829-838.
96. Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. *N Engl J Med*. 2018;379(21):2027-2039.
97. Zou HY, Friboulet L, Kodack DP, et al. PF-06463922, an ALK/ROS1 inhibitor, overcomes resistance to first and second generation ALK inhibitors in preclinical models. *Cancer Cell*. 2015;28(1):70-81.
98. Solomon BJ, Besse B, Bauer TM, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. *Lancet Oncol*. 2018;19(12):1654-1667.
99. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N Engl J Med*. 2018;378(8):731-739.
100. Hong DS, DuBois SG, Kummar S, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. *Lancet Oncol*. 2020;21(4):531-540.
101. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. *Lancet Oncol*. 2020;21(2):271-282.
102. Shaw AT, Ou SH, Bang YJ, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med*. 2014;371(21):1963-1971.
103. Andre F, Bachelot T, Campone M, et al. Targeting FGFR with dovitinib: preclinical and clinical data in breast cancer. *Clin Cancer Res*. 2013;19(13):3693-3702.
104. Rugo HS, Olopade O, DeMichele A, et al. Veliparib/carboplatin plus standard neoadjuvant therapy for high-risk breast cancer: first efficacy results from the I-SPY 2 TRIAL. Paper presented at: 36th Annual San Antonio Breast Cancer Symposium; 2013:abstract S5-02.
105. Chang J, Liu X, Wang S, et al. Prognostic value of FGFR gene amplification in patients with different types of cancer: a systematic review and meta-analysis. *PLoS One*. 2014;9(8):e105524.
106. National Institutes of Health. The Cancer Genome Atlas Program. http://cancergenome.nih.gov
107. Powell MA, Sill MW, Goodfellow PJ, et al. A phase II trial of brivanib in recurrent or persistent endometrial cancer: an NRG Oncology/Gynecologic Oncology Group Study. *Gynecol Oncol*. 2014;135(1):38-43.
108. Loriot Y, Necchi A, Park SH, et al. Erdafitinib in locally advanced or metastatic urothelial carcinoma. *N Engl J Med*. 2019;381(4):338-348.
109. Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. *Lancet Oncol*. 2020; 21(5):671-684.
110. Fang Y, Liao G, Yu B. Small-molecule MDM2/X inhibitors and PROTAC degraders for cancer therapy: advances and perspectives. *Acta Pharmaceut Sinica B*. 2020;10(7):1253-1278.
111. Bardia A, Mayer IA, Vahdat LT, et al. Sacituzumab govitecan-hziy in refractory metastatic triple-negative breast cancer. *N Engl J Med*. 2019;380(8):741-751.
112. Tap WD, Wainberg ZA, Anthony SP, et al. Structure-guided blockade of CSF1R kinase in tenosynovial giant-cell tumor. *N Engl J Med*. 2015;373(5):428-437.
113. Tsimberidou AM, Levit LA, Schilsky RL, et al. Trial Reporting in Immuno-Oncology (TRIO): an American Society of Clinical Oncology-Society for Immunotherapy of Cancer statement. *J Clin Oncol*. 2019;37(1):72-80.
114. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science*. 2015;348(6230):124-128.
115. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med*. 2018;378(22):2093-2104.
116. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med*. 2015;372(26):2509-2520.
117. Goodman AM, Piccioni D, Kato S, et al. Prevalence of PDL1 amplification and preliminary response to immune checkpoint blockade in solid tumors. *JAMA Oncol*. 2018;4(9):1237-1244.
118. Goodman AM, Kato S, Bazhenova L, et al. Tumor mutational burden as an independent predictor of response to immunotherapy in diverse cancers. *Mol Cancer Ther*. 2017;16(11):2598-2608.
119. Tsimberidou AM, Wen S, Hong DS, et al. Personalized medicine for patients with advanced cancer in the phase I program at MD Anderson: validation and landmark analyses. *Clin Cancer Res*. 2014;20(18):4827-4836.
120. Tsimberidou AM, Hong DS, Ye Y, et al. Initiative for Molecular Profiling and Advanced Cancer Therapy (IMPACT): an MD Anderson precision medicine study. *JCO Precis Oncol*. 2017;2017:PO.17.00002.

58 Viral Infections in Patients with Cancer

Fareed Khawaja
Roy F. Chemaly

KEY CONCEPTS

- Viral infections caused by herpes simplex virus (HSV) 1 and 2, varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus, and human herpesvirus 6, can reactivate in immunosuppressed patients and lead to increased morbidity and mortality.
- Cutaneous HSV and VZV infections have characteristic appearances on physical examination, and confirmation can be obtained with polymerase chain reaction–based molecular assays. Treatment of patients with severe HSV and VZV infections requires the use of intravenous treatment dose of acyclovir, and if started early, it may reduce serious complications.
- CMV reactivation has varied clinical presentations in patients with hematologic malignancies and hematopoietic cell transplantation (HCT) recipients. Specific viral loads thresholds trigger initiation of antiviral therapy to prevent end-organ disease and serious complications.
- Adenovirus infections can range from upper respiratory tract infection, pneumonia, gastrointestinal infections, or asymptomatic viremia. Treatment is indicated in immunocompromised patients, such as HCT recipients, with disseminated disease. Cidofovir is the only commercially available agent with in vitro activity against adenoviruses.
- Community respiratory viral infections are commonly diagnosed in patients with cancer and are associated with increased morbidity and mortality in immunosuppressed patients in particular.
- Hepatitis B and C viral infections are common in certain parts of the world. Patients with cancer should undergo testing for both viruses before chemotherapy. Prevention of hepatitis B with entecavir or tenofovir is recommended in high-risk patients to prevent fulminant liver failure. Hepatitis C is treated with intent to cure and can be postponed until after chemotherapy.

Viral infections are an important cause of morbidity and mortality in patients with cancer, specifically among patients with hematologic malignancies or recipients of hematopoietic cell transplantation (HCT). Patients with cancer with viral infections may have longer hospitalizations and delays in cancer-related treatment such as chemotherapy, surgery, or radiation. DNA viruses, such as herpes simplex virus (HSV), varicella zoster virus (VZV), and cytomegalovirus (CMV), are well known to cause serious infections in patients with hematologic malignancies or after HCT, resulting in intense monitoring and prophylaxis directed against such viruses.[1] Respiratory viral infections are also common among patients with cancer; these include infections related to adenovirus, influenza, parainfluenza, respiratory syncytial virus (RSV), rhinovirus, human coronavirus (HCoV), and human metapneumovirus (hMPV).[2] Modern tools of diagnosis can quickly identify viral pathogens, but treatment options are limited for many of these infections. This chapter provides an overview of viral infections in patients with cancer. Special focus is placed on those with hematologic malignancies and HCT recipients because this population is uniquely susceptible to viral infections.

HUMAN HERPESVIRUSES

Infections related to human herpesviruses (HHVs) are common among patients with cancer.[3] Morbidity and mortality from these viruses are high among immunosuppressed patients. Herpesviruses are double-stranded DNA viruses. The herpesvirus group has eight members, six of which are important pathogens

in immunosuppressed patients (ie, patients with hematologic malignancies, solid-organ or stem cell transplant recipients).[4,5] This group of pathogens includes HSV 1 and 2, VZV, CMV, Epstein-Barr virus (EBV), and HHV-6.

Herpesviruses establish a latent phase after primary infection. The reactivation of these DNA viruses can be triggered by several stimuli; this is perhaps best recognized in the recurrent blisters and ulcers associated with HSV. The likelihood of reactivation of these viruses is increased during profound T-cell immunosuppression because host defenses against these viruses are dependent on virus-specific helper and cytotoxic T lymphocytes. Over the past decade, substantial improvements have been made in the techniques used to detect these infections, such as real-time polymerase chain reaction (PCR), as well as the development of effective antiviral agents and the use of different strategies for prophylaxis and treatment.

Herpes Simplex Virus

Among the most common causes of mucocutaneous lesions in immunocompromised patients are HSV types 1 and 2.[5] Approximately 40% to 60% of seropositive patients undergoing induction chemotherapy for leukemia or conditioning for HCT will experience HSV reactivation, usually in early stages, when immunosuppression is most intense.[5] HSV reactivation may also cause severe disease during neutropenia. Patients with a CD4 count less than 50 cells per cubic millimeter of blood who received purine analogs or alemtuzumab are at highest risk of reactivation.[5] It was previously believed that HSV-1 infections presented as oropharyngeal or esophageal diseases, and HSV-2 was associated with genital lesions. More recent studies have shown that there is much overlap between the sites of reactivation for HSV-1 and HSV-2.[6–8] Other clinical presentations for HSV-1 or -2 infections can range from fever, malaise, myalgia, dysphagia, and bleeding to severe oral pain and odynophagia. Table 58–1 lists different syndromes associated with HSV infections.

Diagnosis

With the advancement of molecular diagnostics, real-time PCR directly on tissue samples has become the new standard of diagnosis of HSV-1 or -2 infections. Real-time PCR can detect HSV in a number of samples, including skin tissue, cerebrospinal fluid (CSF), and vitreous humor. It is more sensitive than previous diagnostic tools, such as viral cell cultures.[9,10] Other testing includes direct fluorescent antibody testing, which is a rapid antigen test for HSV; the sensitivity is poor compared with real-time PCR. The role of HSV-1 and -2 antibody testing is largely used to detect evidence of prior infections.

TABLE 58–1 Human Herpes Simplex Virus-1 or -2 Related Syndromes

Site	Disease
Oral cavity and gastrointestinal tract	Herpes labialis Gingivostomatitis Pharyngitis Esophagitis Hepatitis
Cutaneous	Herpetic whitlow Herpes gladiatorum Erythema multiforme Eczema herpeticum
Ocular and central nervous system	Keratitis Acute retinal necrosis Conjunctivitis Chorioretinitis Meningoencephalitis

Prophylaxis

Antiviral prophylaxis should be strongly considered in HSV-seropositive patients at risk for reactivation during intensive chemotherapy for acute leukemia and during early stages of HCT.[4,5] Oral acyclovir and valacyclovir are the agents of choice for prophylaxis. If patients are receiving intravenous (IV) foscarnet, ganciclovir, or valganciclovir for treatment of another viral infection, then they do not need to continue acyclovir prophylaxis.[11] Guidelines suggest that continuing prophylaxis for over 1 year after HCT significantly reduces reactivation and may even decrease the risk of acyclovir-resistant HSV.[5,11,12]

Therapy

The available antiviral agents for the treatment of HSV disease include acyclovir, valacyclovir, famciclovir, foscarnet, and cidofovir (Tables 58–2 and 58–3).[4,11] The most commonly used drug is acyclovir. The bioavailability of oral valacyclovir and famciclovir is three to five times superior to that of oral acyclovir. All of these drugs are dependent on the virus-encoded thymidine kinase for their intracellular phosphorylation for activity.

Treatment of patients with HSV with either oral or IV therapy is based on the severity of disease and if the patient can tolerate or absorb oral therapy. Severe HSV-1 and -2 infections in immunocompromised patients with hematologic malignancies or prior HCT, such as herpes meningoencephalitis and hepatitis, are initially treated with IV acyclovir (5–10 mg/kg every 8 hour). Otherwise, an oral regimen can be used for milder HSV disease (famciclovir, 500 mg three times a day, or valacyclovir, 1 g three times

TABLE 58–2 Antiviral Compounds

Antiviral	Dosage	Mechanism of Action	Active Against
Acyclovir	5–10 mg/kg IV every 8 hours	Inhibits DNA polymerase	HSV, VZV
Famciclovir	500 mg PO every 8 hours	Inhibits DNA polymerase	HSV, VZV
Valacyclovir	0.5–1 g every 8–12 hours	Inhibits DNA polymerase	HSV, VZV
Ganciclovir	5 mg/kg every 12 hours	Inhibits DNA polymerase	CMV, HSV
Foscarnet	60 mg/kg IV every 8 hours	Inhibits DNA polymerase	CMV, HSV, VZV, HHV-6
Cidofovir[a]	5 mg/kg IV once a week	Inhibits DNA polymerase	CMV, ADV, HSV, VZV, BK
Letermovir	480 mg PO daily	CMV DNA terminase complex inhibition	CMV
Oral ribavirin	600 mg every 8 hours	Inhibits RNA polymerase	HCV, RSV
Inhaled ribavirin	2 g over 2–3 hours every 8 hours or 6 g continuously over 18 hours	Inhibits RNA polymerase	RSV
Amantadine	100 mg PO every 12 hours or 200 mg PO daily	Inhibits M2 Protein	Influenza A only
Rimantadine	100 mg PO every 12 hours	Inhibits M2 Protein	Influenza A only
Oseltamivir	75 mg PO every 12 hours	Neuraminidase inhibitor	Influenza A and B
Peramivir	600 mg once	Neuraminidase Inhibitor	Influenza A and B
Zanamivir	Two inhalations every 12 hours (IV formulation available, clinical trial)	Neuraminidase inhibitor	Influenza A and B
Baloxavir	40 mg PO once (patient weight, 40 kg to <80 kg) 80 mg PO once (patient weight, ≥80 kg)	cap-dependent endonuclease inhibitor	Influenza A and B

[a]Licensed for cytomegalovirus (CMV) retinitis.
ADV, adenovirus; HCV, hepatitis C virus; HSV, herpes simplex viruses; IV, intravenous; PO, oral; RSV, respiratory syncytial virus; VZV, varicella zoster virus.

TABLE 58–3 Common and Serious Toxicities of Antivirals

Acyclovir	Transient renal insufficiency (IV), nausea, vomiting, agitation, confusion, TTP (rare)
Famciclovir	Headache, somnolence, nausea, diarrhea
Valacyclovir	Headache, nausea, vomiting, TTP (rare)
Ganciclovir	Anemia, neutropenia (more common), thrombocytopenia, fever, phlebitis, anorexia
Foscarnet	Nephrotoxicity (major toxicity), electrolyte disturbances (hypocalcemia, hypophosphatemia, hyperphosphatemia, hypomagnesemia, hypokalemia), diarrhea, nausea, vomiting
Cidofovir	Headache, rash, severe nephrotoxicity, metabolic acidosis, decreased intraocular pressure, neutropenia
Letermovir	Peripheral edema, headaches, GI complaints (nausea, vomiting, diarrhea), arrhythmia (tachycardia, atrial fibrillation), thrombocytopenia
Ribavirin	Fatigue, headache, nausea, rash, pruritus, conjunctivitis (inhalation, health care workers administering ribavirin), hemolytic anemia (cardiac and pulmonary events have occurred), worsening respiratory status, including death (inhalation)
Oseltamivir	Insomnia, vertigo, nausea, vomiting (most common), bronchitis
Zanamivir	Headache, nausea, diarrhea, cough, bronchospasm, decline in lung function (some fatal outcomes)
Peramivir	Hypertension, increased serum glucose, GI complaints (diarrhea, constipation, vomiting), increase in liver enzymes, rash, delirium
Baloxavir	Diarrhea, rash, eyelid edema, delirium, hallucinations

GI, gastrointestinal; IV, intravenous; TTP, thrombotic thrombocytopenic purpura

a day) can be used in patients who can tolerate oral therapy.[4,5] Foscarnet and cidofovir can be used for resistant disease but are only available in IV formulations only.[11]

Varicella Zoster Virus

VZV reactivation occurs primarily in older adults, seropositive organ transplant and HCT recipients, patients with cancer, and those with acquired immunodeficiency

syndrome (AIDS). Disseminated VZV infection can be life threatening in HCT recipients and patients receiving intensive corticosteroid therapy.[5]

The clinical manifestations of VZV infection are primary varicella infection (chickenpox) and herpes zoster (shingles). The clinical presentation includes low-grade fever, malaise, and a vesicular rash that evolves to scabs. Constitutional symptoms usually develop after the onset of rash and include pruritus, anorexia, and listlessness. Primary VZV infection (chickenpox) occurs mainly in children younger than 10 years of age.

Reactivation of latent VZV or herpes zoster is frequently observed among patients with cancer, mainly patients with leukemia or lymphoma, as well as in HCT recipients.[4,5] Comparatively, solid tumor patients do not have as high a risk of VZV reactivation.[13] Visceral herpes zoster may follow cutaneous dissemination in immunocompromised patients and can result in pneumonia, encephalitis, retinal necrosis, hepatitis, and small bowel disease. Cutaneous VZV eruption can be complicated by secondary bacterial infections, thrombocytopenia, and vasculitis (Fig. 58–1).

Diagnosis

In cases of shingles in immunocompromised patients, the diagnosis can be made based on clinical observation of typical dermatomal distribution of a vesicular rash. However, immunocompromised patients commonly develop multidermatomal or disseminated cutaneous disease, which can make the clinical diagnosis less certain on visual inspection alone. The diagnosis can be established with the use of real-time PCR, which has replaced immunofluorescent staining and viral culture.[14] In some cases, a biopsy is required to establish the diagnosis because other diseases can mimic VZV, such as streptococcal impetigo, graft-versus-host disease (GVHD), and various noninfectious bullous diseases.



FIGURE 58–1 Hemorrhagic vesicular lesions of herpes zoster.

Therapy

The treatment of choice for chickenpox or VZV in immunocompromised patients is high-dose IV acyclovir (10 mg/kg every 8 hours) (see Tables 58–2 and 58–3). Early initiation of acyclovir is paramount because it may reduce progression to end-organ disease and usually prevents death in patients with reactivated infection. Therapy can be changed to an oral agent after clinical improvement has occurred, including resolution of fever or healing or crusting of lesions. The options for an oral regimen for treatment of localized herpes zoster among patients with mild immunosuppression include acyclovir (rarely used because of bioavailability and pills burden), valacyclovir, and famciclovir.[15]

Prevention of Infection and Postexposure Prophylaxis

In immunocompetent patients older than 50 years of age, VZV vaccinations are recommended to prevent reactivation or severe VZV infection. However, immunocompromised patients may not receive the live zoster vaccines (Zostavax) because of the risk for viral reactivation. Additionally, because of concomitant chemotherapy, there are concerns regarding efficacy. Recent studies regarding the use of the recombinant zoster vaccine (Shingrix) in solid tumor patients receiving chemotherapy, patients with hematologic malignancy, and autologous HCT recipients demonstrated both safety and clinical efficacy.[16–18] This has not been replicated in allogeneic HCT recipients, but further studies are underway. In patient who are at high risk of shingles or recurrent VZV disease, antiviral prophylaxis with oral valacyclovir or acyclovir should be strongly considered in VZV-seropositive patients during intensive chemotherapy and during the early stages of HCT.[4,5]

Immunosuppressed patients with negative VZV titers and no history of chickenpox should be offered varicella zoster immune globulin after being in close contact with individuals with either chickenpox or herpes zoster infection. Close contact includes prolonged face-to-face contact, a household or playmate contact, or exposure to a roommate in a shared hospital room. Varicella zoster immune globulins, if available, should be administered within 96 hours of exposure to be most effective in preventing infections.[5] Immunocompromised persons should avoid contact with individuals who developed a rash after receiving the live zoster vaccines. No additional precautions are required if a rash has not developed.[5,11]

Infection Control Considerations

VZV can be transmitted from person to person, potentially resulting in an outbreak in a hospital

or clinic setting. To prevent nosocomial transmission, immunocompromised patients with cutaneous lesions suspicious of VZV eruption and those with disseminated zoster should be placed under contact and respiratory isolation.[19] In addition, it is recommended that the family members, caregivers, and visitors of patients scheduled to undergo transplant be vaccinated against VZV, preferably at least 4 weeks before conditioning regimen.[5,11]

Cytomegalovirus

Evidence of prior CMV infection is present in more than half of the US population.[20] Therefore, reactivation of latent CMV infection is of primary concern in the hematologic malignancy and HCT patient populations.[5,11] CMV reactivation can manifest as asymptomatic viremia, a mononucleosis-like syndrome with lymphadenopathy, or more severe disease with end-organ damage. Other symptoms of CMV reactivation include fever, splenomegaly, lymphocytosis, polyradiculopathy, or pancytopenia. Manifestations of end-organ disease include retinitis, encephalitis, and hepatitis, but pneumonitis and gastrointestinal (GI) disease are the most common after allogeneic HCT.[5]

The most common sites of CMV infection in the GI tract are the esophagus and colon. The hallmarks of CMV colitis are abdominal pain and diarrhea. CMV esophagitis is associated with pain and dysphagia. On upper endoscopy, ulcerations can be seen in the esophagus, and a biopsy must be obtained to rule out other infectious causes, such as HSV and candida esophagitis. Similarly, the diagnosis of CMV colitis requires biopsy. In a retrospective study at our institution, 72% of patients diagnosed with GI CMV disease had hematologic malignancies, 25% had AIDS, and the overall CMV-attributable mortality rate was 42%.[21] Independent predictors of mortality were disseminated CMV and diagnosis of AIDS.[21]

CMV pneumonitis can be associated with a high mortality rate in patients with high-risk leukemia and in HCT recipients.[5] Pneumonitis typically presents with severe dyspnea, hypoxia, and interstitial disease on chest radiographs. Similar to GI disease, finding of CMV from bronchoscopy specimens without accompanying pathology is of unclear significance. Preexisting thrombocytopenia, present in most patients with leukemia and HCT recipients, often prevents acquisition of a biopsy specimen that can accurately confirm a diagnosis of CMV pneumonitis. A study of autopsy-proven CMV pneumonia in HCT and patients with hematologic malignancies showed that incidence decreased over the time of the study (from 1990 to 2004).[22]

Risk Factors

Patients with HCT and hematologic malignancies are at highest risk for CMV infection and reactivation. In patients with leukemia, those at highest risk include patients who have received purine analogs (eg, fludarabine) and T-cell–depleting monoclonal antibodies (mAbs, eg, alemtuzumab).[5,23] Reactivation can occur in almost 5% of those receiving purine analogs and in 15% to 66% of those receiving alemtuzumab, with the highest risk period for the latter group being in the first 1 to 3 months after therapy.[5] Reactivation in the setting of alemtuzumab therapy was, however, significantly reduced (0% vs 35% in the control arm) with prophylaxis using valganciclovir 450 mg orally twice per day compared with 500 mg/day of valacyclovir.[24]

In HCT recipients, the highest risk group is the CMV-seropositive recipient, regardless of donor serostatus, followed by CMV-seronegative recipients with seropositive donors.[5] Nonmyeloablative regimens for HCT recipients have resulted in decreased risk of CMV reactivation, although cases have occurred later after transplant.[25] The period of highest risk is in the first 100 days after transplant, although prophylaxis and preemptive strategies have resulted in CMV infections after day 100 from transplantation.[26] Risk factors for late disease in HCT recipients include GVHD, CMV reactivation before day 100 posttransplant, steroid use, low CD4 count (<50 cells per cubic millimeter of blood), use of unmatched stem cells, cord blood, T-cell–depleted stem cells, and receipt of allograft-negative donors in CMV-positive recipients.[11,27] CMV can also be transmitted to HCT recipients from seropositive donors and from blood products.[5] The use of CMV-seronegative blood for transfusions and leukoreduction of blood products has resulted in significantly reduced CMV infections.[5]

Diagnosis

Diagnosis of CMV depends on the site of infection. For detection of disseminated infection or reactivation, the two types of tests available and recommended for diagnosis of CMV include pp65 testing and detection of DNA.[11] Serologic testing is not useful, except for donor selection for transplant, because CMV antibodies demonstrate evidence of prior exposure rather than active infection. For detection of end-organ disease such as in the liver and lungs, the recommended approach is biopsy with detection of viral inclusions on histopathology or by immunohistochemistry (Fig. 58–2), which has greater sensitivity. If available, in situ PCR and nucleic acid hybridization are also useful diagnostic tools for biopsy samples. Detection of CMV DNA is a widely available test in transplant centers, using quantitative real-time PCR (rt-PCR) for CMV DNA detection.[5,11,28]

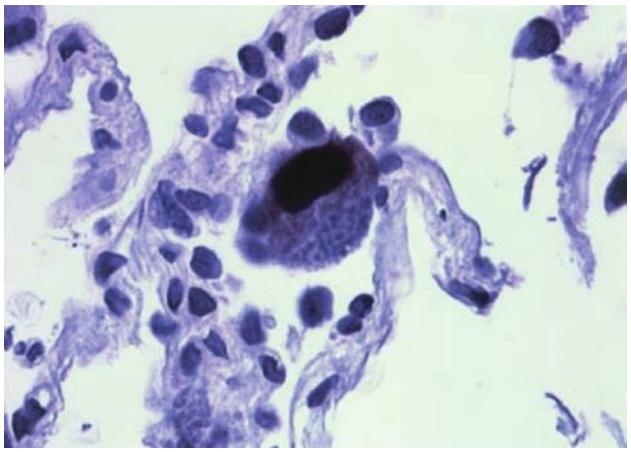


FIGURE 58–2 **Typical cytomegalovirus inclusions in the lung parenchyma of a patient with lymphoma and pneumonia.**

Prevention of Cytomegalovirus Infections in Hematopoietic Cell Transplantation Recipients

There are two main strategies to prevent of CMV infections in HCT recipients, preemptive therapy or chemoprophylaxis.[28–30] Preemptive strategy involves monitoring in whole blood or plasma for CMV DNAemia or antigenemia in HCT recipients on a weekly basis after transplantation. CMV-targeted therapy would be initiated at a predetermined CMV viral load cutoff based on the risk for CMV disease. By initiating therapy early on, the risks of CMV end-organ disease and other virus-associated complications are reduced in HCT recipients.

In HCT recipients with prior evidence of CMV infection based on pre-transplant serology (seropositive), a newly approved agent, letermovir, that works on the viral terminase complex of CMV is indicated as a prophylactic agent for clinically significant CMV reactivation within 100 days after transplantation. Letermovir was found to significantly reduce the incidence of CMV infection in HCT recipients at high risk for reactivation compared with placebo.[31,32] In addition, letermovir has no antiviral activity against any other herpesviruses, and valacyclovir or acyclovir should be given for HSV or VZV chemoprophylaxis in patients at risk. In clinical trials, letermovir was found to be safe and well tolerated.[31,32] The most common side effects were vomiting and development of edema.[31,32] Importantly, letermovir was not found to be myelotoxic or nephrotoxic.[31,32] Table 58–2 lists the available antiviral agents for herpes viruses and respiratory viruses. For HCT recipients with no prior evidence of CMV infection (seronegative), no CMV chemoprophylaxis is indicated.

When ordering blood products for HCT recipients, special considerations are taken in CMV-seronegative HCT recipients who received a bone marrow graft or peripheral stem cells from a seronegative donor to prevent seroconversion and thus increase the risk of CMV reactivation.[28] Two strategies exist to reduce the risk of seroconversion, the use of seronegative blood product donors or leukocytes reduction. It is not clear which of the two options are superior, but seeking CMV seronegative donors is labor intensive and costly for many blood banks.

Therapy

The selection of CMV directed antiviral therapy is limited because the preferred agents are associated with major toxicities. Table 58–2 and 58–3 describe the different specific antiviral agents and related toxicities. The most commonly used antiviral agents for CMV include ganciclovir, valganciclovir, foscarnet, and cidofovir.

Ganciclovir functions as a competitive inhibitor of viral DNA polymerase. Its major side effect is myelosuppression, limiting its use as a prophylactic agent and requiring frequent blood count monitoring.[5] Dosing for treatment is 5 mg/kg intravenously every 12 hours.[5] Valganciclovir, a prodrug of ganciclovir available in capsule form, is significantly better absorbed than its prodrug ganciclovir in oral form.[5] A common induction dose is 900 mg twice daily by mouth.

An alternative agent, foscarnet, functions as a noncompetitive inhibitor of the pyrophosphate-binding site of CMV DNA polymerase, which does not require phosphorylation to become active.[5] Foscarnet is typically used when resistance to ganciclovir is suspected or bone marrow suppression is excessive with ganciclovir. It is also useful in patients with delayed engraftment.[28] Side effects of foscarnet include nephrotoxicity, azotemia, and electrolyte abnormalities.

Cidofovir, a nucleotide analog, has been approved for treatment of CMV retinitis in patients with human immunodeficiency virus (HIV). It works as a competitive inhibitor of the CMV DNA polymerase. Its role in treatment or prophylaxis of CMV in immunocompromised patients, however, is limited because of nephrotoxicity. The long half-life makes once-weekly administration possible but also results in lasting impact of adverse effects.[28] Modalities used to reduce risk of nephrotoxicity include hydration and premedicating with probenecid.

Human Herpes Virus 6

HHV-6 is a β-herpesvirus with two subtypes (A and B). Primary infection with HHV-6 is very common in children. Exanthem subitum, the most common cause of fever and hospitalization of infants younger than 1 year of age, is caused by HHV-6 subtype B.[4,5] In addition to fever, children present with mild upper

respiratory symptoms and a classic diffuse maculopapular exanthem. It is unclear whether HHV-6 subtype A causes any primary infection. In immunosuppressed individuals, typically patients with AIDS and transplant recipients, HHV-6 may cause opportunistic viral infections. Because this infection is very common early in life, positive titers are found in more than 95% of adults. In immunosuppressed individuals, especially HCT recipients, this virus occasionally may cause interstitial pneumonia, fever, encephalitis, hepatitis, and delayed engraftment.[11] Up to 40% to 60% of HCT recipients may demonstrate viremia by PCR, but the significance of this finding is unclear.

Molecular assays such as rt-PCR are used for the diagnosis of HHV-6 DNAemia. Similarly, CSF samples are tested with real-time PCR to detect HHV-6 when viral encephalitis is suspected. Multiplex molecular assays include HHV-6 on the panel in addition to other pathogens. This technology yields fast results and is able to detect other possible pathogens. However, the risk of false-negative result is possible and places patients at risk of receiving toxic antiviral therapy.[33] We advise confirming the presence of HHV-6 DNA in CSF with a quantitative HHV-6 by PCR from CSF and correlating with clinical findings and magnetic resonance imaging of the brain.

A unique phenomena associated with HHV-6 is viral integration into the germline and vertically transmitted, resulting in chromosomally integrated HHV-6 (ciHHV-6).[33,34] The hallmark of ciHHV-6 is markedly elevated viral loads in blood or CSF, possibly exceeding 5.5 log10 copies/mL.[33] Unfortunately, ciHHV-6 may be seen in HCT recipients and can pose a major diagnostic challenge because the presence of ciHHV-6 does not eliminate the possibility of HHV-6 encephalitis.[35] We recommend considering ciHHv-6 when elevated viral loads persist despite lack of clinical symptoms or after effective therapy.

Therapy

Both ganciclovir and foscarnet are used to treat HHV-6 infections, but this is based upon in vitro studies only because clinical experience is minimal. Both ganciclovir and foscarnet have been reported to be effective against HHV-6 meningoencephalitis after HCT in a small number of patients.[4]

Epstein-Barr Virus

EBV infection is very common in the adult population. EBV is the cause of infectious mononucleosis and has also been linked to several geographically defined cancers. EBV-associated posttransplant lymphoproliferative disorder (PTLD) is an important cause of morbidity and mortality in HCT and solid-organ transplant recipients. PTLD is reported in 0.45% to 29% of HCT recipients, depending on the source of hematopoietic cells (cord blood with the highest risk), manipulation of those cells, and immunosuppressive regimen.[36] Although variable in incidence, PTLD can be fulminant and lethal. The disease results from suppression of cytotoxic T-cell function. The first step in the management of PTLD is to reduce the dose of any immunosuppressive therapy if possible. Another therapeutic approach using the anti-CD20 mAb (rituximab) has been tested for therapy of patients with EBV-induced PTLD. It has been successful for the treatment or prevention of PTLD in solid-organ transplant and HCT recipients as well as those with proven EBV-associated lymphomas.[4,5] Another approach is use of EBV-cytotoxic T lymphocytes (CTLs), typically derived from EBV-positive stem cell donors or from third-party donors.[36,37] There is no apparent role for antivirals in treatment of EBV-associated PTLD. Treatment with rituximab and EBV-targeted CTLs has resulted in more than 85% survival compared with less than 20% before these modalities were available.[36]

Adenovirus

Adenoviruses are a common cause of self-limited respiratory and GI infections in normal individuals. Transmission occurs by aerosolized droplets or the oral–fecal route. Adenovirus infections have been recognized in patients undergoing intensive chemotherapy for hematologic and occasionally other malignancies, but they are especially prevalent among HCT recipients.[4] The frequency of adenovirus infections among HCT recipients has varied from 3% to 21%, and it is more prevalent among children than adults. There is no seasonal variation, and the onset of infection from time of transplantation can be quite variable, although the median interval period is about 50 days.[4]

Important risk factors have been identified for adenovirus infections, including childhood, allogeneic transplantation (particularly umbilical cord blood), GVHD, total-body irradiation (in children), T-cell–depleting conditioning regimens, alemtuzumab, corticosteroid therapy, and lymphopenia.[4]

Immunocompromised patients may have asymptomatic infection, single-organ disease, or disseminated disease.[4] The most common disease is gastroenteritis presenting as fever and diarrhea, which may become bloody. Infections of the respiratory tract may vary from mild upper respiratory tract infection (URI) to severe pneumonitis with respiratory failure. Adenovirus may cause nephritis, and as many as 50% of patients with positive urine cultures develop hemorrhagic cystitis.[38] Hepatitis may lead to liver failure and death. Other types of infection include encephalitis, pancreatitis, and disseminated infection with multiple-organ failure.

Diagnosis

Adenovirus may be detected in upper and lower respiratory specimens, urine, stool, blood, and infected tissues. The diagnosis can be established by viral culture, which is considered as the gold standard of detection. Viral culture requires both time and expertise to perform, making it difficult to use in a clinical setting. More rapid diagnosis using commercially available molecular-based, such as real-time PCR, are more commonly used to detect adenovirus DNA in blood or urine. The use of real-time PCR has been adopted as the standard of care for detection of adenovirus in HCT and patients with hematologic malignancies,[39] but in resource-limited settings, rapid antigen detection can also be used. Adenovirus is commonly added to the panel of commercially available multiplex molecular assays for CSF, stool, and respiratory samples.

In allogeneic HCT recipients, the risk of serious adenovirus infections in both adult and pediatric patients may be modified with early intervention.[40] At our center, we recommend weekly adenovirus screening with real-time PCR from blood in high-risk allogenic HCT recipients, such as cord or haploidentical HCT recipients, mismatched transplant recipients receiving postconditioning cyclophosphamide, HCT recipients taking high-dose steroids for treatment of GVHD, and patients treated with alemtuzumab. Because no vaccines are available commercially and no chemoprophylactic agents have been approved, preemptive monitoring remains the only preventive strategy. There is no specific threshold for adenovirus viral load that definitively correlates with clinically relevant infection because some patients with asymptomatic DNAemia may have spontaneous resolution. Some experts recommend treatment if DNAemia exceeds 1000 copies/mL in blood in high-risk HCT recipients.[41] There is no guidance on management of patients with hematologic malignancies or other patients with cancer with asymptomatic DNAemia, and testing should be restricted to patients with suspected adenovirus-related syndromes.

Outcomes

The mortality rate from symptomatic infection is about 25%, but it is 60% to 75% in patients with disseminated disease.[42] Death is mainly caused by pneumonitis, hepatitis, or multiorgan failure. Many patients who die have other concomitant infections. There is no established therapy for these infections, and options are very limited. In one series of 45 patients, IV cidofovir produced successful results in 69% and was as effective in asymptomatic patients as in those with definite disease.[43] In fact, most HCT centers use cidofovir, in conjunction with reduction in immunosuppression, to treat patients with adenovirus infection.[44]

New therapeutic options are under investigation for treatment of patients with adenovirus. Brincidofovir is an oral lipid conjugate of cidofovir with improved bioavailability and reduced toxicity.[45] Early studies in pediatric HCT recipients with asymptomatic adenovirus viremia have demonstrated antiviral efficacy.[46] Immunotherapy with adenovirus-specific CTLs is under investigation. Some centers with access to off-the-shelf CTLs have used them for treatment of patients with adenovirus infections with some success.[37]

Infection Control

Adenovirus can spread via droplets and has led to outbreaks in HCT units.[47,48] Adenovirus can also spread through fomites, necessitating strict hand hygiene practices for anyone interacting with a suspected or confirmed case of adenovirus infection.[19] Patients diagnosed with adenovirus should be placed in a single-patient room. Health care workers should use gloves, masks, and gowns to prevent the spread of adenovirus to other patients.[19]

COMMUNITY RESPIRATORY VIRAL INFECTIONS

Infections caused by community respiratory viruses (CRV) were not recognized as significant infectious complications for patients with cancer until the early 1990s, especially for patients undergoing chemotherapy for acute leukemia and to HCT recipients, allogeneic HCT in particular.[49] Early surveys indicated that about 30% of respiratory illnesses occurring during the winter and spring among these patient populations were caused by CRVs. Recent studies have reported CRVs as the cause of as few as 5% to as many as 48% of respiratory infections.[49] Patients infected with CRVs often have symptoms of rhinorrhea, cough (productive or nonproductive), fever, myalgias, or weakness. More severe signs and symptoms include dyspnea and hypoxia or septic shock caused by complications. This group of viruses include rhinovirus, influenza, RSV, parainfluenza virus (PIV), hMPV, and seasonal HCoV.[2]

The most common, and often lethal, complication associated with CRVs is progression from an URI to pneumonia or lower respiratory tract infection (LRI). In a retrospective study conducted at our institution, progression from URI to pneumonia was noted in 35% of HCT and hematologic malignancy patients who were diagnosed with any CRV infections.[49] Many of these pneumonias may be caused by co-infection with a bacterial or fungal pathogen.[50] CRVs that were previously thought to cause non–life-threatening infections, such as HCoV and rhinovirus, were associated in some

studies with mortality rates of 54% and 41%, respectively, when the CRV was detected in the lower respiratory tract of patients with cancer.[51,52] Additionally, progression to LRI is associated with increased length of hospital stay and increased use of mechanical ventilation. CRVs are also associated with long-term pulmonary impairment in HCT recipients and increased risk of 2-year non–relapse-related mortality.[53] To prevent these complications from occurring, appropriate infection control measures and identification of risk factors for progression to LRI are crucial.

Infection Control

Epidemics of CRV have occurred on leukemia and transplant units, where the virus may be transmitted by patients, visitors, and hospital personnel.[19] Outpatient clinics may serve as an important starting point for epidemics. Also, epidemics may occur among these susceptible patients in the absence of a recognized epidemic in the community. An additional complication from CRVs is that immunocompromised patients may have prolonged viral shedding (in some cases >100 days) after resolution of symptoms.[5,54] Shedding of influenza virus continued despite antiviral therapy, halting only when lymphopenia resolved.[5,54] Patients with symptoms consistent with CRVs should undergo diagnostic workup, and isolation precautions should be initiated while the diagnosis is underway. Isolation precautions include placing the patient in a single-patient room and the use of gloves, masks, and gown for health care workers interacting with the patient, along with enforcement of strict hand hygiene.[19] Visitors and health care workers who display symptoms should undergo testing and be restricted from visiting patients at risk of contracting CRVs. A study from our center also demonstrated that high influenza vaccine uptake among health care workers was associated with decreased nosocomial transmission of CRVs.[55]

Predisposing Factors

Several important predisposing factors for these infections have been identified in HCT recipients and patients with hematologic malignancies. These include age older than 65 years, severe neutropenia, severe lymphopenia, allogeneic transplantation, transplant conditioning regimen, GVHD, and corticosteroid therapy (>1 mg/kg body weight).[4,49,56,57] HCT recipients are at greatest risk within the first 100 days post-transplant, although nonmyeloablative transplant has resulted in an increase in disease occurring after this initial period.[4,56] Neutropenia, lymphopenia, marrow or cord blood as source of transplant, age older than 65 years, GVHD, smoking history, and allogeneic HCT were risk factors for progression from RSV URI to pneumonia.[2,49] Aerosolized ribavirin reduced the likelihood of developing pneumonia in leukemia and HCT recipients who presented with URI.[2] An immunodeficiency scoring index (ISI) developed at MD Anderson Cancer Center has been useful in estimating outcomes and appropriate use of ribavirin for RSV infections in allogeneic HCT recipients with RSV infections.[58] The ISI included risk factors for progression to pneumonia and mortality. Factors given the most weight are neutropenia, lymphopenia, and age 40 years or older followed by other factors like GVHD, corticosteroid use, myeloablative conditioning regimen, and early period after transplantation (pre-engraftment or within 30 days of engraftment).[58] Without therapy, patients in the highest risk category all progressed to pneumonia compared with 15% of those who received antiviral therapy. The subsequent mortality rate in untreated high-risk patients who progressed to pneumonia was 100% compared with 50% for those with pneumonia who received antiviral therapy.[58]

Diagnosis

The diagnosis of CRV infection is established with samples collected from nasopharyngeal wash or swab for URI and bronchoalveolar lavage or tracheal aspirate for LRI.[49,59] The preferred laboratory assay is the nucleic acid amplification test to detect RNA from samples. The use of molecular diagnostic is preferred because of higher sensitivity and rapid results. In addition, commercially available respiratory viral multiplex PCR can detect multiple pathogens and can be used to rule out CRVs.[60] Rapid antigen detection tests are available for influenza, PIV, hMPV, and RSV; however, the sensitivities of these assays are lower compared with molecular assays. Viral culture can be performed, but this is a labor-intensive process that requires expertise, and material many centers do not have access to.

Specific Viruses and Therapeutics

Many of the CRVs have no therapeutic options. In contrast, influenza has multiple therapeutic options that can be used in immunocompromised patients. RSV has limited treatment options for only a subset of patients. There is no treatment available for PIV, HCoV, rhinovirus, and hMPV.

Influenza

Influenza virus infection is associated with a wide spectrum of presentation and natural course of disease in severely immunocompromised patients. In a recent study at the US National Institutes of Health, immunocompromised patients exhibited less prominent symptoms, such as cough, chills, myalgias, or dyspnea, than

non-immunocompromised hosts.[54] Physical examination findings demonstrating pulmonary compromise were also more common in non-immunocompromised hosts, but radiographic abnormalities on chest imaging were more common in the immunocompromised patients.[54] Finally, immunocompromised patients exhibited more severe disease despite similar cytokine profiles, with prolonged viral shedding and higher risk of developing drug-resistant influenza virus.[54] Currently, all patients with cancer diagnosed with or suspected to have influenza should be treated with antiviral therapy because they are at risk for complications.[61] Early treatment of patients with influenza (within 24–48 hours of presentation) is associated with better survival and decreased risk of progression to LRI in immunocompromised patients.[62]

Preferred agents are neuraminidase inhibitors (NAIs), which include oseltamivir (Tamiflu), peramivir (Rapivab), and zanamivir (Relenza). Oseltamivir is the only oral agent available in this class. The duration of therapy in immunocompromised patients is not clear, with most experts recommending 10 days. Oseltamivir is also recommended for treatment of influenza in severely ill patients. Peramivir is a single-dose IV NAI, which has recently been approved by the Food and Drug Administration (FDA); however, it has not been well studied in patients with cancer or severely ill patients. Zanamivir is the only inhaled NAI, and it is not as commonly used as oseltamivir. M-2 inhibitors, such as amantadine and rimantadine, are no longer recommended as first-line therapy because of high rates of resistance of most circulating influenza strains and the high incidence of side effects. Recently, baloxavir (Xofluza) was approved by the FDA for treatment of patients with influenza A and B infections. Baloxavir has a novel mode of action against influenza and acts by inhibiting cap-dependent endonuclease, thus inhibiting viral mRNA replication, and is only available as an oral formulation.[63] Because of its unique mechanism of action, baloxavir has been used when oseltamivir-resistant influenza strains are suspected or confirmed.[64] Another advantage is that baloxavir is given as a single dose because of its long half-life[63]; however, this could be a factor for the emergence of resistance as seen in clinical trials.[64,65] In one of the trials, 13.1% of children treated with baloxavir had a specific mutation conferring resistance to baloxavir (PA/138X) in a cohort of 81 patients.[63,65] Finally, there are no published data yet on the use of baloxavir in patients with cancer with influenza infections. Table 58–3 summarizes the different agents.

Respiratory Syncytial Virus

RSV is associated with high mortality rate among HCT recipients and patients with hematologic malignancies.[2,39,66] RSV, types A and B, occurs year round but peaks during the cold seasons. Risk factors for progression to LRI in immunocompromised patients include neutropenia, lymphopenia, marrow or cord blood as source of transplant, age older than 65 years, GVHD, smoking history, and allogeneic HCT.[66] The ISI is used to identify high-risk patients and initiate antiviral treatment to reduce the risk of progression and mortality. Table 58–4 illustrates the variables used to calculate the ISI, and Figure 58–3 demonstrates the treatment pathway used for RSV at our center using the ISI.

TABLE 58–4 Immunodeficiency Scoring Index for Respiratory Syncytial Virus Infections in Hematopoietic Cell Transplant Recipients

Variables	Allocated Score	
ANC <500/μL	3	Max score: 12
ALC <200/μL	3	Low risk: 0–2
Age 0 years or older	2	Moderate risk: 3–6
Myeloablative conditioning regimen	1	High risk is 7–12
GVHD (acute or chronic)	1	
Corticosteroid use (within 30 days)	1	
Recent HCT (within 30 days) or pre-engraftment period	1	

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; GVHD, graft-versus-host disease.

Ribavirin is the main stay therapy for RSV infections in immunocompromised patients, allogeneic HCT in particular, and patients with hematologic malignancies.[2,66] HCT recipients with RSV infections at moderate to high risk for complications based on ISI had measurable benefits with the use of ribavirin early on in their infection.[58,67] In patients with leukemia, lack of aerosolized ribavirin and high APACHE (Acute Physiology And Chronic Health Evaluation) II scores were independent predictors of developing pneumonia in this population.[58,68] Ribavirin is administered by aerosolization over 2 to 3 hours every 8 hours or continuously over 18 hours, requiring the patient's confinement in a scavenge tent.[66,69] More recently, the rising cost of aerosolized ribavirin has led most centers to switch to oral ribavirin.[70] In a retrospective study, we found that oral ribavirin dosed at 600 mg every 8 hours was safe and equivalent to aerosolized inhaled ribavirin in terms of reduction in progression to LRI.[71] Ribavirin may also be combined with intravenous immunoglobulins (IVIGs) when the infection progresses to the lower tract.[2,66] Palivizumab, a humanized mAb directed against the F glycoprotein of RSV, is

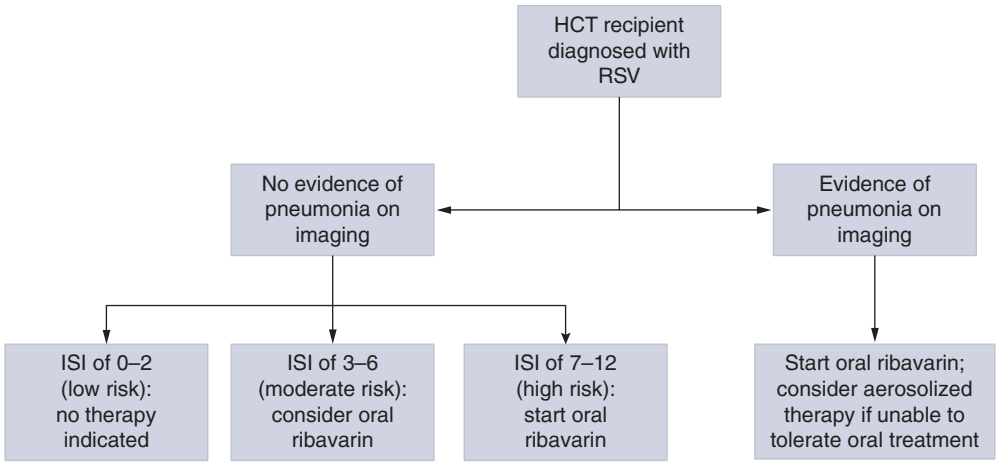


FIGURE 58–3 Management of respiratory syncytial virus (RSV) infection after hematopoietic cell transplantation (HCT) based on the immunodeficiency scoring index (ISI).

currently available and approved for prophylaxis of RSV infection in high-risk pediatric patients.[2] Most patients with RSV pneumonia are being treated with combination therapy, but the limited numbers of patients and lack of clinical trial data reported make interpretation of outcomes difficult.

Parainfluenza

There are four strains of PIV that circulate in the community, PIV 1, PIV 2, PIV 3 and PIV 4; PIV 3 is the most common circulating strain. Mortality rates associated with PIV can range between 10% to 30% in hematologic malignancy and HCT patients.[59] Progression to LRI is associated with lymphopenia, neutropenia, steroids use, high APACHE II score, and infections soon after HCT.[59,72] A study of PIV pneumonia in HCT recipients showed that high oxygen requirement, low monocytes count, relapsed or refractory malignancy and high-dose steroids were associated with mortality rates ranging from 13% to 55%.[72,73] Therapeutic options are limited, with some centers using ribavirin with or without IVIGs.

Metapneumovirus

hMPV is a paramyxovirus similar to RSV that was first described in children but recognized as a significant cause of respiratory infection in immunocompetent and immunocompromised adults.[57,74] Fatal cases in HCT recipients were reported with mortality rates as high as 43%,[75] but another study of HCT recipients from France showed a lower mortality rate, even with LRI.[76] At our center, we reported a low 30-day mortality rate of 10% associated with metapneumovirus pneumonia in patients with cancer.[77]

Rhinovirus

Human rhinovirus is a small RNA virus and a member of the Picornaviridae family.[78] With the increased use of molecular assays, rhinovirus has become the most diagnosed cause of URI in HCT recipients, as well as the general population.[52,79] Rhinovirus is unique in many ways because it is able to circulate all year round. Among HCT recipients, rhinovirus infections may present with mild to severe disease such as LRI, and these infections can result in prolonged shedding.[80] Furthermore, rhinovirus LRI in HCT recipients could be associated with an increased mortality rate, up to 41% in one study, comparable to RSV-related mortality rates.[52] Hypoalbuminemia and the presence of coinfections were associated with progression to LRI.[52] Unfortunately, no commercially available therapeutic options are available for management of rhinovirus infections.[81]

Human Coronavirus

HCoV is a member of the notorious Coronaviridae family. There are four common strains that circulate in the community, 229E, NL-63, OC43, and HKU1. Zoonotic Coronaviridae may mutate and jump to humans, resulting in endemic or pandemic spread of new strains of coronavirus such as the severe acute respiratory syndrome coronavirus 1 and 2 (SARS-CoV 1 and SARS-CoV 2) and the Middle Eastern respiratory syndrome coronavirus (MERS-CoV). The discussion of these zoonotic viruses is outside of the scope of this chapter.

Similar to rhinovirus, seasonal HCoV has become more commonly diagnosed with the use of molecular assays.[51,59] HCoV among HCT recipients carries significant mortality rates when the disease progresses to

LRI.[51] HCT recipients also shed HCoV for prolonged periods of time after the initial infection.[51] No therapeutic options are available for HCoV so far.

HEPATITIS VIRUSES

Hepatitis B

Hepatitis B (HBV) and C (HCV) infections are common in many countries. There is a global epidemic of HBV infections, affecting more than 350 million individuals worldwide. Chronic HBV or HCV infections can lead to progressive liver disease, cirrhosis, and hepatocellular cancer. Hepatitis can be a serious problem in patients with cancer for various reasons. Chemotherapy-induced immunosuppression may lead to reactivation and fulminant infection in patients with chronic HBV infection. Furthermore, the presence of hepatitis may require substantial delays in the administration of antineoplastic therapy. In HCT recipients, reactivation is more likely in those who have received high-dose steroids, fludarabine, rituximab, or alemtuzumab.[11] To prevent reactivation in high-risk patients, antiviral therapy is recommended before immunosuppressive therapy.[82] Normally, entecavir (Baraclude) is used as a first-line antiviral agent in patients who do not have co-infections with HIV. In cases of co-infection with HIV or resistant hepatitis B virus, tenofovir can be used instead.[83] Patients who are not eligible for antiviral prophylaxis should undergo serial HBV DNA monitoring by PCR while on active chemotherapy.[82]

Hepatitis C

HCV is one of the most common chronic bloodborne pathogen worldwide. In the United States, four million individuals (1.6% of the population) have been infected.[84] HCV is the leading indication for liver transplantation. HCV transmission occurs primarily through exposure to infected blood. It can be acquired from IV drug abuse, blood transfusion before 1992, solid-organ transplantation from infected donors, unsafe medical practices, occupational exposure to infected blood, birth to an infected mother, sexual contact with an infected person, and possibly intranasal cocaine use.[4]

Antibody testing should be the first test used to assess exposure to HCV, but in cases of persistent liver disease with immunocompromised status that may prevent adequate response, HCV RNA testing is recommended.[84] Patients who are seropositive for HCV should be tested for HCV RNA to determine if or the amount of circulating virus (Fig. 58–4).[84] The combination of pegylated interferon-α (INF-α) plus ribavirin produced sustained virologic responses (SVRs) in only 4% of genotype 1 infections.[84] Notably, even treated patients without SVRs exhibited slower progression to cirrhosis and portal hypertension.[84] In addition, there is an important link between HCV infection and various cancers, including hepatocellular carcinoma; lymphomas; and esophageal, prostate, and thyroid cancers.[84] This led to an expanded role for testing and treatment of HCV infection for prevention or treatment of malignancies. The treatment of HCV is also being revolutionized by new directly acting antiviral that are being introduced and promise to reduce the complications associated with HCV infections as well as improving outcomes. Treatment is uniformly recommended for HCV-infected HCT recipients, although timing should be at least 2 years after transplant with no evidence of GVHD and off immunosuppression.[11] No active or passive immunizations are available for HCV.

PARVOVIRUS B19 INFECTION

Parvovirus B19 causes erythema infectiosum in children. It has been associated with aplastic crises in diseases in which the lifespan or production of red blood cells is reduced.[85] Anti-B19 immunoglobulin G has been found to be more prevalent among patients with cancer undergoing chemotherapy than among the general population. In one study, 63% of the seropositive patients with cancer had unexplained anemia.[86] Prolonged erythroid aplasia in childhood acute lymphocytic leukemia was associated with detection of parvovirus B19 DNA in the bone marrow. Several chronic lymphocytic leukemia patients have developed severe parvovirus B19 infections that manifested by a flulike illnesses followed by anemia from pure red cell aplasia in the bone marrow. These infection could be associated with incapacitating polyarthritis. IVIGs are used as treatment options this infection but with significant risk of relapse.[87] A new concern is the potential risk parvovirus B19 infection or reactivation for patients taking dasatinib (a tyrosine kinase inhibitor).[88]

POLYOMAVIRUS INFECTION

BK Virus

Polyoma hominis, or BK virus, infects 80% of the general population without recognized clinical manifestations.[4] It persists in the genitourinary tract and is a major cause of hemorrhagic cystitis among allogeneic HCT recipients. About 60% to 80% of these patients may have persistent viruria, and 5% to 15% may develop hemorrhagic cystitis.[4] Risk is higher in high-risk allogeneic HCT recipients, such as after cord blood transplantation.[4] Patients with hemorrhagic cystitis have higher viral loads in the urine, as detected by PCR.[11] The disease may vary from asymptomatic microscopic hematuria to

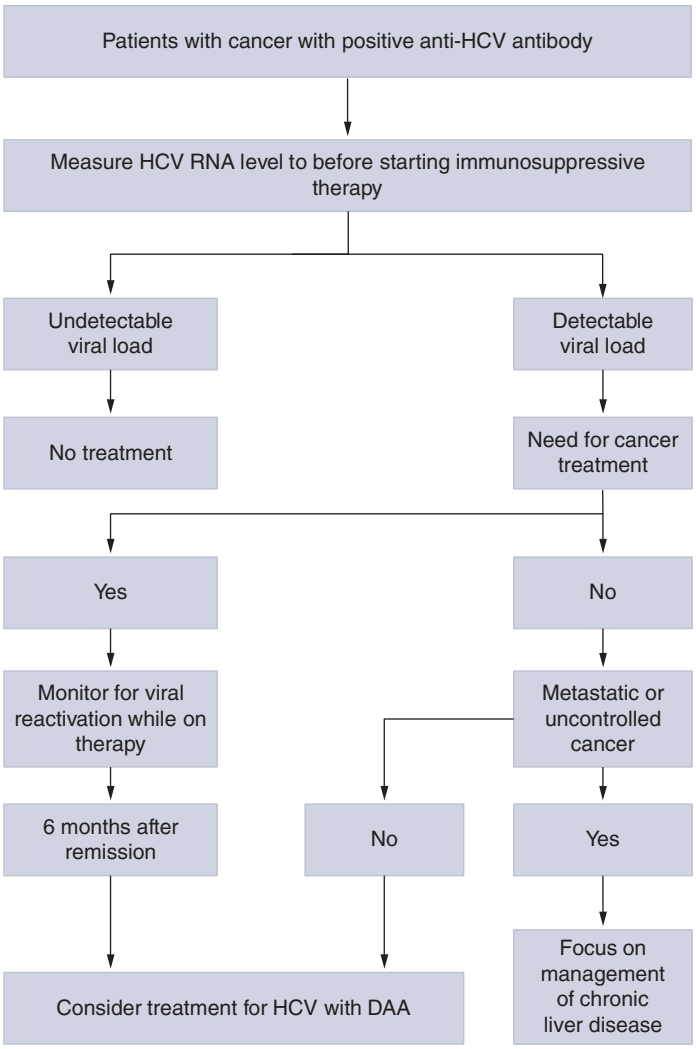


FIGURE 58–4 **Management of hepatitis C viral (HCV) infection. DAA, direct-acting antiviral.**

severe dysuria, frequency, and passage of clots, which may cause outflow obstruction and renal failure. Supportive therapy includes red blood cells and platelets transfusions, saline bladder irrigations, and cauterization. The use of quinolones is of unclear benefit. IV cidofovir has been used and successful treatment of refractory cystitis with hyperbaric oxygen therapy was reported,[89] but no specific therapy is currently recommended.[4] The use of third-party CTLs are under investigation.[37]

JC Virus

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the brain caused by the JC virus, a polyomavirus related to BK virus.[90] The disease results from reactivation of latent infection. About 80% of adults demonstrate JC virus antibodies by middle age. PML was first described in patients with CLL and Hodgkin disease. During the AIDS pandemic, PML was common during HIV infection.[91] With the advancement of effective antiretroviral therapy and public health initiatives to screen patients early, the incidence of PML in this patient population decreased over time.[91–93] With the use of immunomodulating therapies for different diseases, drug-related PML became more notable.[92,93] Symptoms related to PML include visual disturbances, speech defects, and mental deterioration leading to dementia and coma. The mortality rate is 80% at 1 year, and the mean time from diagnosis to death is 4 months. An association has been reported with steroid use, fludarabine, cyclophosphamide, methotrexate, mycophenolate, and mAbs such as rituximab and natalizumab.[90,94] Therapeutic choices are limited, with therapy attempted with cytarabine, cidofovir, interleukin-2, IFN-α, IVIGs, zidovudine, ganciclovir, donor lymphocytes infusion, and, if possible, discontinuation of GVHD prophylaxis.[95]

MD ANDERSON CLINICAL PRACTICE TIPS

- Clinical suspicion for HSV or VZV infections in high-risk, immunocompromised patients should prompt empiric therapy until a diagnostic workup is completed. This is important because early antiviral therapy can help reduce the duration of symptoms and reduce the risk of progression of the disease.
- In adult HCT recipients who are CMV seropositive, letermovir for at least 100 days after transplantation reduced the incidence of clinically significant CMV infections with possible improvement in all-cause and nonrelapse mortality.
- Because of the chromosomal integration of HHV-6, presence of DNA in blood may not accurately reflect an active infection. Correlating with clinical findings and brain imaging can help prevent unnecessary and toxic antiviral therapy.
- Patients with suspected community-acquired respiratory viral infection should be immediately placed in a single-patient room, and infection control precautions should be implemented. Visitors and health care workers who show signs of respiratory viral infection should be restricted from patient care areas. By using safe and aggressive infection control practices, outbreaks of respiratory viral infections can be prevented among most vulnerable patients.
- Influenza occurs most commonly during the fall and winter season. Early start of directed antiviral therapy in immunocompromised patients may reduce progression to pneumonia and other complications.
- Among high-risk HCT recipients and patients with hematologic malignancies with RSV infections, oral ribavirin is recommended to reduce the risk of progression to pneumonia. Additionally, patients who receive ribavirin have improved survival. Use of aerosolized ribavirin is no longer recommended because of its exorbitant cost.

REFERENCES

1. Center for International Blood and Marrow Transplant Research (CIBMTR); National Marrow Donor Program (NMDP); European Blood and Marrow Transplant Group (EBMT); American Society of Blood and Marrow Transplantation (ASBMT); et al. Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective. *Bone Marrow Transplant*.. 2009;44(8): 453-558.
2. Chemaly RF, Shah DP, Boeckh MJ. Management of respiratory viral infections in hematopoietic cell transplant recipients and patients with hematologic malignancies. *Clin Infect Dis*.. 2014;59(suppl 5):S344-S351.
3. Zembower TR. Epidemiology of infections in cancer patients. *Cancer Treat Res*. 2014;161:43-89.
4. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant*. 2009;15(10):1143-1238.
5. Angarone M, Ison MG. Prevention and early treatment of opportunistic viral infections in patients with leukemia and allogeneic stem cell transplantation recipients. *J Natl Compr Canc Netw*. 2008;6(2):191-201.
6. Arduino PG, Porter SR. Herpes simplex virus type 1 infection: overview on relevant clinico-pathological features. *J Oral Pathol Med*. 2008;37(2):107-121.
7. Lafferty WE, Downey L, Celum C, Wald A. Herpes simplex virus type 1 as a cause of genital herpes: impact on surveillance and prevention. *J Infect Dis*. 2000;181(4):1454-1457.
8. Sizemore JM Jr, Lakeman F, Whitley R, et al. The spectrum of genital herpes simplex virus infection in men attending a sexually transmitted disease clinic. *J Infect Dis*. 2006;193(7):905-911.
9. Magaret AS, Wald A, Huang ML, et al. Optimizing PCR positivity criterion for detection of herpes simplex virus DNA on skin and mucosa. *J Clin Microbiol*. 2007;45(5):1618-1620.
10. Ramchandani M, Kong M, Tronstein E, et al. herpes simplex virus type 1 shedding in tears and nasal and oral mucosa of healthy adults. *Sex Transm Dis*. 2016;43(12):756-760.
11. Zaia J, Baden L, Boeckh MJ, et al. Viral disease prevention after hematopoietic cell transplantation. *Bone Marrow Transplant*. 2009;44(8):471-482.
12. Erard V, Wald A, Corey L, et al. Use of long-term suppressive acyclovir after hematopoietic stem-cell transplantation: impact on herpes simplex virus (HSV) disease and drug-resistant HSV disease. *J Infect Dis*. 2007;196(2):266-270.
13. Kim ST, Park KH, Oh SC, et al. Varicella zoster virus infection during chemotherapy in solid cancer patients. *Oncology*. 2012;82(2):126-130.
14. Sauerbrei A, Eichhorn U, Schacke M, Wutzler P. Laboratory diagnosis of herpes zoster. *J Clin Virol*. 1999;14(1):31-36.
15. Tyring S, Barbarash RA, Nahlik JE, et al. Famciclovir for the treatment of acute herpes zoster: effects on acute disease and postherpetic neuralgia. A randomized, double-blind, placebo-controlled trial. Collaborative Famciclovir Herpes Zoster Study Group. *Ann Intern Med*. 1995;123(2):89-96.
16. Bastidas A, de la Serna J, El Idrissi M, et al. Effect of recombinant zoster vaccine on incidence of herpes zoster after autologous stem cell transplantation: a randomized clinical trial. *JAMA*. 2019;322(2):123-133.
17. Dagnew AF, Ilhan O, Lee WS, et al. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in adults with haematological malignancies: a phase 3, randomised, clinical trial and post-hoc efficacy analysis. *Lancet Infect Dis*. 2019;19(9): 988-1000.
18. Vink P, Delgado Mingorance I, Maximiano Alonso C, et al. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in patients with solid tumors, vaccinated before or during chemotherapy: a randomized trial. *Cancer*. 2019;125(8):1301-1312.
19. Ariza-Heredia EJ, Chemaly RF. Update on infection control practices in cancer hospitals. *CA Cancer J Clin*. 2018;68(5): 340-355.
20. Bate SL, Dollard SC, Cannon MJ. Cytomegalovirus seroprevalence in the United States: the national health and nutrition examination surveys, 1988-2004. *Clin Infect Dis*. 2010;50(11):1439-1447.
21. Torres HA, Kontoyiannis DP, Bodey GP, et al. Gastrointestinal cytomegalovirus disease in patients with cancer: a two decade experience in a tertiary care cancer center. *Eur J Cancer*. 2005;41(15):2268-2279.
22. Torres HA, Aguilera E, Safdar A, et al. Fatal cytomegalovirus pneumonia in patients with haematological malignancies: an autopsy-based case-control study. *Clin Microbiol Infect*. 2008;14(12):1160-1166.
23. Lamba R, Carrum G, Myers GD, et al. Cytomegalovirus (CMV) infections and CMV-specific cellular immune reconstitution following reduced intensity conditioning allogeneic stem cell transplantation with alemtuzumab. *Bone Marrow Transplant*. 2005;36(9):797-802.
24. O'Brien S, Ravandi F, Riehl T, et al. Valganciclovir prevents cytomegalovirus reactivation in patients receiving alemtuzumab-based therapy. *Blood*. 2008;111(4):1816-1819.
25. Boeckh M, Murphy WJ, Peggs KS. Recent advances in cytomegalovirus: an update on pharmacologic and cellular therapies. *Biol Blood Marrow Transplant*. 2015;21(1):24-29.
26. Boeckh M, Nichols WG, Chemaly RF, et al. Valganciclovir for the prevention of complications of late cytomegalovirus infection after allogeneic hematopoietic cell transplantation: a randomized trial. *Ann Intern Med*. 2015;162(1):1-10.
27. Fries BC, Riddell SR, Kim HW, et al. Cytomegalovirus disease before hematopoietic cell transplantation as a risk for complications after transplantation. *Biol Blood Marrow Transplant*. 2005;11(2):136-148.
28. Boeckh M, Ljungman P. How we treat cytomegalovirus in hematopoietic cell transplant recipients. *Blood*. 2009;113(23):5711-5719.
29. Ljungman P, de la Camara R, Robin C, et al. Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7). *Lancet Infect Dis*. 2019;19(8):e260-e272.
30. Girmenia C, Lazzarotto T, Bonifazi F, et al. Assessment and prevention of cytomegalovirus infection in allogeneic hematopoietic stem cell transplant and in solid organ transplant: a multidisciplinary consensus conference by the Italian GITMO, SITO, and AMCLI societies. *Clin Transplant*. 2019;33(10):e13666.
31. Marty FM, Ljungman P, Chemaly RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. *N Engl J Med*. 2017;377(25):2433-2444.
32. Chemaly RF, Ullmann AJ, Stoelben S, et al. Letermovir for cytomegalovirus prophylaxis in hematopoietic-cell transplantation. *N Engl J Med*. 2014;370(19):1781-1789.
33. Ogata M, Fukuda T, Teshima T. Human herpesvirus-6 encephalitis after allogeneic hematopoietic cell transplantation: what we do and do not know. *Bone Marrow Transplant*. 2015;50(8):1030-1036.
34. Pellett PE, Ablashi DV, Ambros PF, et al. Chromosomally integrated human herpesvirus 6: questions and answers. *Rev Med Virol*. 2012;22(3):144-155.
35. Hill JA, Sedlak RH, Zerr DM, et al. Prevalence of chromosomally integrated human herpesvirus 6 in patients with human

herpesvirus 6-central nervous system dysfunction. *Biol Blood Marrow Transplant*. 2015;21(2):371-373.
36. Styczynski J, Einsele H, Gil L, Ljungman P. Outcome of treatment of Epstein-Barr virus-related post-transplant lymphoproliferative disorder in hematopoietic stem cell recipients: a comprehensive review of reported cases. *Transpl Infect Dis*. 2009;11(5):383-392.
37. Tzannou I, Papadopoulou A, Naik S, et al. Off-the-shelf virus-specific t cells to treat BK virus, human herpesvirus 6, cytomegalovirus, Epstein-Barr virus, and adenovirus infections after allogeneic hematopoietic stem-cell transplantation. *J Clin Oncol*. 2017;35(31):3547-3557.
38. Lion T. Adenovirus infections in immunocompetent and immunocompromised patients. *Clin Microbiol Rev*. 2014;27(3):441-462. doi:10.1128/CMR.00116-13.
39. Matthes-Martin S, Feuchtinger T, Shaw PJ, et al. European guidelines for diagnosis and treatment of adenovirus infection in leukemia and stem cell transplantation: summary of ECIL-4 (2011). *Transpl Infect Dis*. 2012;14(6):555-563.
40. Lion T, Baumgartinger R, Watzinger F, et al. Molecular monitoring of adenovirus in peripheral blood after allogeneic bone marrow transplantation permits early diagnosis of disseminated disease. *Blood*. 2003;102(3):1114-1120.
41. Hiwarkar P, Kosulin K, Cesaro S, et al. Management of adenovirus infection in patients after haematopoietic stem cell transplantation: state-of-the-art and real-life current approach: a position statement on behalf of the Infectious Diseases Working Party of the European Society of Blood and Marrow Transplantation. *Rev Med Virol*. 2018;28(3):e1980.
42. La Rosa AM, Champlin RE, Mirza N, et al. Adenovirus infections in adult recipients of blood and marrow transplants. *Clin Infect Dis*. 2001;32(6):871-876.
43. Ljungman P, Ribaud P, Eyrich M, et al. Cidofovir for adenovirus infections after allogeneic hematopoietic stem cell transplantation: a survey by the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant*. 2003;31(6):481-486.
44. Cesaro S, Berger M, Tridello G, et al. A survey on incidence and management of adenovirus infection after allogeneic HSCT. *Bone Marrow Transplant*. 2019;54(8):1275-1280.
45. Ison MG. Adenovirus infections in transplant recipients. *Clin Infect Dis*. 2006;43(3):331-339.
46. Grimley MS, Chemaly RF, Englund JA, et al. Brincidofovir for asymptomatic adenovirus viremia in pediatric and adult allogeneic hematopoietic cell transplant recipients: a randomized placebo-controlled phase II trial. *Biol Blood Marrow Transplant*. 2017;23(3):512-521.
47. Swartling L, Allard A, Torlen J, et al. Prolonged outbreak of adenovirus A31 in allogeneic stem cell transplant recipients. *Transpl Infect Dis*. 2015;17(6):785-794.
48. Venard V, Carret A, Corsaro D, et al. Genotyping of adenoviruses isolated in an outbreak in a bone marrow transplant unit shows that diverse strains are involved. *J Hosp Infect*. 2000;44(1):71-74.
49. Chemaly RF, Ghosh S, Bodey GP, et al. Respiratory viral infections in adults with hematologic malignancies and human stem cell transplantation recipients: a retrospective study at a major cancer center. *Medicine (Baltimore)*. 2006;85(5):278-287.
50. Magira EE, Chemaly RF, Jiang Y, et al. Outcomes in invasive pulmonary aspergillosis infections complicated by respiratory viral infections in patients with hematologic malignancies: a case-control study. *Open Forum Infect Dis*. 2019;6(7):ofz247.
51. Ogimi C, Waghmare AA, Kuypers JM, et al. Clinical significance of human coronavirus in bronchoalveolar lavage samples from hematopoietic cell transplant recipients and patients with hematologic malignancies. *Clin Infect Dis*. 2017;64(11):1532-1539.
52. Seo S, Waghmare A, Scott EM, et al. Human rhinovirus detection in the lower respiratory tract of hematopoietic cell transplant recipients: association with mortality. *Haematologica*. 2017;102(6):1120-1130.
53. Sheshadri A, Chemaly RF, Alousi AM, et al. Pulmonary impairment after respiratory viral infections is associated with high mortality in allogeneic hematopoietic cell transplant recipients. *Biol Blood Marrow Transplant*. 2019;25(4):800-809.
54. Memoli MJ, Athota R, Reed S, et al. The natural history of influenza infection in the severely immunocompromised vs nonimmunocompromised hosts. *Clin Infect Dis*. 2014;58(2):214-224.
55. Frenzel E, Chemaly RF, Ariza-Heredia E, et al. Association of increased influenza vaccination in health care workers with a reduction in nosocomial influenza infections in cancer patients. *Am J Infect Control*. 2016;44(9):1016-1021.
56. Schiffer JT, Kirby K, Sandmaier B, et al. Timing and severity of community acquired respiratory virus infections after myeloablative versus non-myeloablative hematopoietic stem cell transplantation. *Haematologica*. 2009;94(8):1101-1108.
57. Boeckh M. The challenge of respiratory virus infections in hematopoietic cell transplant recipients. *Br J Haematol*. 2008;143(4):455-467.
58. Shah DP, Ghantoji SS, Ariza-Heredia EJ, et al. Immunodeficiency scoring index to predict poor outcomes in hematopoietic cell transplant recipients with RSV infections. *Blood*. 2014;123(21):3263-3268.
59. Hirsch HH, Martino R, Ward KN, et al. Fourth European Conference on Infections in Leukaemia (ECIL-4): guidelines for diagnosis and treatment of human respiratory syncytial virus, parainfluenza virus, metapneumovirus, rhinovirus, and coronavirus. *Clin Infect Dis*. 2013;56(2):258-266.
60. Huang HS, Tsai CL, Chang J, et al. Multiplex PCR system for the rapid diagnosis of respiratory virus infection: systematic review and meta-analysis. *Clin Microbiol Infect*. 2018;24(10):1055-1063.
61. Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. *Clin Infect Dis*. 2019;68(6):895-902.
62. Vilar-Compte D, Shah DP, Vanichanan J, et al. Influenza in patients with hematological malignancies: experience at two comprehensive cancer centers. *J Med Virol*. 2018;90(1):50-60.
63. Hayden FG, Sugaya N, Hirotsu N, et al. Baloxavir marboxil for uncomplicated influenza in adults and adolescents. *N Engl J Med*. 2018;379(10):913-923.
64. Fujita M, Matsumoto H, Inafuku Y, et al. A retrospective observational study of the treatment of a nosocomial infection caused by oseltamivir-resistant influenza virus A with baloxavir marboxil. *Respir Investig*. 2020;58(5):403-408.
65. Baker J, Block SL, Matharu B, et al. Baloxavir marboxil single-dose treatment in influenza-infected children: a randomized, double-blind, active controlled phase 3 safety and efficacy trial (miniSTONE-2). *Pediatr Infect Dis J*. 2020;39(8):700-705.
66. Khawaja F, Chemaly RF. Respiratory syncytial virus in hematopoietic cell transplant recipients and patients with hematologic malignancies. *Haematologica*. 2019;104(7):1322-1331.
67. Shah DP, Ghantoji SS, Shah JN, et al. Impact of aerosolized ribavirin on mortality in 280 allogeneic haematopoietic stem cell transplant recipients with respiratory syncytial virus infections. *J Antimicrob Chemother*. 2013;68(8):1872-1880.
68. Azzi JM, Kyvernitakis A, Shah DP, et al. Leukopenia and lack of ribavirin predict poor outcomes in patients with haematological malignancies and respiratory syncytial virus infection. *J Antimicrob Chemother*. 2018;73(11):3162-3169.

69. Torres HA, Aguilera EA, Mattiuzzi GN, et al. Characteristics and outcome of respiratory syncytial virus infection in patients with leukemia. *Haematologica*. 2007;92(9):1216-1223.
70. Chemaly RF, Aitken SL, Wolfe CR, Jain et al. Aerosolized ribavirin: the most expensive drug for pneumonia. *Transpl Infect Dis*. 2016;18(4):634-636.
71. Foolad F, Aitken SL, Shigle TL, et al. Oral versus aerosolized ribavirin for the treatment of respiratory syncytial virus infections in hematopoietic cell transplant recipients. *Clin Infect Dis*. 2019;68(10):1641-1649.
72. Chemaly RF, Hanmod SS, Rathod DB, et al. The characteristics and outcomes of parainfluenza virus infections in 200 patients with leukemia or recipients of hematopoietic stem cell transplantation. *Blood*. 2012;119(12):2738-2745; quiz 969.
73. Seo S, Xie H, Campbell AP, Kuypers JM, et al. Parainfluenza virus lower respiratory tract disease after hematopoietic cell transplant: viral detection in the lung predicts outcome. *Clin Infect Dis*. 2014;58(10):1357-1368.
74. Walsh EE, Peterson DR, Falsey AR. Human metapneumovirus infections in adults: another piece of the puzzle. *Arch Intern Med*. 2008;168(22):2489-2496.
75. Renaud C, Xie H, Seo S, et al. Mortality rates of human metapneumovirus and respiratory syncytial virus lower respiratory tract infections in hematopoietic cell transplantation recipients. *Biol Blood Marrow Transplant*. 2013;19(8):1220-1226.
76. Godet C, Le Goff J, Beby-Defaux A, et al. Human metapneumovirus pneumonia in patients with hematological malignancies. *J Clin Virol*. 2014;61(4):593-596.
77. El Chaer F, Shah DP, Kmeid J, et al. Burden of human metapneumovirus infections in patients with cancer: risk factors and outcomes. *Cancer*. 2017;123(12):2329-2337.
78. To KKW, Yip CCY, Yuen KY. Rhinovirus—from bench to bedside. *J Formos Med Assoc*. 2017;116(7):496-504.
79. Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med*. 2015;373(5):415-427.
80. Parody R, Rabella N, Martino R, et al. Upper and lower respiratory tract infections by human enterovirus and rhinovirus in adult patients with hematological malignancies. *Am J Hematol*. 2007;82(9):807-811.
81. Shah DP, Ghantoji SS, Mulanovich VE, et al. Management of respiratory viral infections in hematopoietic cell transplant recipients. *Am J Blood Res*. 2012;2(4):203-218.
82. Sarmati L, Andreoni M, Antonelli G, et al. Recommendations for screening, monitoring, prevention, prophylaxis and therapy of hepatitis B virus reactivation in patients with haematologic malignancies and patients who underwent haematologic stem cell transplantation-a position paper. *Clin Microbiol Infect*. 2017;23(12):935-940.
83. Chen MB, Wang H, Zheng QH, et al. Comparative efficacy of tenofovir and entecavir in nucleos(t)ide analogue-naive chronic hepatitis B: a systematic review and meta-analysis. *PLoS One*. 2019;14(11):e0224773.
84. Torres HA, Mahale P, Blechacz B, et al. Effect of hepatitis C virus infection in patients with cancer: addressing a neglected population. *J Natl Compr Canc Netw*. 2015;13(1):41-50.
85. Chisaka H, Morita E, Yaegashi N, Sugamura K. Parvovirus B19 and the pathogenesis of anaemia. *Rev Med Virol*. 2003;13(6):347-359.
86. Kuo SH, Lin LI, Chang CJ, et al. Increased risk of parvovirus B19 infection in young adult cancer patients receiving multiple courses of chemotherapy. *J Clin Microbiol*. 2002;40(11):3909-3912.
87. Eid AJ, Brown RA, Patel R, Razonable RR. Parvovirus B19 infection after transplantation: a review of 98 cases. *Clin Infect Dis*. 2006;43(1):40-48.
88. Torres HA, Chemaly RF. Viral infection or reactivation in patients during treatment with dasatinib: a call for screening? *Leuk Lymphoma*. 2007;48(12):2308-2309.
89. Hosokawa K, Yamazaki H, Nakamura T, et al. Successful hyperbaric oxygen therapy for refractory BK virus-associated hemorrhagic cystitis after cord blood transplantation. *Transpl Infect Dis*. 2014;16(5):843-846.
90. Carson KR, Focosi D, Major EO, et al. Monoclonal antibody-associated progressive multifocal leucoencephalopathy in patients treated with rituximab, natalizumab, and efalizumab: a review from the Research on Adverse Drug Events and Reports (RADAR) project. *Lancet Oncol*. 2009;10(8):816-824.
91. Melliez H, Mary-Krause M, Bocket L, et al. Risk of progressive multifocal leukoencephalopathy in the combination antiretroviral therapy era in the French hospital database on human immunodeficiency virus (ANRS-C4). *Clin Infect Dis*. 2018;67(2):275-282.
92. Atkinson AL, Atwood WJ. Fifty years of JC polyomavirus: a brief overview and remaining questions. *Viruses*. 2020;12(9).
93. Kartau M, Verkkoniemi-Ahola A, Paetau A, et al. The incidence and predisposing factors of John Cunningham virus-induced progressive multifocal leukoencephalopathy in southern Finland: a population-based study. *Open Forum Infect Dis*. 2019;6(2):ofz024.
94. Garcia-Suarez J, de Miguel D, Krsnik I, et al. Changes in the natural history of progressive multifocal leukoencephalopathy in HIV-negative lymphoproliferative disorders: impact of novel therapies. *Am J Hematol*. 2005;80(4):271-281.
95. Pelosini M, Focosi D, Rita F, et al. Progressive multifocal leukoencephalopathy: report of three cases in HIV-negative hematological patients and review of literature. *Ann Hematol*. 2008;87(5):405-412.

This page intentionally left blank

59 Fungal Infections in Patients with Cancer

Bruno P. Granwehr
Dimitrios P. Kontoyiannis

KEY CONCEPTS

- Fungal infections are common in patients with cancer.
- Morbidity and mortality associated with fungal infection complicate cancer treatment outcomes.
- Invasive candidiasis is the most common fungal infection in patients with cancer, requiring careful assessment for dissemination, selection of appropriate antifungal agent, removal of infected devices, and duration of therapy.
- Invasive aspergillosis (IA) is the most common mold infection in patients with cancer, requiring vigilance to detect pulmonary or sinus infection, which may require resection or debridement in addition to aggressive antifungal therapy.
- Rare molds that infect patients with cancer include *Fusarium* and *Mucorales* spp., typically affecting patients with hematologic malignancy, with recovery of neutrophils the most important factor in improving mortality.

Fungal infections remain a significant cause of morbidity and mortality in patients with cancer. In the United States, fungal infections were estimated to cost $7.2 billion in 2017, with $4.5 billion for 75,033 hospitalizations.[1] Modern management of infections in cancer requires knowledge of the epidemiology, pathogenesis, treatment, and prevention of such infections. Fungal infections range from nosocomial infections with *Candida* spp. to endemic fungi acquired outside the hospital, such as *Histoplasma capsulatum*.[1] Opportunistic fungi, especially molds, have emerged as a leading cause of death in patients with leukemia or hematopoietic stem cell transplant (HSCT).[2] *Candida auris*, recently identified and disseminating throughout the globe, poses a unique risk, forming biofilm capable of surviving for prolonged periods on surfaces, exhibiting multidrug resistance, often to all approved antifungals, and with a mortality rates as high as 40% to 60%.[3,4]

Fungal infections pose a continuing challenge for oncology patients. Exposure to fungi is common, typically occurring from the natural environment. Patients with cancer are not only susceptible to new infection with endemic fungi (such as *H. capsulatum*) but also reactivation of latent infections. In addition to *Aspergillus* spp., other less opportunistic molds, such as *Fusarium* spp., *Scedosporium* spp., and *Mucorales* spp., cause devastating disease in hematologic patients. Cases of nosocomial infection caused by molds are reported in the setting of hospital construction, leading to routine air sampling and filtration. In contrast, *Candida* spp. are a common component of patients' and health care workers' endogenous microbial flora. Manifestations of infection may not present until the patient receives chemotherapy or undergoes HSCT. In this chapter, we describe the general approach to diagnosis and assessment of risk factors for fungal infection and discuss common and rare causes of fungal infections in patients with cancer.

DIAGNOSIS

Fungal infections may involve several organs, ranging from the skin, brain, lungs, kidneys, and spleen to the liver and other tissues. In addition, evidence of infection may be identified from blood samples, demonstrating active, via polymerase chain reaction (PCR) or antigen testing, or past infection, via antibody testing. In the past two decades, the focus, as with other infectious etiologies, has shifted from culture or other

direct identification of organisms to molecular identification of invasive fungal infections (IFIs). These techniques use biomarkers of IFI, ranging from lateral-flow immunoassays, which can be used at point of care, to PCR-based assays, to antigen identification and next-generation sequencing of blood and other tissue samples, and "nanodiagnostic" testing. These approaches are discussed in more depth in discussion of specific fungal infections.

The diagnosis of IFIs remains problematic, however, despite increased use of fungal biomarkers.[5] The skin and lungs are commonly affected by fungal pathogens and most easily accessible to examination and biopsy. In our institution, a retrospective study of skin biopsies in patients with leukemia suggested that ulcerated or necrotic skin lesions in the context of bacteremia or fungemia were predictive of infection.[6] In fact, skin biopsy revealed infection in 39% of all patients undergoing biopsy.[6] Of patients with biopsy-proven skin infection, 39% of those infections were fungal, led by *Candida* (25%), *Fusarium* (19%), *Mucorales* (13%), *Aspergillus* (9%), *Alternaria* (6%), and *Curvularia* (3%) spp.[6]

The identification of fungal pneumonia, however, is particularly important among patients with hematologic malignancies, with invasive aspergillosis (IA) overtaking invasive candidiasis as the leading cause of IFI in immunocompromised patients.[7] A recent study of patients with acute myeloid leukemia (AML) or undergoing HSCT showed that 10.3% had evidence of IFI on baseline screening chest computed tomography (CT).[8] However, sampling of the lung is more challenging than skin biopsy, particularly in patients with hematologic malignancies, who have increased risk of bleeding with frequent thrombocytopenia.

The gold standard for diagnosis of IFI is culture of biopsy or bronchoscopy samples, but given the challenges of invasive sampling of lung tissue, other approaches are used. To differentiate between fungal infection and other causes of pulmonary infection, studies conducted in Italy examined the impact of high-resolution CT pulmonary angiography (CTPA) on diagnosis of invasive fungal lung disease, in the setting of classical findings of fungal infection of the lungs, such as the halo sign, reverse halo sign, hypodense sign, and pleural effusion.[9,10] In the initial study, involving patients with hematologic malignancies, CTPA resulted in an upgrade of patients from possible to probable or proven diagnosis of IFI.[9] A subsequent study from the group examining the impact of CTPA showed that a vessel occlusion sign (VOS), in which there was "interruption of a vessel at the border of a focal lesion without depiction of the vessel inside the lesion or peripheral to the lesion," was highly associated with fungal pneumonia.[10] In the subset of patients with VOS who underwent bronchoalveolar lavage (BAL), fungal culture results were positive in 11% (vs 0%), and tissue evidence of mold was found in 58% (vs 0%).[10] Approaches such as CTPA may help to differentiate fungal from other causes of pneumonia, but biopsy of a suspicious lesion, such as a pulmonary nodule, remains the most definitive approach to diagnosis.

In the setting of peripheral pulmonary nodules, CT-guided biopsy show a yield of approximately 60% for a specific diagnosis.[11] In a study of patients with hematologic malignancy at our center, 34% of cases whom underwent CT-guided biopsy documented previously unidentified infection, predominantly fungal.[12] Another retrospective study of open lung biopsy revealed 19% previously undiagnosed infectious etiologies.[11] Among the organisms identified, 58% were endemic molds (*Histoplasma* spp., *Coccidioides* spp.), 14% *Aspergillus* spp., and 7% *Cryptococcus* spp.[12] Figure 59–1 suggests an approach to identification of fungal pulmonary pathogens. Important steps include early CT chest to determine pattern and extent of possible fungal infection followed by prompt treatment and diagnostic workup, which may include BAL or biopsy of lung or skin lesions. Despite these efforts, diagnosis is often a challenge if infection is more diffuse or thrombocytopenia is too severe to safely permit biopsy.

Autopsy has historically been another approach to diagnosis of IFIs, but autopsy rates have fallen almost 90% from 0.63 in 100 deaths in 1989 to 1993 to 0.06 in 100 deaths in 2004 to 2008 at our institution.[13] Diagnosis of fungal infections, often manifesting as pulmonary nodules or skin lesions, is challenging but important, given the modification of therapy that may occur based on identification of a particular spp. of fungus or discovery of co-infection, malignancy, or other alternative diagnosis. Other diagnostic tools to detect fungal infection are discussed in the sections specific to each pathogen.

RISK FACTORS

The risk factors for IFI in patients with cancer derive from various defects in the immune response. These immune defects may be attributable to anatomic injury from surgery or radiation, impairment of function of the immune system by malignancy (eg, AML), the effects of chemotherapy or other systemic cancer treatments, and various infections,[14] including cytomegalovirus,[15] influenza,[16] and human immunodeficiency virus (HIV).[17] Severe neutropenia, particularly prolonged, has long been associated with IFIs.[18,19] Chemotherapy resulting in prolonged and severe CD4 lymphocytopenia can also result in infections similar to those seen in untreated patients with HIV or acquired immunodeficiency syndrome (AIDS), such

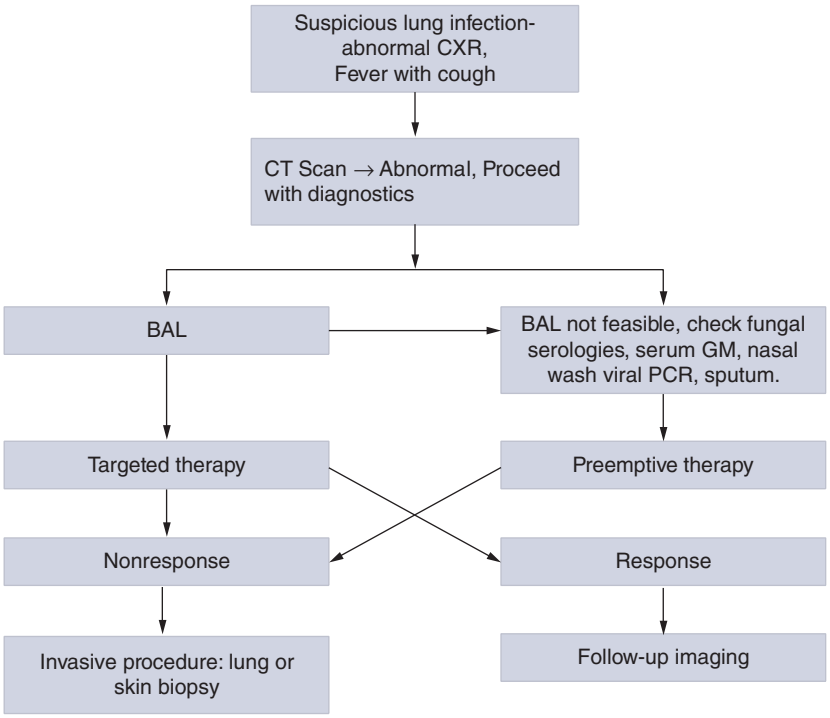


FIGURE 59–1 **Evaluation of suspicion of lung infection.**

as cryptococcosis and endemic fungal infection, such as histoplasmosis and coccidioidomycosis. In addition, conditioning regimens for stem cell transplant and immunosuppressive medications to treat or prevent graft-versus-host disease result in deficient cell-mediated immunity, thus increasing risk for IFI.[13,20] Ongoing work is ascertaining the risk posed by chimeric antigen receptor T-cell (CAR T) therapy for IFI, with a study showing that 5% of patients developed IFI after CAR T infusion.[21] The primary risk factor, however, was severity of cytokine release syndrome (CRS). This finding leads to the question regarding the relative role of treatment of CRS with corticosteroids, tocilizumab, and other medications, the preceding conditioning regimen, persistence of neutropenia, and preceding cancer treatments for the underlying malignancy, as opposed to the CAR T therapy per se.[21–23]

Progress in treatment of patients with cancer by harnessing components of the immune system against tumors has identified new risk factors for IFI. The use of ibrutinib and other kinase inhibitors for treatment of chronic lymphocytic leukemia (CLL), mantle cell lymphoma, and primary central nervous system (CNS) lymphoma has improved outcomes for patients with these cancers. Randomized clinical trials with these agents, however, did not initially demonstrate an increased risk for IFI, including cryptococcosis, histoplasmosis, IA, and *Pneumocystis jirovecii* pneumonia (PJP).[14] A recent multinational "real-life" survey examining ibrutinib-associated IFI showed that 74% of these patients with IFI had CLL, with 63% of IFIs consisting of IA and 26% cryptococcosis.[24] In contrast, the role of checkpoint inhibitors (CPIs) in modulation of immune response and outcomes is unclear. CPIs may play a beneficial role in overcoming the immune exhaustion that accompanies chronic candidiasis, endemic mold infection, and aspergillosis.[25,26] In contrast, treatment with steroids or other immunosuppressive medications for CPI-mediated immunotoxicity, such as pneumonitis or colitis, may increase risk of IFI.

In addition to changes in risk for IFI attributed to immunomodulatory treatments for cancer, disruption of mucocutaneous barriers, including oral and gastrointestinal (GI) mucositis from chemotherapy, as well as skin from central venous catheters (CVCs), predisposes to invasive candidal infection. The disruption of mucosal barriers is further emphasized by the finding, in a recent study, that 9% of patients with candidemia patients were co-infected with *Clostridium difficile*.[27]

Given the many risk factors associated with IFI in patients with cancer, various models have been developed to predict this important complication of cancer treatment. These models help to guide prophylaxis and enhanced monitoring of those at highest risk, particularly patients with hematologic malignancy. A recent study used a retrospective cohort of patients with hematologic malignancy to develop a risk prediction score for IFIs.[20] The score emphasizes the central roles played by lymphopenia, relapsed or refractory malignancy, prolonged neutropenia (>10 days), and

prior history of IFI in identifying patients at highest risk of IFI.[20]

Finally, a recently identified risk for development of IFI is the change in the microbiome attributable to broad-spectrum antibacterial therapy. Prolonged use of broad-spectrum antibacterials may result in suppression of normal bacterial flora and candidal overgrowth in the oropharynx and GI tract. Antifungal therapy or prophylaxis may also alter the mycobiome, leading to breakthrough infection with non–*Candida albicans* spp., such as *Candida krusei* (resistant to fluconazole).[28]

In summary, treatment for patients with cancer may result in increased risk of IFI, deriving from destruction of mucosal barriers due to direct injury (eg, surgery, Interventional radiology-guided drainage), cytotoxic chemotherapy, or radiation. New cancer treatments have also altered the immune response to attack malignancy, unexpectedly leading to identification of IFI. This has led to the suggestion to conduct systematic assessments of novel cancer treatments for immunosuppressive effects that may lead to infection, including IFI.[14]



FIGURE 59–2 **Typical appearance of oropharyngeal candidiasis on the palatal and buccal mucosa.**

CANDIDIASIS

Candidiasis remains the most common IFI in patients with cancer. Modern medical care continues to increase in complexity, involving frequent use of antimicrobials and devices that alter patient flora and disrupt the mucocutaneous barrier, respectively. *Candida* spp. commonly arise from the patient's endogenous flora, but hospital-acquired cases have been attributed to contaminated equipment, solutions, and hospital personnel.[28] Manifestations of candidiasis range from local infection of the skin or oral mucosa to candidemia and widely disseminated infection. These syndromes of candidiasis are discussed in the sections to follow, with treatment recommendations for candidemia and disseminated candidiasis detailed in the Therapy section at the end of this Candidiasis portion of the chapter.

Superficial Candidiasis

Oral Infection

Thrush is the most common superficial candidal infection among patients with cancer, typically those with cancers involving the head and neck undergoing chemoradiation.[29] Oropharyngeal candidiasis is characterized by whitish plaques on the buccal mucosa, palate, or tongue (Fig. 59–2) that may be painful if removed, exposing the erythematous base. Oral thrush may also be a manifestation of esophagitis.[29] The diagnosis is commonly made clinically but is typically confirmed by finding yeasts and pseudohyphae on scraping or culture. Treatment may consist of clotrimazole 10-mg troches or nystatin suspension for 7 to 14 days.[28] In moderate to severe cases affecting patients with cancer, however, oral or intravenous (IV) fluconazole daily may be required, with voriconazole, echinocandins, and very rarely amphotericin B formulations used in refractory cases.[28]

Esophagitis

Esophageal candidiasis may cause dysphagia, retrosternal pain, and odynophagia in patients with cancer.[30] Serious complications of this infection can occur, including chronic esophageal strictures, bronchoesophageal fistulas, and mediastinitis. Esophagoscopy with biopsy and culture are necessary to confirm the diagnosis of candidal esophagitis.[28] Unfortunately, thrombocytopenia often makes esophagoscopy challenging, so empiric therapy is often used. Esophageal candidiasis requires systemic therapy of 14 to 21 days' duration, typically using fluconazole 200 to 400 mg (3–6 mg/kg) daily as initial therapy.[28] Caspofungin or other echinocandins may be used if fluconazole fails or is not well tolerated, but it is available only as an IV preparation.[28] Itraconazole, voriconazole, posaconazole, and amphotericin B formulations are rarely indicated for these infections.[28] Reduction in immunosuppression, if possible, and treatment of HIV in infected patients, also enhance recovery from esophageal candidiasis.

Urinary Tract Infection

Patients with cancer, as with many other hospitalized patients, may develop primary infections of the

urinary tract in the setting of urinary obstruction and particularly Foley or nephrostomy catheters. Differentiating between colonization and infection is challenging in the presence of urinary catheters. Urinalysis may be normal, and high organism counts alone are insufficient to confirm infection. In febrile neutropenic patients, however, candiduria should be considered as a harbinger of disseminated candidiasis. Recent guidelines recommend treatment with fluconazole for 14 days with fluconazole 400 mg (6 mg/kg/day). IV lipid amphotericin B formulations may be used to treat resistant *Candida* spp.[28] Amphotericin B deoxycholate bladder irrigation 50 mg/L in sterile water may be administered for 5 days. Of note, echinocandins are not excreted in the urinary tract, so they should not be used in this setting. Relapse of infection will, however, be likely unless the urinary catheter and other indwelling devices, such as nephroureteral stents or nephrostomy tubes, in the urinary tract are removed.

Candidemia

The US Centers for Disease Control and Prevention (CDC) estimated that there were 22,660 cases of candidemia in 2017.[31] Candidemia remains the most common etiology of fungemia in patients with cancer, with *Cryptococcus* spp. and mold less frequently isolated in a European cancer cohort.[32] Rates of infection were highest among patients 65 years of age or older, men, and those of Black race, with an all-cause mortality rate of 25%.[31] Neutropenia, colonization of the oropharynx and other sites, corticosteroid use, presence of CVCs, active malignancy, recent abdominal surgery, hemodialysis, receipt of total parenteral nutrition, and persistent fever in the setting of broad-spectrum antibacterial therapy are associated with candidemia.[31,33] Recent work also demonstrates an association between *Clostridioides difficile* infection and candidemia, with 9% of patients with candidemia also having *C. difficile* infection.[27]

A study from a multicenter database suggested that the species of *C. albicans* may soon represent a minority of candidemia episodes, particularly among patients with hematologic malignancy.[32] Updated nationwide CDC surveillance shows that 38% of candidemia cases are caused by *C. albicans*, 30% *C. glabrata*, then less common *Candida parapsilosis* (14%) and *Candida tropicalis* (8%).[31] With increasing use of prophylaxis against fungal infections in at-risk patients, *Candida* spp. identified in breakthrough cases vary according to the duration and type of antifungal prophylaxis. *C. albicans* is more common in patients with less than 7 days of, or altogether without, antifungal prophylaxis.[34] Breakthrough candidemia in patients on longer duration of prophylaxis, such as patients with leukemia, are identified as *C. glabrata* or *C. krusei*.[34] Studies also point to increased incidence of multidrug-resistant *C. glabrata* candidemia in patients given fluconazole or even caspofungin prophylaxis.[34,35] The latter finding is of concern because caspofungin is often used as an empiric antifungal to manage *C. glabrata*.

Candidemia results in an overall 12-week crude mortality rate of 49% in patients with cancer.[32] *C. parapsilosis* candidemia has been associated with CVCs.[36] Patients with *C. parapsilosis*, including noncancer patients from a multicenter database, were less likely to be neutropenic and immunosuppressed, perhaps explaining the lower mortality rate.[36] *C. krusei* has been associated with prior antifungal use, hematologic malignancy (including stem cell transplant), neutropenia, and corticosteroid use.[36]

Disseminated Candidiasis

Disseminated candidiasis is difficult to differentiate from other disseminated fungal and bacterial infections. Persistent fever in the setting of antibacterial therapy with associated liver dysfunction may suggest consideration of disseminated candidiasis.[36] In patients with cancer, disseminated candidiasis typically originates from the GI tract or CVCs. Dissemination can affect multiple organs, such as the kidneys, heart, GI tract, lung, liver, spleen, and skin.[37] This syndrome typically affects patients with prolonged immunosuppression, with predisposition for liver and spleen leading to the characterization as hepatosplenic candidiasis. *C. tropicalis* is more likely to cause the characteristic skin lesions associated with disseminated candidiasis and occasionally causes a syndrome of skin lesions and painful myositis.[38] Lesions may appear as clusters of pustules or larger nodules and may even develop necrotic centers similar to ecthyma gangrenosum.[39] The common presentation is nontender, firm, nonblanching, raised nodules that are pink to red in color (Fig. 59–3). The variety of syndromes associated with candidiasis is diverse, overlapping with syndromes associated with other fungal, as well as bacterial and viral etiologies. This diversity of presentations emphasizes the importance of approaches to diagnosis of invasive candidiasis.

Diagnosis

When *Candida* infection is suspected, appropriate samples of blood and other available tissues need to be obtained and processed to identify the organism. Identification should be to the *Candida* species level, given the relevance of species in management. Culture-based techniques continue to provide the foundation for the laboratory identification of candidiasis, although 40% of patients with widespread infection demonstrated at autopsy examination had multiple negative blood cultures.[37] The diagnosis of disseminated candidiasis



FIGURE 59–3 Widespread nodular skin lesions in a patient with disseminated candidiasis.

may also be difficult to establish because culture of the organism from nonsterile sites, such as sputum, urine, and feces, may be positive in patients without infection. Identification of *Candida* spp. in respiratory samples is common but of unclear significance. A recent study showed that there was an association between colonization with *Candida* spp. in a cohort of HSCT patients and increased mortality, but treatment with antifungals did not have an impact on mortality.[40] Nonculture diagnostic approaches include β-D-glucan,[41] mannan antigen with antimannan antibody,[42] *Candida* PCR, and T2Candida.[43] These US Food and Drug Administration–approved tools for identification of candidemia have sensitivities that range from 58% to 91% and specificities that range from 80% to 98%.[44] The gold standard, however, remains culture.[28] Notably, blood cultures typically demonstrate *Candida* spp. within 72 to 96 hours, but *C. glabrata* requires longer incubation.[33] Given the challenge of appropriate diagnosis and morbidity associated with failure to treat the severely immunocompromised, empiric therapy for invasive candidiasis is commonly given for those who continue to be ill in the setting of broad-spectrum antibacterial therapy.

Therapy

Therapy for patients with candidiasis includes three classes of medications: azoles (eg, fluconazole, voriconazole), echinocandins (eg, caspofungin), and the polyenes (eg, amphotericin B).[28] Dosing regimens, major toxicities, and general considerations for antifungal agents are shown in Tables 59–1 to 59–3. Timely appropriate therapy, within 24 hours, is necessary because the mortality rate for candidemia ranges from 24% for *C. parapsilosis* to as high as 53% for *C. krusei*.[36] *C. glabrata* exhibits decreased susceptibility to fluconazole.[33] The mortality rate, however, is not significantly different from *C. albicans* candidemia.[33] *C. krusei*, inherently resistant to fluconazole, is increasingly isolated in institutions where fluconazole is commonly used for prophylaxis.[45] *C. lusitaniae*, more commonly seen in patients with stem cell transplant or neutropenia, is of concern because of amphotericin B resistance.[46]

TABLE 59–1 Dosage Regimens for Serious Fungal Infections

Drug	Loading Dose	Daily Dose	Route
D-AMB	—	1–1.5 mg/kg	IV only
Lipid AMB	—	3–5 mg/kg	IV only
Fluconazole	800 mg (12 mg/kg)	400–800 mg (6 mg/kg/day)	IV, PO
Isavuconazole	372 mg q 8 hours ϕορ two days	372 mg	IV, PO
Itraconazole IV	200 mg bid ϕορ two days	200 mg	IV
Itraconazole solution	200 mg bid ϕορ two days	200 mg	PO
Posaconazole tablets	300 mg bid ϕορ two doses	300 mg	PO
Posaconazole IV	300 mg bid ϕορ two doses	300 mg	IV
Posaconazole (suspension)	—	200 mg every 6h	PO
Voriconazole IV	6 mg/kg every 12 hours ϕορ two doses	4 mg/kg every 12 hours	IV
Voriconazole tablets	—	200 mg every 12 hours (>40 kg)	PO
		100 mg q 12 hours (<40 kg)	
Caspofungin	70 mg ϕορ one dose	50 mg	IV
Micafungin	—	150 mg	IV
Anidulafungin	200 mg ϕορ one dose	100 mg	IV

bid, twice a day; D-AMB, amphotericin B deoxycholate; IV, intravenous; PO, oral; q, every.

TABLE 59–2 Major Toxicities of Antifungal Agents

Amphotericin B	Infusion related (eg, headache, chills, hypotension), nephrotoxicity, hypokalemia, hypomagnesemia, anemia
Fluconazole	Nausea, vomiting, headache, hepatotoxicity (rare), drug interactions
Isavuconazole	Nausea, vomiting, diarrhea, headache, shortening of QT interval
Itraconazole	Nausea, vomiting, headache, hepatotoxicity (rare), pulmonary edema, drug interactions
Posaconazole	Hepatotoxicity (rarely requires discontinuation)
Voriconazole	Visual disturbances, rash, nausea, vomiting, headache, hepatotoxicity, drug interactions
Echinocandins (eg, caspofungin)	Fever, nausea, flushing, rash, some drug interactions, phlebitis

TABLE 59–3 Therapeutic Options for Disseminated and Major Organ Candidiasis

Regimen	Advantages	Disadvantages
D-AMB	Broad-spectrum activity	Acute chronic toxicities; minimally effective in patients with neutropenia and with chronic disseminated candidiasis; IV preparations only
Lipid formulations of AMB	Broad-spectrum activity, reduced nephrotoxicity; higher doses can be administered	Only prospective randomized trial showed no advantage in efficacy over D-AMB despite higher doses; more expensive; IV preparations only
Fluconazole	PO and IV preparation; as effective as AMB in randomized trials of nonneutropenic individuals; minimal toxicity; more effective for chronic disseminated candidiasis; little experience in neutropenic patients but appears to be as effective as AMB	Variable activity against *Candida glabrata* and *Candida dubliniensis*; inactive against *Candida krusei*; some drug–drug interactions
Voriconazole	PO and IV preparation; may be used for stepdown oral therapy; provides antimold activity for at-risk patients; excellent ocular and CNS penetration	QT prolongation, ocular toxicity, drug–drug interactions
Echinocandins (eg, caspofungin)	Broad-spectrum activity; minimal toxicity; in randomized trials, as active as AMB and fluconazole; limited experience in neutropenic patients	No oral preparation
Flucytosine	Synergistic with AMB and fluconazole; combination of flucytosine and AMB may be superior to AMB alone for chronic disseminated candidiasis and *Candida tropicalis* infection	No IV preparation; causes myelosuppression; often need monitoring of serum concentrations; emergence of resistance if used alone

AMB, amphotericin B; CNS, central nervous system; IV, intravenous; PO, oral.

Recently published guidelines suggest that echinocandins be used as first-line therapy in neutropenic patients with candidemia, with lipid formulations of amphotericin B as second-line therapy.[28] Species-specific recommendations, however, are provided, given inherent differences in resistance. The guidelines emphasize that if a therapeutic approach is resulting in clinical improvement, then current therapy can be continued. For treatment of *C. glabrata* infection, an echinocandin or lipid formulation of amphotericin B is recommended.[28] For infection with *C. parapsilosis*, an azole or lipid formulation of amphotericin B is recommended. For *C. krusei*, fluconazole is contraindicated because of innate resistance.[28] For neutropenic patients with invasive candidiasis, echinocandins are now first-line therapy, with lipid formulations of amphotericin B an alternative but avoided because of the potential for toxicity, especially renal. Voriconazole is recommended in patients who also require mold coverage or as stepdown therapy in treatment of susceptible isolates.[28] In candidemia and invasive candidiasis, fluconazole may be used in patients who have no prior exposure to azoles and are not critically ill.[28] If fluconazole is used, the initial recommended dose is 12 mg/kg followed by 6 mg/kg/day to avoid inadequate doses (see Table 59–1). Notable is that isavuconazole,

the newest azole, with antimold activity, is not recommended for management of candidemia. It was recently shown in a clinical trial to be inferior to an echinocandin (caspofungin) in the treatment of patients with invasive candidiasis.[47]

Caspofungin was the first Food and Drug Administration (FDA)–approved echinocandin, showing broad-spectrum activity against *Candida* spp. In comparison with amphotericin B deoxycholate (D-AMB) in a study of invasive candidiasis (80% of which was candidemia), caspofungin showed similar outcomes with fewer adverse events.[28] Of note, however, few patients were neutropenic in this study. There are three currently available echinocandins: caspofungin, micafungin, and anidulafungin. They are comparable in their efficacy, although only one study in nononcologic candidemia patients directly compared micafungin and caspofungin and showed equivalent outcomes.[48]

Management of candidemia involves several important points, included in the recent guidelines. These include identification of the species causing candidemia, use of echinocandins as first-line therapy, daily blood cultures until negative, 14-day duration of appropriate therapy after negative blood culture results, echocardiography to assess for valvular vegetation, funduscopic eye examination for endophthalmitis, and stepdown from IV therapy to oral therapy with fluconazole, depending on clinical picture and susceptibility of species isolated.[49] An additional recommendation is to remove CVCs, which are further discussed later, given the challenge of removal in select patient populations.[49]

Patients with cancer with indwelling intravascular catheters typically require them for chemotherapy or supportive care. The removal of surgically implanted catheters is particularly difficult, given thrombocytopenia is often present in the oncologic patient population. Studies suggest a role for catheter removal, particularly if it is clear that the catheter is the source, or in the setting of persistent candidemia without other source. Removal of the catheter may improve response rates to treatment and reduce duration of candidemia.[28] Infection with *C. parapsilosis*, in particular, is associated with persistent candidemia without catheter removal.[28]

Given the complexity of diagnostic, pharmacologic, and non-pharmacologic interventions to optimize mortality in invasive candidiasis, several studies have explored the utility of routine infectious disease consultations for management of candidemia.[50–52] A study conducted in a tertiary hospital examined the impact of infectious disease consultation on mortality rate using propensity analysis to match underlying comorbidities. The study found that infectious disease consultation resulted in longer median duration of antifungal use and more frequent use of eye examination and echocardiography.[53] Implementation of infectious disease consultation resulted in a significantly lower 90-day mortality rate (29% vs 51%). In the group without infectious disease consultation, 14% of patients were not treated for candidemia. This group considered candidemia a "contaminant" in 10% of cases. Notably, this study included patients with solid (33%–36%) and hematologic (14%–20%) malignancy. These findings emphasize that adherence to guidelines-based therapy improves outcomes, with potential benefit for involvement of infectious disease specialists in management of candidemia.

In summary, *Candida* spp. cause a wide spectrum of syndromes from superficial oral candidiasis to candidemia in patients with cancer. The therapeutic approach should take into consideration host risk factors, medication interactions, antifungal toxicities, and comorbidities when selecting an approach to diagnosis and development of treatment plan. As with other syndromes, a systematic approach using "bundles" of care has been proposed as an approach to improving diagnosis and management of patients with invasive candidiasis.

ASPERGILLOSIS

One of the most common and important IFIs is aspergillosis. *Aspergillus* spp. are the most common invasive mold infections in patients with hematologic cancer.[54] *Aspergillus fumigatus* is the species most commonly associated with infection, although *Aspergillus terreus* and *Aspergillus flavus,* more resistant *Aspergillus* spp., are becoming increasingly common.[54] Infections are typically acquired by spore inhalation, but construction in hospitals and surrounding areas have been associated with infection.[55] The most important risk factor is prolonged neutropenia.[54] In stem cell transplant patients, reported risk factors for increased mortality include poor baseline pulmonary status, high doses of corticosteroids (≥2 mg/kg/day), disseminated aspergillosis, proven IA, increased bilirubin, increased creatinine, human leukocyte antigen–mismatched stem cells, and IA occurring 40 or more days after transplant.[56] Recent pandemics have also identified respiratory viral infections, such as influenza, as a risk factor for invasive pulmonary aspergillosis (IPA). Initially seen with H1N1 pandemic but subsequently noted in other influenza seasons, of those with IPA during influenza infection, a multicenter cohort study showed that 19% of patients admitted to an intensive care unit (ICU) with influenza infection were diagnosed with IPA compared with 5% of those without influenza infection. Risk factors for IPA in the multicenter cohort included male gender, corticosteroid exposure, and influenza but not hematologic malignancy.[57] The viral etiology of the most

recent pandemic, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has also been associated with IPA, although there are ongoing efforts to carefully define postviral IPA, particularly in hosts without other significant risk factors.[58]

Pulmonary Infection

The most common syndrome associated with aspergillosis is pneumonia. Because of the angioinvasive nature of the infection, symptoms suggesting pulmonary involvement are pulmonary embolism, pleuritic chest pain, fever, hemoptysis, and friction rub.[59] Initial chest x-ray examination may initially be unremarkable with fever proceeding in the setting of broad-spectrum antibacterials.[59]

Radiologic findings are variable, with wedge-shaped infarcts, necrotizing bronchopneumonia, lobar consolidation, or diffuse infiltrates noted.[59] If suspicion is high for infection, early CT scan of the thorax is essential, potentially demonstrating a halo sign (area of low attenuation surrounding a nodular infiltrate), an important early sign that disappears in 75% of cases within the first week[59] (Fig. 59–4). Analysis of radiologic studies from a clinical trial suggested that patients with the halo sign had an improved response to treatment and an improved mortality rate compared with those who did not exhibit the halo sign.[60] Cavitation occurs as the infection progresses, with lesions often increasing in size until neutrophil recovery occurs. Differentiation from other molds such as mucormycosis can be difficult. A study suggested that CT scans of the thorax with more than 10 nodules and pleural effusion are more often seen in pulmonary mucormycosis rather than IPA.[60]



FIGURE 59–4 Computed tomography scan showing nodular lesions in lung of patient on high-dose adrenal corticosteroid therapy who developed sudden onset of pleuritic chest pain and a pleural friction rub caused by pulmonary aspergillosis. The chest radiograph was normal.

Sinusitis

Immunocompromised patients may exhibit acute sinusitis as a component of invasive diseases, occurring in 15% to 20% of neutropenic patients.[61] Fever, headache, cough, epistaxis, and sinus discharge are signs and nonspecific symptoms suggestive of fungal sinusitis.[61] On examination, necrotic lesions may be seen in the nose or palate, with accurate diagnosis improved by examination and confirmed by biopsy by experienced otolaryngologists.[62] Imaging of the sinuses by CT or MRI scan may show opacification of the sinuses or bony destruction. The mortality rate may be as high as 20% in patients with leukemia in remission to 100% for those with invasive sinusitis who have refractory leukemia or undergoing HSCT.[61]

Skin Infection

Aspergillosis as part of dissemination is discussed later, although primary cutaneous infection occurs with direct inoculation. These infection are rarely associated with central venous access device.[63] Mechanism of spread is presumed to be via inoculation during catheter insertion or possibly dressing changes or application. Initially, lesions may appear as erythematous plaques, progressing to necrotic ulcers with black eschars.[63] *A. flavus* is the most common cause of cutaneous IA.

Disseminated Infection

Given the angioinvasive nature of aspergillosis, hematogenous dissemination occurs in approximately 20% of patients with active hematologic malignancy or HSCT.[64] Common sites of dissemination include the CNS, GI tract, and skin. GI involvement is apparent in 40% to 50% of cases, affecting the esophagus and large bowel.[65] Perforation or massive hemorrhage may occur in this setting. Skin infection may also occur, evolving from erythematous plaques to ulcers that ultimately may be covered by black eschar.[66] Given the broad differential diagnosis of skin lesions in this patient population, skin biopsy is critical.

Diagnosis

A continuing challenge in management of aspergillosis is early and reliable diagnosis.[59] Tissue biopsies from infected tissue may reveal invading hyphae. Paradoxically, cultures of the biopsy specimens fail to grow the fungus in more than 50% of cases. Histology correlates with culture in 78% of cases.[67] Similarly, blood cultures will rarely (except in the case of *A. terreus*) demonstrate the organism, in contrast to fusariosis.[68] Unfortunately, *Aspergillus* spp. also fail to grow well from sputum

or bronchoscopy, with only 30% of biopsy-proven aspergillosis cases growing mold in sputum cultures.[69] In BAL specimens, cytology may show evidence of pulmonary aspergillosis in up to 42% of culture positive cases, using Gomori-methenamine-silver stain, as opposed to calcofluor white stain.[70] The yield of bronchoscopy is improved by performing this procedure as early as possible after identification of abnormalities on chest imaging. Among stem transplant patients, the yield ranges from 72% to 78% with early bronchoscopy (<4 days) compared with 22% to 28% with late bronchoscopy (≥5 days), with consequent impact on mortality.[71] Because of these challenges of diagnosis, patients commonly receive preemptive antifungal therapy for presumed fungal pneumonia while undergoing workup.

To further increase the likelihood of detection of pulmonary aspergillosis, various non–culture-based tests have been developed. Galactomannan and 1,3-β-D-glucan are the most commonly used tests.[44,61] A sandwich enzyme-linked immunosorbent assay used to detect the polysaccharide cell wall component of *Aspergillus* spp., galactomannan can be detected in the serum and BAL fluid of infected patients.[59] The most recent guidelines from the Infectious Diseases Society of America (IDSA) suggest performing bronchoscopy, when feasible, with routine galactomannan on serum and BAL specimens.[61] Sensitivity of serum galactomannan ranges from 60% to 80% and specificity from 80% to 95%,[72] but the test has been studied primarily in hematologic malignancy patients with profound neutropenia. The positive predictive value of this test is poor in patients with solid tumors and other cancers.[59] In BAL specimens, galactomannan shows 85% to 90% sensitivity and 90% to 95% specificity.[72] A recent study of BAL specimens compared performance of galactomannan and a novel lateral-flow device test.[73] The study found that specificity of lateral flow was significantly better than galactomannan, particularly among patients without hematologic malignancy. Among solid tumor patients, for example, specificity was 16% for galactomannan compared with 100% for the lateral-flow device.[73] An additional challenge occurs in interpreting a galactomannan in context of prophylaxis with antimold activity. A recent study suggested a false-positive rate up to 86% for those on active antimold therapy.[74] In fact, the most recent guidelines from the IDSA do not recommend routine screening of blood for galactomannan in patients who are on mold-active antifungal prophylaxis or treatment.[61]

1,3-β-D-Glucan is an integral component of the cell-wall of several yeasts and fungi.[59] The serum assay for 1,3-β-D-glucan has cross-reactivity with other molds but may be used to detect IA.[61,72] Sensitivity ranges from 67% to 80% and specificity of 80-% to 95%, but false positives are noted because of cirrhosis, hemodialysis, and some chemotherapeutic agents.[59,72] Blood-based *Aspergillus* PCR tests are available but include various methodologies and are not FDA approved, so care is recommended in using PCR alone to diagnose IA.[44,61] Appropriate selection of patients with risk factors for IA, for example, with hematologic malignancy and HSCT, will increase the positive predictive value of serum galactomannan and 1,3-β-D-glucan, improving the utility of these tests (see Fig. 59–1).

Therapy

Early diagnosis of aspergillosis using the various available tools has allowed for earlier treatment, but challenges continue in assessing the impact of various treatments, given categorization of infection as proven, probable, or possible.[62] Table 59–4 describes various principles for management of aspergillosis. Persistence of neutropenia is a host factor that is critical in determining the outcome of infection, regardless of therapy.[75] In fact, in a study comparing voriconazole and isavuconazole, the 6-week mortality rate was approximately 45% in both treated groups with persistent neutropenia.[75]

Voriconazole is currently recommended as first-line therapy for patients with IPA.[61] A randomized trial comparing voriconazole with D-AMB for patients with definite or probable aspergillosis showed a decreased mortality rate in the voriconazole group (71% vs 58%). Both oral and IV formulations are available, with decreased nephrotoxicity compared with amphotericin B. Voriconazole does, however, cause visual disturbances, hallucinations, and liver dysfunction in a subset of patients.

Posaconazole was previously only available as an oral solution. Posaconazole tablets are now available, with considerably improved absorption, with minimal impact from food, mucositis, or elevated gastric pH.[76] Despite resultant elevated liver function test results caused by dramatically increased posaconazole levels

TABLE 59–4 Principles of Therapy for Aspergillosis

Early, aggressive treatment with high doses of voriconazole, isavuconazole, or a lipid formulation of D-AMB
Rapid tapering of dose of adrenal corticosteroids if possible
Consideration for G-CSF–primed granulocyte transfusions in select cases
Long-term antifungal therapy, which should be individualized based on response
Debridement of necrotic tissue of localized disease (onychomycosis, sinusitis, abscess)

D-AMB, amphotericin B deoxycholate; G-CSF, granulocyte colony-stimulating factor.

in tablet form, no clinically significant hepatotoxicity occurred.[76] In a retrospective, monocentric study, posaconazole given as salvage therapy was associated with increased response to therapy and decreased mortality rate compared with liposomal amphotericin B (L-AMB) with or without caspofungin.[77] In addition, nephrotoxicity and change in liver function test results were more likely in the L-AMB–containing regimens.

Isavuconazole, the most recent FDA-approved azole approved for treatment of IA, is available in oral and IV formulations.[78] This antifungal is approved for treatment of IA and mucormycosis. The oral and IV formulations are well tolerated, with fewer drug–drug interactions than other azoles, such as voriconazole. The QTc is shortened, rather than prolonged, by this agent. Unfortunately, however, a recent study of breakthrough IFIs in hematologic malignancy and HSCT patients showed a 10.2% rate of breakthrough IFI in those on isavuconazole prophylaxis.[79] In addition, IPA complicated 6.8% of courses of prophylaxis with isavuconazole, compared with 1.3% of posaconazole and 0% of voriconazole courses.[79] Although adding another azole to the armamentarium of antifungals against IA is helpful, clinicians need to remain vigilant of IFIs that may develop while patients are taking even the newest antifungals.

Lipid formulations of amphotericin B are now recommended in lieu of amphotericin B deoxycholate, given the decreased risk of nephrotoxicity. In a randomized study of early treatment of aspergillosis, in neutropenic patients, dosages of 10 mg/kg/day were compared with 3 mg/kg/day with comparable outcomes (46% high dose vs 50% low dose), but the higher dosage resulted in greater nephrotoxicity (32% vs 20%).[61]

Echinocandins inhibit the synthesis of β-(1,3)-D-glucan, an essential component of the fungal cell wall. A disadvantage of echinocandins is that they are available only as an IV preparation.[61] In a noncomparative trial of 90 patients with definite or probable aspergillosis who had failed other therapy, a complete or partial response occurred in 45%.[80] Responses were observed in 50% of patients with pulmonary infection but in only 26% of those with neutropenia.[80]

Treatment of IA is challenging, particularly in the setting of prolonged neutropenia. This has led to the use of combination therapy. A recent randomized, placebo-controlled trial of HSCT recipients and patients with hematologic malignancy of voriconazole combined with placebo or anidulafungin failed to demonstrate a difference in overall or 6-week mortality rate.[81] In a subgroup with radiographic findings consistent with IA and elevated serum galactomannan, the mortality rate was significantly higher in the monotherapy group (15.7% vs 27.3%; $P = .037$).[81]Antifungal agents used for prophylaxis against aspergillosis in high-risk patients have included posaconazole, itraconazole, voriconazole, aerosolized or nebulized formulations of amphotericin B, and micafungin.[54,61] Posaconazole is the only agent currently FDA approved for the indication of prevention of IA in patients with acute leukemia and high-risk stem cell transplant recipients, but significant expense continues to limit the utility of this agent.[80]

The diagnosis and selection of the appropriate antifungal form the foundation of management in IA. An often-overlooked aspect is the appropriate follow-up of patients with IA. IDSA guidelines recommend therapeutic drug monitoring to assure appropriate levels to address infection.[61] In addition, guidelines suggest that serum galactomannan (GM) should be measured periodically (eg, weekly) in patients with baseline elevated serum GM, given correlation with response.[61] Data do not suggest serum β-D-glucan can be monitored in the same way, to demonstrate treatment response. Efforts are ongoing to establish systematic approaches to assessment of radiologic response to treatment of IA.

In summary, IA includes a variety of syndromes, from isolated sinusitis, to pneumonia, to disseminated infection. Key elements of management begin with assessment of risk factors for IA, leading to diagnostic imaging (chest, head, or both if there is evidence of sinusitis); serum GM, serum β-D-glucan, or both; and timely bronchoscopy with cultures and GM from BAL fluid (if pneumonia is present)[44,61] (see Table 59–4). If the diagnosis is established, then there should be careful selection of appropriate antifungals; examining drug–drug interactions, with assessment of drug levels to assure adequacy; discontinuation of unnecessary immunosuppressive medications; and finally appropriate follow-up imaging and biomarkers (eg, serum GM) to monitor the course of IA[44,61] (see Table 59–4).

CRYPTOCOCCOSIS

Cryptococci are encapsulated yeasts that have a worldwide distribution, with a dramatic increase in incidence corresponding with the HIV/AIDS.[82] *Cryptococcus neoformans* is the most common pathogen, found in the pigeon excretions, with infection acquired by inhalation into the lungs. Patients with HIV/AIDS had the highest incidence of infection before the initiation of highly active antiretroviral therapy.[82] Factors associated with cryptococcosis in patients with cancer include lymphopenia, chemotherapy, and corticosteroid use less than 1 month before diagnosis.[83] Those at particular risk include those with lymphoma or CLL. In addition, as mentioned earlier in the chapter, the use of ibrutinib and other kinase inhibitors for treatment of CLL, mantle cell lymphoma, and primary CNS lymphoma has been shown to increase risk for IFI,

including cryptococcosis, histoplasmosis, IA, and PJP.[14] Risk in patients with hematologic malignancy remains generally low because of widespread use of fluconazole and other agents for antifungal prophylaxis.

Pneumonia

Given inhalation as the mechanism of entry, the lungs typically serve as the primary sites of infection. However, fewer than 40% of patients present with symptoms suggestive of pneumonia.[82] Symptoms may, however, include chest pain, fever, or dyspnea. Chest radiographic findings may include single or multiple nodules, airspace consolidation, reticular patterns, ground-glass opacities, cavitary lesions, and occasionally pleural effusions, with all findings unilateral or bilateral.[82] Cryptococcal pneumonia can rapidly progress, resulting in higher mortality rates in patients with cancer. For susceptible patients, finding of this organism in a patient with chest radiography and symptoms consistent with infection is sufficient indication for therapy. In a series from a cancer center, fine-needle aspiration, BAL, and open lung biopsy had a yield of more than 90% on culture.[83]

Central Nervous System Infection

Many series showed a predominance of CNS infection in patients with cancer, primarily with meningoencephalitis, but rarely with meningitis alone or with cryptococcoma. Depending on degree of immunosuppression, patients may exhibit an indolent course with initial symptoms of fever and headache.[82] As the disease progresses, symptoms may include nausea, vomiting, dizziness, somnolence, irritability, confusion, photophobia, or obtundation. Absence of nuchal rigidity (a finding exhibited in only 15% of patients), does not rule out infection.[82] Patients infected with *Cryptococcus gattii* can include those with no apparent immunosuppression, but with high predilection for CNS involvement.[82] In patients with CNS disease, findings include elevated opening pressure, decreased glucose, and high protein concentration. Leukocyte count may also be elevated, with lymphocyte predominance.[83] Available diagnostic tests include India ink, serum cryptococcal antigen, and fungal culture. India ink detects 50% of infections, whereas serum cryptococcal antigen is positive in 90% of cerebrospinal fluid (CSF) and 70% of blood in patients with CNS infection.

Disseminated Infection

Multiple organs, including the liver, prostate, eyes, skin, and bone, may serve as sites of dissemination. Serum cryptococcal antigen has greater than 90% sensitivity and specificity for invasive cryptococcal disease.[82] Skin lesions, present in only approximately 10% of patients, tend to be painless and located on the face, neck, and scalp.[82] The lesions may appear as papules, plaques, ulcerations, acneiform lesions, or even draining sinuses. With wide use of azole-based antifungal prophylaxis, skin, soft tissue, and osteoarticular lesions appear to be less common.[82]

Therapy

Treatment of patients with cryptococcal disease depends largely on the site of infection. D-AMB combined with flucytosine is the traditional approach of choice for severe pulmonary cryptococcosis and CNS disease in non-HIV-infected immunocompromised patients as induction therapy.[82] Flucytosine is available only as an oral preparation with myelosuppressive toxicity (see Tables 59–1 and 59–2). The recommended dosage is D-AMB 0.7 to 1.0 mg/kg/day plus flucytosine 100 mg/kg/day for 2 week, as induction therapy, consolidation with fluconazole 400 to 800 mg/day for 8 weeks, and then 200 mg/day maintenance therapy for 6 to 12 months.[82] In mild to moderate cases of pulmonary disease, fluconazole 400 mg/day alone may be given for 6 to 12 months.[82] Of note, synergy has been noted between some antifungal agents and calcineurin inhibitors, associated with improved outcomes for solid-organ transplant patients,[84] potentially of relevance in HSCT recipients (although not established).

Management of cryptococcal meningitis requires monitoring of CSF pressure and appropriate measures if elevated pressures (>25 cm) are noted to prevent complications and reduce mortality rates.[82] Complications of elevated intracranial pressures (>25 cm) include papilledema, hearing loss, vision loss, severe headache, and cognitive impairment. Therefore, management is aggressive, including daily lumbar punctures, if the CSF pressure remains greater than 25 cm. If necessary, a temporary lumbar drainage or ventriculostomy catheter may be placed, although permanent ventricular shunt placement should be avoided unless all other measures have failed.[82] Timely intervention is necessary to prevent irreversible neurologic complications and death.

Given the complexity of treatment and toxicity of the treatment regimens, involvement of infectious disease consultants has shown a benefit in mortality, similar to findings in invasive candidiasis.[85] Patients with an infectious disease consult were more likely to undergo lumbar puncture and receive treatment with amphotericin B and 5-Flucytosine (when appropriate) and had a significantly lower mortality rate at 90 days (27% vs 45%; P <.001). Cryptococcal infections may cause significant complications and death if not considered early and treated. This has become particularly important because innovative new treatments for cancer, such as ibrutinib and other kinase inhibitors, modulate the immune response in unpredictable way, leading to IFIs, such as cryptococcosis.

FUSARIOSIS

Humans are exposed to various *Fusarium* spp. found in the air and soil. Syndromes include superficial (cutaneous, keratitis, onychomycosis), locally invasive, and disseminated infection. The most common species that cause human disease are isolates belonging to the *Fusarium solani* complex (~50% of cases), but others include *Fusarium moniliforme, Fusarium oxysporum,* and *Fusarium dimerum*.[86] Entry points for infection by *Fusarium* spores are typically the skin, onychomycosis, and respiratory tract. Risk factors for invasive fusariosis among patients with hematologic malignancy include uncontrolled hematologic cancer (71%), stem cell transplant (47%), and neutropenia (82%).[86] The mortality rate was highest in patients with fungemia in one retrospective study, with an abysmal 6% survival rate at 12 weeks.[86] The all-cause mortality rate was 66% but with 50% attributable to fusariosis.

Sinus infection and pneumonia occur in 80% of patients, and blood culture results are positive in 50% to 70% of cases.[87] In neutropenic patients, dissemination occurs 75% of the time and is characterized by multiple skin lesions.[88] Skin lesions may appear as red or gray macules, pustules, or classically papules with central necrosis or eschar (Fig. 59–5). Lesions may also appear to be different types of lesions at different stages of evolution.[88] Myalgias or subcutaneous lesions can also be noted in disseminated fusariosis. In non-neutropenic patients with less severe immunocompromise, infection may be relatively localized, with paronychia, erythematous nodules, hemorrhagic bullae, or trauma-associated tender, necrotic lesions.[87]

Therapy

The significance of in vitro susceptibility results is unclear, with conflicting reports of species-specific susceptibility to amphotericin B in some series but others not demonstrating such an association. Azoles, particularly voriconazole and posaconazole, exhibit variable in vitro activity against different *Fusarium* spp.[87] Posaconazole and voriconazole have both been used as salvage therapy after initial monotherapy with high-dose lipid formulations of amphotericin B failed.[87] Combination therapy has been used with anecdotal success, but definitive evidence of effectiveness is lacking. Mortality remains in the 50% to 60% range, with new treatment options needed.[89] In neutropenic patients, however, neutrophil recovery is the critical component improving outcomes.[86]



FIGURE 59–5 Skin lesions in a patient with disseminated fusariosis.

MUCORMYCOSIS

Mucormycosis is an infection caused by molds of the order *Mucorales* present in the environment, acquired by inhalation of spores.[80] These molds, similar to *Aspergillus* spp., are angioinvasive, causing thrombosis and infarction. Macrophages and neutrophils are key components of the immune response to mucormycosis. Patients with acute leukemia, diabetic ketoacidosis, or iron overload; HSCT recipients; and patients treated with adrenal corticosteroids are at risk for mucormycosis.[80] Syndromes include rhinocerebral, pulmonary, GI, and cutaneous.[90] Whereas patients with hematologic malignancies tend to have pulmonary or disseminated disease, those with diabetes have predominantly sinus involvement.[91]

The overall mortality rate is 44%, but patients with cancer with definite or probably mucormycosis have a mortality rate of 71%.[80] Patients with neutropenia are more likely to have disseminated disease, which has a mortality rate greater than 90%.

Therapy

Amphotericin B, more recently in lipid formulations, has been the most commonly used approach to treatment for mucormycosis.[90,91] High doses of amphotericin B (5–10 mg/kg per day) can be provided with lipid formulations.[91] Other modalities that have been used include hyperbaric oxygen, surgical intervention, immunomodulatory therapy with granulocyte-macrophage colony-stimulating factor (GM-CSF) or interferon-γ (INF-γ), and granulocyte transfusions.[91] The addition of posaconazole typically occurs in transition to oral therapy but rarely may be used as a front-line agent if there is a contraindication to amphotericin B formulations or relatively mild, localized disease that has been surgically resected.[91] Isavuconazole, useful in IA, also has activity against *Mucorales* spp., providing an option for stepdown to oral therapy as well.[78] In addition to monotherapy with amphotericin B formulations, various combinations of antifungals, including echinocandins, are given with any or all of the these modalities.[91] A review of the common nonendemic fungi and associated syndromes is provided in Table 59–5.

TABLE 59–5 Major Fungal Infections and Syndromes

Organism	Infections/ Syndromes	Comments
Candida spp.	Thrush Esophageal candidiasis Urinary tract infection Candidemia Disseminated candidiasis	*Candida parapsilosis* can be resistant to echinocandins *Candida krusei* fluconazole resistant *Candida glabrata* can be fluconazole resistant
Aspergillus spp.	Pulmonary Sinusitis Skin infection Disseminated	Bronchoscopy or biopsy of nodules Head and neck surgery evaluation, debridement Biopsy skin; rare blood culture positive
Cryptococcus spp.	Pneumonia CNS Disseminated	Check serum *Cryptococcus Ag* Low threshold for lumbar puncture in immunocompromised patients
Fusarium spp.	Sinus infection Pneumonia Skin infection Dissemination	Bronchoscopy or biopsy of nodules Head and neck surgery evaluation, debridement Biopsy skin; blood culture positive
Mucormycosis	Rhinocerebral Pulmonary Gastrointestinal Cutaneous	Urgent debridement of rhinocerebral disease Bronchoscopy or biopsy of nodules Hyperbaric oxygen

Ag, antigen; CNS, central nervous system.

ENDEMIC FUNGI

The list of common endemic fungi that may infect patients with cancer in North America include *Coccidioides immitis* and *H. capsulatum*.[92] The distribution of these organisms is determined by climate and geography. These may infect patients without severe immunosuppression and may manifest as lung lesions that may even be confused with malignancy, such as lung cancer, or as disseminated disease.[92] In patients with hematologic malignancies with cellular immunity impaired by the disease process or by treatments including corticosteroids (eg, CLL) and more recently, ibrutinib and other kinase inhibitors, these infections may represent reactivation of latent infection.[92]

Histoplasmosis

Presentation of histoplasmosis is with pulmonary lesions in solid tumor patients but is predominantly with disseminated disease in patients with hematologic malignancies.[92] In the United States, histoplasmosis is most common in the Ohio and Mississippi River valleys. Hepatosplenomegaly and mucocutaneous ulcerations, particularly in the oral cavity, may be present.[92] Histoplasmosis is identified by culture from infected tissues, including respiratory samples and rarely the bloodstream on culture. Histoplasmosis antigen testing can be used to detect evidence of histoplasmosis in urine.[93] Guidelines suggest using liposomal AMB (3–5 mg/kg/day) for severe pulmonary or disseminated disease followed by itraconazole (200 mg twice daily for 2 days; then 200 mg/day).[93] For most infections requiring treatment, therapy is provided for 6 to 9 months.[93] Severely immunocompromised patients may require even more prolonged therapy. Successful therapy with voriconazole has been used for histoplasmosis.[94]

Coccidioidomycosis

C. immitis is reported to cause fever, hypoxemia, and diffuse pulmonary infiltrates in immunocompromised patients.[92] In the United States, coccidioidomycosis is endemic to west Texas, central California, southern New Mexico, and southern Arizona. Disseminated infection may involve the skin and bone. In patients with hematologic malignancy, results of serologic tests may be negative. As in most cases, specimens from the lung, CSF, or other tissue provide the best approach for diagnosis.[95] The most recent guidelines recommend therapy for severe pulmonary or severe disseminated infection with an amphotericin B formulation, D-AMB (0.7–1.0 mg/kg/day) or L-AMB (3–5 mg/kg/day).[96] For meningitis, guidelines recommend fluconazole (400–800 mg/day), initially with increase in fluconazole dose and then with IV amphotericin B formulations if failing to response to therapy.[95,96] Suppression with fluconazole is recommended to be lifelong after coccidioidal meningitis. Voriconazole and posaconazole are additional options available for treatment failure with other agents.[96] In addition, recent guidelines emphasize the role of surgical resection in cases of cavitary lung infection not responsive to therapy.[96] After starting aggressive therapy for most symptomatic syndromes on presentation, fluconazole (400 mg/day) or itraconazole (400 mg/day) is continued for at least 1 year for most cases and indefinitely for immunocompromised patients.[95,96] Lifelong therapy with fluconazole or voriconazole, which penetrate the CNS, is recommended for those with meningitis.[95]

ADJUVANT THERAPY FOR FUNGAL INFECTIONS

White Blood Cell Transfusions

Recovery of neutropenia is essential to recovery from IFI. Almost five decades ago, transfusions of leukocytes

were first used to assist neutropenic patients in recovery. Some studies have suggested that this approach could be effective in management of IFI, but doubts remain. Issues include the challenge of the dose of cells and the length of time when they remain active.[97] Administration of granulocyte colony-stimulating factor (G-CSF) has allowed healthy volunteers to provide adequate numbers of cells.[97] The effectiveness of this approach may be as a bridge to recovery of bone marrow. Finally, clinical issues with granulocyte transfusions include an initial worsening of respiratory symptoms, although skin and soft tissue infections appear to improve.

Cytokines

Proinflammatory cytokines, exemplified by IFN-γ, tumor necrosis factor α, and interleukin-2, are produced by Th1 lymphocytes, activating effector immune cells.[98] Treatment with IFN-γ, sometimes in combination with GM-CSF, has been used to stimulate immune response to fungal infections.[98] IFN-γ enhances hyphal damage to fungal pathogens by neutrophils and monocytes.[98] The duration and depth of neutropenia can be decreased by use of colony-stimulating factors, including G-CSF (filgrastim) and GM-CSF (sargramostim, molgramostim).[80] GM-CSF may be of particular use because it not only increases number of granulocytes but also improves function of macrophages and granulocytes.[98] Case reports and case series have suggested potential benefit of several of these adjunct therapies, although data are not adequate to make firm recommendations for use of these immunomodulators.

Surgical Resection

Surgical resection is a valuable adjunct to therapy for IFI. A recent study describes patients undergoing resection as a component of therapy for a broad array of fungal infections from 1984 through 2009.[99] Patients with hematologic malignancy and suspected pulmonary IFI on appropriate systemic antifungal therapy underwent resection in select circumstances. These included progression of fungal infection despite therapy, importantly with neutropenia not considered a contraindication. If needed, platelets were transfused over 50 × 10^9/L. After surgery, nearly 90% of patients underwent further chemotherapy or stem cell transplant, with mortality rates of 7% and 48% at 30 days and 1 year, respectively.[99] Fungal organisms isolated were predominantly *Aspergillus* spp. (88%) and *Mucorales* spp. (8%). Over the time of the retrospective study, the surgical procedures became less invasive, shifting from lobectomy and open limited resections to video-assisted thoracoscopic procedures.[99] Therefore, surgical resection, via open or video-assisted thoracoscopy, presents a viable option for management of focal fungal infection that fails to respond to antifungal therapy alone, even in patients with hematologic malignancies.

SUMMARY

Fungi are ubiquitous in nature, often forgotten with the focus on bacterial and viral organisms. The fungi known to complicate cancer treatment, including aspergillosis, invasive candidiasis, pneumocystis, and mucormycosis, are associated with the largest economic burden.[1] Fungal infections remain significant causes of morbidity and mortality in patients with cancer. Increasing use of immunomodulatory agents with unknown effect on immune response to infection and aggressive cancer treatment of sicker patients with multiple comorbidities have led to increasing concern for infectious complications of cancer treatment. The identification, careful workup of complications, and management of patients with fungal infections will play a central role in improving outcomes of cancer treatment.

MD ANDERSON PRACTICE TIPS

- If patients remain febrile on broad-spectrum antibacterial therapy with negative bacterial culture results, consider IFIs.
- Perform thorough physical examination to find skin nodules, oral lesions, nuchal rigidity, genital lesions, or other findings that may suggest fungal infection, such as skin lesion suggesting disseminated candidiasis, nuchal rigidity suggesting cryptococcal meningitis, or an oral ulcer suggesting histoplasmosis.
- If obtaining a biopsy of a lung or skin nodule or other suspicious lesion, send for fungal culture in addition to pathology.
- Perform early bronchoscopy and send samples for cytopathology, fungal cultures, and galactomannan, which can detect possible IA or other IFI.
- In patients with cancer, particularly in the ICU, dose antifungals aggressively with therapeutic drug monitoring to avoid inadequate drug levels in this population.
- Assess for infected devices or lines, other sites of disseminated infection, underlying immune defects, and degree of immunosuppression and use this information to guide the duration of antifungal therapy.

REFERENCES

1. Benedict K, Jackson BR, Chiller T, Beer KD. Estimation of direct healthcare costs of fungal diseases in the United States. *Clin Infect Dis*. 2019;68:1791-1797.
2. Bodey GP. Fungal infections complicating acute leukemia. *J Chronic Dis*. 1966;19:667-687.
3. Lamoth F, Kontoyiannis DP. The Candida auris alert: facts and perspectives. *J Infect Dis*. 2018;217:516-520.
4. Lockhart SR, Etienne KA, Vallabhaneni S, et al. Simultaneous emergence of multidrug-resistant Candida auris on 3 continents confirmed by whole-genome sequencing and epidemiological analyses. *Clin Infect Dis*. 2017;64:134-140.
5. Marchetti O, Lamoth F, Mikulska M, et al. ECIL recommendations for the use of biological markers for the diagnosis of invasive fungal diseases in leukemic patients and hematopoietic SCT recipients. *Bone Marrow Transplant*. 2012;47:846-854.
6. Farmakiotis D, Ciurea AM, Cahuayme-Zuniga L, Kontoyiannis DP. The diagnostic yield of skin biopsy in patients with leukemia and suspected infection. *J Infect*. 2013;67:265-272.
7. Perfect JR, Hachem R, Wingard JR. Update on epidemiology of and preventive strategies for invasive fungal infections in cancer patients. *Clin Infect Dis*. 2014;59(suppl 5):S352-S355.
8. Bitterman R, Hardak E, Raines M, et al. Baseline chest computed tomography for early diagnosis of invasive pulmonary aspergillosis in hemato-oncological patients: a prospective cohort study. *Clin Infect Dis*. 2019;69:1805-1808.
9. Stanzani M, Sassi C, Lewis RE, et al. High resolution computed tomography angiography improves the radiographic diagnosis of invasive mold disease in patients with hematological malignancies. *Clin Infect Dis*. 2015;60:1603-1610.
10. Stanzani M, Sassi C, Battista G, Lewis RE. Beyond biomarkers: how enhanced CT imaging can improve the diagnostic-driven management of invasive mould disease. *Med Mycol*. 2019;57:S274-S286.
11. Lewis RE, Albert NP, Liao G, et al. High-dose induction liposomal amphotericin B followed by de-escalation is effective in experimental Aspergillus terreus pneumonia. *J Antimicrob Chemother*. 2013;68:1148-1151.
12. Gupta S, Sultenfuss M, Romaguera JE, et al. CT-guided percutaneous lung biopsies in patients with haematologic malignancies and undiagnosed pulmonary lesions. *Hematol Oncol*. 2010;28:75-81.
13. Lewis RE, Cahyame-Zuniga L, Leventakos K, et al. Epidemiology and sites of involvement of invasive fungal infections in patients with haematological malignancies: a 20-year autopsy study. *Mycoses*. 2013;56:638-645.
14. Chamilos G, Lionakis MS, Kontoyiannis DP. Call for action: invasive fungal infections associated with ibrutinib and other small molecule kinase inhibitors targeting immune signaling pathways. *Clin Infect Dis*. 2018;66:140-148.
15. Yong MK, Slavin M, Kontoyiannis DP. Invasive fungal disease and cytomegalovirus infection: is there an association? *Curr Opin Infect Dis*. 2018.
16. Crum-Cianflone NF. Invasive aspergillosis associated with severe influenza infections. *Open Forum Infect Dis*. 2016;3:ofw171.
17. Brooks JT, Kaplan JE, Holmes KK, et al. HIV-associated opportunistic infections—going, going, but not gone: the continued need for prevention and treatment guidelines. *Clin Infect Dis*. 2009;48:609-611.
18. Steinbach WJ, Marr KA, Anaissie EJ, et al. Clinical epidemiology of 960 patients with invasive aspergillosis from the PATH Alliance registry. *J Infect*. 2012;65:453-464.
19. Bodey GP. The changing face of febrile neutropenia-from monotherapy to moulds to mucositis. Fever and neutropenia: the early years. *J Antimicrob Chemother*. 2009;63 Suppl 1:i3-i13.
20. Stanzani M, Lewis RE, Fiacchini M, et al. A risk prediction score for invasive mold disease in patients with hematological malignancies. *PLoS One*. 2013;8:e75531.
21. Hill JA, Li D, Hay KA, et al. Infectious complications of CD19-targeted chimeric antigen receptor-modified T-cell immunotherapy. *Blood*. 2018;131:121-130.
22. Lewis RE, Kontoyiannis DP. Infectious disease consultation for candidaemia. *Lancet Infect Dis*. 2020;20:164.
23. Haidar G, Dorritie K, Farah R, et al. Invasive mold infections after chimeric antigen receptor-modified T-cell therapy: a case series, review of the literature, and implications for prophylaxis. *Clin Infect Dis*. 2019.
24. Ruchlemer R, Ben-Ami R, Bar-Meir M, et al. Ibrutinib-associated invasive fungal diseases in patients with chronic lymphocytic leukaemia and non-Hodgkin lymphoma: an observational study. *Mycoses*. 2019;62:1140-1147.
25. Daver N, Kontoyiannis DP. Checkpoint inhibitors and aspergillosis in AML: the double hit hypothesis. *Lancet Oncol*. 2017;18:1571-1573.
26. Abers MS, Lionakis MS, Kontoyiannis DP. Checkpoint inhibition and infectious diseases: a good thing? *Trends Mol Med*. 2019;25:1080-1093.
27. Tsay S, Williams SR, Benedict K, et al. A tale of two healthcare-associated infections: Clostridium difficile coinfection among patients with candidemia. *Clin Infect Dis*. 2019;68:676-679.
28. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62:e1-e50.
29. Samonis G, Skordilis P, Maraki S, et al. Oropharyngeal candidiasis as a marker for esophageal candidiasis in patients with cancer. *Clin Infect Dis*. 1998;27:283-286.
30. Roseff SA, Sugar AM. Oral and esophageal candidiasis. In: Bodey GP, ed. *Candidiasis: Pathogenesis, Diagnosis, and Treatment*. 2nd ed. Raven Press; 1993:185-203.
31. Tsay SV, Mu Y, Williams S, et al. Burden of candidemia in the United States, 2017. *Clin Infect Dis*. 2020.
32. Cornely OA, Gachot B, Akan H, et al. Epidemiology and outcome of fungemia in a cancer Cohort of the Infectious Diseases Group (IDG) of the European Organization for Research and Treatment of Cancer (EORTC 65031). *Clin Infect Dis*. 2015;61:324-331.
33. Klevay MJ, Horn DL, Neofytos D, et al. Initial treatment and outcome of Candida glabrata versus Candida albicans bloodstream infection. *Diagn Microbiol Infect Dis*. 2009;64:152-157.
34. Kullberg BJ, Arendrup MC. Invasive candidiasis. *N Engl J Med*. 2015;373:1445-1456.
35. Farmakiotis D, Kontoyiannis DP. Epidemiology of antifungal resistance in human pathogenic yeasts: current viewpoint and practical recommendations for management. *Int J Antimicrob Agents*. 2017;50:318-324.
36. Horn DL, Neofytos D, Anaissie EJ, et al. Epidemiology and outcomes of candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry. *Clin Infect Dis*. 2009;48:1695-1703.
37. Maksymiuk AW, Thongprasert S, Hopfer R, et al. Systemic candidiasis in cancer patients. *Am J Med*. 1984;77:20-27.
38. Kontoyiannis DP, Vaziri I, Hanna HA, et al. Risk factors for Candida tropicalis fungemia in patients with cancer. *Clin Infect Dis*. 2001;33:1676-1681.
39. Bae GY, Lee HW, Chang SE, et al. Clinicopathologic review of 19 patients with systemic candidiasis with skin lesions. *Int J Dermatol*. 2005;44:550-555.

40. Pendleton KM, Dickson RP, Newton DW, et al. Respiratory tract colonization by Candida species portends worse outcomes in immunocompromised patients. *Clin Pulm Med*. 2018;25:197-201.
41. He S, Hang JP, Zhang L, et al. A systematic review and meta-analysis of diagnostic accuracy of serum 1,3-beta-D-glucan for invasive fungal infection: focus on cutoff levels. *J Microbiol Immunol Infect*. 2015;48:351-361.
42. Clancy CJ, Nguyen MH. Diagnosing invasive candidiasis. *J Clin Microbiol*. 2018;56.
43. Clancy CJ, Pappas PG, Vazquez J, et al. Detecting Infections Rapidly and Easily for Candidemia Trial, Part 2 (DIRECT2): a prospective, multicenter study of the T2Candida Panel. *Clin Infect Dis*. 2018;66:1678-1686.
44. Johnson MD, Lewis RE, Dodds Ashley ES, et al. Core recommendations for antifungal stewardship: a statement of the Mycoses Study Group Education and Research Consortium. *J Infect Dis*. 2020;222:S175-S198.
45. Hachem R, Hanna H, Kontoyiannis D, et al. The changing epidemiology of invasive candidiasis: Candida glabrata and Candida krusei as the leading causes of candidemia in hematologic malignancy. *Cancer*. 2008;112:2493-2499.
46. Atkinson BJ, Lewis RE, Kontoyiannis DP. Candida lusitaniae fungemia in cancer patients: risk factors for amphotericin B failure and outcome. *Med Mycol*. 2008;46:541-546.
47. Kullberg BJ, Viscoli C, Pappas PG, et al. Isavuconazole versus caspofungin in the treatment of candidemia and other invasive candida infections: the ACTIVE Trial. *Clin Infect Dis*. 2018.
48. Pappas PG, Rotstein CM, Betts RF, et al. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. *Clin Infect Dis*. 2007;45:883-893.
49. Mellinghoff SC, Hartmann P, Cornely FB, et al. Analyzing candidemia guideline adherence identifies opportunities for antifungal stewardship. *Eur J Clin Microbiol Infect Dis*. 2018;37:1563-1571.
50. Farmakiotis D, Kyvernitakis A, Tarrand JJ, Kontoyiannis DP. Early initiation of appropriate treatment is associated with increased survival in cancer patients with Candida glabrata fungaemia: a potential benefit from infectious disease consultation. *Clin Microbiol Infect*. 2015;21:79-86.
51. Lee RA, Zurko J, Camins BC, et al. Impact of infectious disease consultation on clinical management and mortality in patients with candidemia. *Clin Infect Dis*. 20194;68(9):1585-1587.
52. Jones TM, Drew RH, Wilson DT, et al. Impact of automatic infectious diseases consultation on the management of fungemia at a large academic medical center. *Am J Health Syst Pharm*. 2017;74:1997-2003.
53. Mejia-Chew C, O'Halloran JA, Olsen MA, et al. Effect of infectious disease consultation on mortality and treatment of patients with candida bloodstream infections: a retrospective, cohort study. *Lancet Infect Dis*. 2019;19:1336-1344.
54. Leventakos K, Lewis RE, Kontoyiannis DP. Fungal infections in leukemia patients: how do we prevent and treat them? *Clin Infect Dis*. 2010;50:405-415.
55. Vonberg RP, Gastmeier P. Nosocomial aspergillosis in outbreak settings. *J Hosp Infect*. 2006;63:246-254.
56. Upton A, Kirby KA, Carpenter P, et al. Invasive aspergillosis following hematopoietic cell transplantation: outcomes and prognostic factors associated with mortality. *Clin Infect Dis*. 2007;44:531-540.
57. Schauwvlieghe A, Rijnders BJA, Philips N, et al. Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. *Lancet Respir Med*. 2018;6:782-792.
58. Arastehfar A, Carvalho A, van de Veerdonk FL, et al. COVID-19 associated pulmonary aspergillosis (CAPA)—from immunology to treatment. *J Fungi (Basel)*. 2020;6(2):91.
59. Kontoyiannis DP, Bodey GP. Invasive aspergillosis in 2002: an update. *Eur J Clin Microbiol Infect Dis*. 2002;21:161-172.
60. Georgiadou SP, Sipsas NV, Marom EM, Kontoyiannis DP. The diagnostic value of halo and reversed halo signs for invasive mold infections in compromised hosts. *Clin Infect Dis*. 2011;52:1144-1155.
61. Patterson TF, Thompson GR 3rd, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;63:e1-e60.
62. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis*. 2008;46:1813-1821.
63. Allo MD, Miller J, Townsend T, Tan C. Primary cutaneous aspergillosis associated with Hickman intravenous catheters. *N Engl J Med*. 1987;317:1105-1108.
64. Patterson TF, Kirkpatrick WR, White M, et al. Invasive aspergillosis. Disease spectrum, treatment practices, and outcomes. I3 Aspergillus Study Group. *Medicine (Baltimore)*. 2000;79:250-260.
65. Young RC, Bennett JE, Vogel CL, et al. Aspergillosis. The spectrum of the disease in 98 patients. *Medicine (Baltimore)*. 1970;49:147-173.
66. Mays SR, Bogle MA, Bodey GP. Cutaneous fungal infections in the oncology patient: recognition and management. *Am J Clin Dermatol*. 2006;7:31-43.
67. Shah AA, Hazen KC. Diagnostic accuracy of histopathologic and cytopathologic examination of Aspergillus species. *Am J Clin Pathol*. 2013;139:55-61.
68. Kontoyiannis DP, Sumoza D, Tarrand J, et al. Significance of aspergillemia in patients with cancer: a 10-year study. *Clin Infect Dis*. 2000;31:188-189.
69. Tarrand JJ, Lichterfeld M, Warraich I, et al. Diagnosis of invasive septate mold infections. A correlation of microbiological culture and histologic or cytologic examination. *Am J Clin Pathol*. 2003;119:854-858.
70. Fernández-Cruz A, Magira E, Heo ST, et al. Bronchoalveolar lavage fluid cytology in culture-documented invasive pulmonary aspergillosis in patients with hematologic diseases: analysis of 67 episodes. *J Clin Microbiol*. 2018;56(10):e00962-18.
71. Shannon VR, Andersson BS, Lei X, et al. Utility of early versus late fiberoptic bronchoscopy in the evaluation of new pulmonary infiltrates following hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2010;45:647-655.
72. Lamoth F. Galactomannan and 1,3-beta-d-glucan testing for the diagnosis of invasive aspergillosis. *J Fungi (Basel)*. 2016;2(3):22.
73. Miceli MH, Goggins MI, Chander P, et al. Performance of lateral flow device and galactomannan for the detection of Aspergillus species in bronchoalveolar fluid of patients at risk for invasive pulmonary aspergillosis. *Mycoses*. 2015;58:368-374.
74. Duarte RF, Sanchez-Ortega I, Cuesta I, et al. Serum galactomannan-based early detection of invasive aspergillosis in hematology patients receiving effective antimold prophylaxis. *Clin Infect Dis*. 2014;59:1696-1702.
75. Kontoyiannis DP, Selleslag D, Mullane K, et al. Impact of unresolved neutropenia in patients with neutropenia and invasive aspergillosis: a post hoc analysis of the SECURE trial. *J Antimicrob Chemother*. 2018;73:757-763.
76. Jung DS, Tverdek FP, Kontoyiannis DP. Switching from posaconazole suspension to tablets increases serum drug levels in leukemia patients without clinically relevant hepatotoxicity. *Antimicrob Agents Chemother*. 2014;58:6993-6995.
77. Raad II, Hanna HA, Boktour M, et al. Novel antifungal agents as salvage therapy for invasive aspergillosis in patients with

hematologic malignancies: posaconazole compared with high-dose lipid formulations of amphotericin B alone or in combination with caspofungin. *Leukemia*. 2008;22:496-503.
78. Miceli MH, Kauffman CA. Isavuconazole: a new broad-spectrum triazole antifungal agent. *Clin Infect Dis*. 2015;61:1558-1565.
79. Fontana L, Perlin DS, Zhao Y, et al. Isavuconazole prophylaxis in patients with hematologic malignancies and hematopoietic cell transplant recipients. *Clin Infect Dis*. 2020;70:723-730.
80. Kontoyiannis DP, Lewis RE. Treatment principles for the management of mold infections. *Cold Spring Harb Perspect Med*. 2014;5(4):a019737.
81. Marr KA, Schlamm HT, Herbrecht R, et al. Combination antifungal therapy for invasive aspergillosis: a randomized trial. *Ann Intern Med*. 2015;162:81-89.
82. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50:291-322.
83. Kontoyiannis DP, Peitsch WK, Reddy BT, et al. Cryptococcosis in patients with cancer. *Clin Infect Dis*. 2001;32:E145-E150.
84. Kontoyiannis DP, Lewis RE, Alexander BD, et al. Calcineurin inhibitor agents interact synergistically with antifungal agents in vitro against Cryptococcus neoformans isolates: correlation with outcome in solid organ transplant recipients with cryptococcosis. *Antimicrob Agents Chemother*. 2008;52:735-738.
85. Spec A, Olsen MA, Raval K, Powderly WG. impact of infectious diseases consultation on mortality of cryptococcal infection in patients without HIV. *Clin Infect Dis*. 2017;64:558-564.
86. Campo M, Lewis RE, Kontoyiannis DP. Invasive fusariosis in patients with hematologic malignancies at a cancer center: 1998-2009. *J Infect*. 2010;60:331-337.
87. Lionakis MS, Kontoyiannis DP. Fusarium infections in critically ill patients. *Semin Respir Crit Care Med*. 2004;25:159-169.
88. Bodey GP, Boktour M, Mays S, et al. Skin lesions associated with Fusarium infection. *J Am Acad Dermatol*. 2002;47:659-666.
89. Lamoth F, Kontoyiannis DP. Therapeutic challenges of non-aspergillus invasive mold infections in immunosuppressed patients. *Antimicrob Agents Chemother*. 2019;63(11):e01244-19.
90. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis*. 2005;41:634-653.
91. Spellberg B, Walsh TJ, Kontoyiannis DP, et al. Recent advances in the management of mucormycosis: from bench to bedside. *Clin Infect Dis*. 2009;48:1743-1751.
92. Torres HA, Rivero GA, Kontoyiannis DP. Endemic mycoses in a cancer hospital. *Medicine (Baltimore)*. 2002;81:201-212.
93. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2007;45:807-825.
94. Freifeld A, Proia L, Andes D, et al. Voriconazole use for endemic fungal infections. *Antimicrob Agents Chemother*. 2009;53:1648-1651.
95. Galgiani JN, Ampel NM, Blair JE, et al. Coccidioidomycosis. *Clin Infect Dis*. 2005;41:1217-1223.
96. Galgiani JN, Ampel NM, Blair JE, et al. 2016 Infectious Diseases Society of America (IDSA) clinical practice guideline for the treatment of coccidioidomycosis. *Clin Infect Dis*. 2016;63:e112-e146.
97. Drewniak A, Kuijpers TW. Granulocyte transfusion therapy: randomization after all? *Haematologica*. 2009;94:1644-1648.
98. Safdar A. Strategies to enhance immune function in hematopoietic transplantation recipients who have fungal infections. *Bone Marrow Transplant*. 2006;38:327-337.
99. Nebiker CA, Lardinois D, Junker L, et al. Lung resection in hematologic patients with pulmonary invasive fungal disease. *Chest*. 2012;142:988-995.

60

Endocrine and Metabolic Complications of Cancer Therapy

Rachael Hosein
Sara Bedrose
Rebecca Jeun
Jeena M. Varghese
Sonali N. Thosani

KEY CONCEPTS

- Immune checkpoint inhibitors have become mainstays of therapy for a broad range of cancers and can lead to a variety of endocrinopathies, including hypophysitis, thyroiditis, primary hypothyroidism, Graves disease, primary adrenal insufficiency, lipodystrophy, and autoimmune diabetes.
- A broad range of antineoplastic agents, including agents that target the phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway and tyrosine kinase inhibitors (TKIs), alter glucose homeostasis and can lead to hyperglycemia, which may require monitoring and treatment.
- Hormone-suppressive therapies, radiation treatments, chemotherapeutics, and corticosteroids can all lead to increased bone fragility, which may be ameliorated by antiresorptive agents such as bisphosphonates or denosumab.
- Patients who receive cranial or craniospinal radiation therapy are at risk for hypothalamic and pituitary dysfunction, and those who receive radiation to the head and neck or other sites close to the thyroid are at risk for hypothyroidism and thyroiditis.
- Cytotoxic chemotherapy and radiation therapy are common causes of hypogonadism and infertility in both male and female cancer survivors and should be discussed with patients before initiation of therapy.
- Childhood cancer survivors, especially those who received abdominal radiation or total-body irradiation, are at increased risk of diabetes mellitus and metabolic syndrome as long-term sequelae of cancer treatment and need continued follow-up and screening for these conditions in survivorship care.

In the past two decades, cancer research has rapidly advanced, spurred by the development of high-throughput technology and the maturation of genomic and proteomic research methods. These advances have resulted in treatments that have substantial effects on the outcomes of certain cancers.

Current cancer treatments include surgery, radiation, cytotoxic chemotherapy, hormonal therapy, targeted therapy, and immunotherapy. Adverse effects of antineoplastic agents on the endocrine system are caused by several different mechanisms and can range from a subtle laboratory abnormality with limited clinical significance to potentially lethal clinical syndromes. Antineoplastic agents are cytotoxic to endocrine cells and result in glandular dysfunction and can also interfere with the synthesis or postsynthesis processing of hormones at different levels (ie, transcription, translation, or posttranslation). An agent may inhibit or induce secretion of a hormone by interacting with receptors, perturbing intracellular second messenger metabolism, interfering with hormone delivery by changing carrier protein levels in serum, competing for binding on the carrier protein, or interacting with signal transduction pathways, which can alter hormonal action in the end organs.

Immune checkpoint inhibitors have become a cornerstone for the treatment of different advanced cancers. These drugs, represented mainly by monoclonal antibodies, anti–cytotoxic T-lymphocyte antigen 4 (CTLA-4), anti–programmed cell death protein 1 (PD-1) and anti–PD-1 ligand molecules (PD-L1 and L2), reactivate the immune system against tumor cells and trigger a myriad of autoimmune side effects, including several important endocrine side effects.

This chapter summarizes the endocrine complications of cancer therapy and discusses screening and surveillance of these complications in patients with cancer and survivors.

METABOLIC DISORDERS

Glucose Metabolism Disorders

Diabetes Mellitus

Serum glucose is under continuous complex regulation and affected by many processes, such as gut absorption, cellular uptake, gluconeogenesis, and glycogenolysis. Multiple hormones play important roles in overall glucose homeostasis, including insulin, glucagon, growth hormone (GH), cortisol, somatostatin, and incretins.

Glucocorticoids are used with many chemotherapy protocols and can have transient or permanent effects on glucose levels by increasing insulin resistance. They can unmask preexisting prediabetes or worsen glycemic control in patients with stable diabetes, sometimes leading to hyperglycemic emergencies such as diabetic ketoacidosis or nonketotic hyperosmolar coma. Most patients with hyperglycemia secondary to glucocorticoids, especially in high doses, require insulin therapy to achieve blood glucose control. Despite concerns for mitogenic effects of insulin, large-scale studies have shown that insulin therapy is safe in patients with cancer.[1,2] Traditional basal bolus insulin protocols for diabetes may cause hypoglycemia in the setting of glucocorticoid induced hyperglycemia[3] because patients typically require higher prandial insulin doses in the setting of high-dose steroids.[4] Neutral protamine Hagedorn insulin concurrently administered with prednisone was as effective as long-acting insulin at controlling blood glucose concentrations, had a lower risk of hypoglycemia, and required a lower total daily insulin dose.[5] Cost-effective and well-tolerated alternatives to insulin include metformin and dipeptidyl peptidase 4 (DPP-4) inhibitors.[6]

A number of antineoplastic agents, including signal transduction inhibitors, L-asparaginase, streptozocin, interferon-α (IFN-α), and immune checkpoint inhibitors, have also been associated with impaired glucose homeostasis and frank diabetes mellitus (Table 60–1).

Inhibition of the phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway results in peripheral insulin resistance, increased gluconeogenesis, and hepatic glycogenolysis.[7] Disruption of glucose homeostasis is considered an on-target effect of inhibition of this pathway. As such, hyperglycemia was a frequent adverse event in trials of the mTOR inhibitors everolimus and temsirolimus as well as the isoform specific PI3K inhibitors idelalisib and alpelisib.[1,2,8] Hyperglycemia was the most common grade 3 or 4 adverse event leading to dose reduction or discontinuation of the drug in phase 3 studies of alpelisib.[9–11]

The risk of developing hyperglycemia was about 20% in children with acute lymphoblastic leukemia treated with either pegylated *Escherichia coli* asparaginase or native asparaginase.[12] A combined insulin deficiency and insulin resistance syndrome is thought to occur, but the exact mechanism is unknown.[13] Long-term insulin therapy may not be needed in some cases of L-asparaginase–induced diabetes mellitus.[13] L-asparaginase-associated pancreatitis, with resultant islet cell destruction, can result in hyperglycemia and may necessitate insulin therapy.[14] Diabetic ketoacidosis has also been reported during L-asparaginase therapy. Another potential complication is hypoglycemia after cessation of L-asparaginase; thus, close monitoring of blood glucose is recommended.

Streptozocin is associated with a 6% to 60% incidence of glucose intolerance with most cases mild or moderate in severity and reversible upon discontinuation of the drug.[15]

IFN therapy has broad antiproliferative and immunomodulatory activity and was previously more widely used in conditions such as melanoma and chronic myelogenous leukemia (CML) but now has largely been supplanted by newer targeted therapies. Certain patients taking IFN may experience earlier development of type 1 diabetes with anti-islet autoantibodies detectable at onset.[16,17]

Several tyrosine kinase inhibitors (TKIs) are associated with alterations in glucose homeostasis. Nilotinib is the most frequently implicated, but hyperglycemia has been noted with pazopanib, sunitinib, and imatinib.[18] Improvement in glycemic control and even frank hypoglycemia have been noted with pazopanib and sunitinib.[18,19]

We recommend monitoring fasting serum glucose levels before initiating and during these therapies. Additionally, it might be helpful to determine the levels of anti-islet autoantibodies before starting IFN therapy in patients with family history of type 1 diabetes mellitus.[16]

Immune Checkpoint Inhibitors and Diabetes

Since the approval of ipilimumab by the Food and Drug Administration (FDA) in 2011 for the treatment of melanoma, immune checkpoint inhibitors have become an integral part of treatment regimens for a range of malignancies, including lung cancer, kidney cancer, bladder cancer, head and neck cancer, and Hodgkin lymphoma. These agents have multisystem complications, and endocrinopathies are the most common immune-related adverse events (irAEs). Of the immune-mediated endocrinopathies, the most common is immune-mediated thyroid disease, hypophysitis, and primary adrenal insufficiency. More recently, a form of type 1 diabetes mellitus has become apparent as a rare consequence of immune checkpoint inhibitor therapy. Immune-mediated thyroid, pituitary, and adrenal pathology are discussed later in this chapter.

TABLE 60–1 Antineoplastic Drugs That Cause Hyperglycemia

Therapy Type	Drug	Mechanism	Main Indications
PI3K/Akt/mTOR inhibitors	Everolimus	Inhibits mTOR	Advanced hormone receptor positive, HER2-negative breast cancer PNET of pancreatic origin Advanced renal cell carcinoma
	Temsirolimus	Inhibits mTOR	Advanced renal cell carcinoma
	Idelalisib	Inhibits PI3 kinase (delta isoform)	Relapsed CLL Relapsed follicular B-cell non-Hodgkin lymphoma Relapsed small lymphocytic lymphoma
	Alpelisib	Inhibits PI3 kinase (α isoform)	Advanced or metastatic breast cancer
Tyrosine kinase inhibitors	Nilotinib	Inhibits Bcr-Abl, c-KIT and PDGFRA	Ph+ CML
	Pazopanib	Inhibits VEGFR-2, Kit, and PDGFR-β	Advanced renal cell carcinoma Advanced soft tissue sarcoma
	Sunitinib	Inhibits VEGFR2, PDGFRB, c-KIT and FLT3	Advanced renal cell carcinoma GIST PNET
	Imatinib	Inhibits Bcr–Abl, c-KIT and PDGFRA	CML Chronic eosinophilic leukemia Ph+ ALL GIST
Cytotoxic enzyme	L-Asparaginase	Deamination and depletion of serum asparagine	ALL
Nitrosourea	Streptozocin	DNA alkylation and inhibits DNA synthesis	Metastatic islet cell carcinoma of pancreas
Cytokine	Interferon alfa	Broad range of immunoregulatory and antiproliferative effects	Melanoma Renal cell carcinoma CML
Somatostatin analogs	Octreotide Lanreotide Pasireotide	Bind somatostatin receptors to inhibit peptide secretion	Unresectable, locally advanced or metastatic gastroenteropancreatic-neuroendocrine tumors
Histone deacetylase inhibitor	Vorinostat	Inhibits class I, II, and IV histone deacetylases	Cutaneous T-cell lymphoma
Immune checkpoint inhibitors	Pembrolizumab	Inhibits PD-1	Metastatic melanoma Metastatic NSCLC HNSCC
	Nivolumab	Inhibits PD-1	Metastatic melanoma Metastatic NSCLC Advanced renal cell carcinoma
	Avelumab	Inhibits PD-L1	Metastatic Merkel cell carcinoma Locally advanced or metastatic urothelial carcinoma Advanced renal cell carcinoma
	Durvalumab	Inhibits PD-L1	Locally advanced or metastatic urothelial carcinoma Unresectable stage III NSCLC

ALL, acute lymphocytic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; F LT3, fms-like tyrosine kinase 3; GIST, gastrointestinal stromal tumor; HER2, human epidermal receptor 2; HNSCC, head and neck squamous cell carcinoma; mTOR, mammalian target of rapamycin; NSCLC, non–small cell lung cancer; PD, programmed cell death protein 1; PDGFRA, platelet-derived growth factor receptor alpha; PD-L1, programmed death ligand 1; Ph, Philadelphia chromosome; PI3K, phosphatidylinositol-3-kinase; PNET, progressive well-differentiated neuroendocrine tumor; VEGFR, vascular endothelial growth factor receptor.

It is thought that immune checkpoint inhibitors trigger immune-mediated damage of pancreatic islet cells (insulitis), leading to a form of drug-induced type 1 diabetes mellitus. This effect has been reported even after a single treatment with immunotherapy.[20] Immune-mediated diabetes is most common with the PD-1 antibody pembrolizumab but has also been reported in patients treated with other PD-1 and PD-L1 antibodies: nivolumab, avelumab, and durvalumab.[21] Patients are typically older and have a higher body mass index than patients who develop spontaneous type 1 diabetes mellitus.[22,23] Patients may already have diabetes-associated autoantibodies at the time of diagnosis and can present in diabetic ketoacidosis.[21,23]

Initial treatment is discontinuation of the immune checkpoint inhibitor and addition of insulin and other diabetes medications to address the hyperglycemia. The role of steroids to treat acute insulitis remains controversial. There is at least one case report of immune-mediated diabetes being successfully treated with infliximab.[24] Spontaneous resolution of diabetes is unlikely even after stopping immune checkpoint inhibitor therapy, and most patients have long-term dependence on insulin therapy.[21]

Glucosuria

Some antineoplastic drugs (eg, ifosfamide, mercaptopurine) cause a proximal tubular defect and lower the renal threshold for glucosuria without affecting glucose metabolism. Delayed onset glucosuria was detected in the majority of adults and children treated with high-dose ifosfamide, cisplatin, and high-dose methotrexate compared with the early postchemotherapy assessment in a prospective study of renal function after treatment.[25]

Lipid Disorders

Lipid disorders are seldom evaluated during active anticancer therapy because patients are often encouraged to maintain a positive metabolic balance via liberal oral intake. However, association between dyslipidemia and malignancy has drawn increasing attention. Several anticancer agents are known to cause dyslipidemia ranging from clinically insignificant changes to severe hypertriglyceridemia causing pancreatitis and other complications. A recent study investigated the association between hyperlipidemia and colorectal cancer (CRC) metastasis and concluded that hyperlipidemia promotes stimulates CRC cells to leave the vasculature and metastasize. Thus, hyperlipidemia is an independent risk factor tumorigenesis and has negative prognostic implications.[26]

Agents Known to Cause Lipid Disorders

Lipid disorders are among the main side effects of vitamin A derivatives, such as bexarotene, which is used in malignancies such as cutaneous T-cell lymphoma (CTCL), acute promyelocytic leukemia, and head and neck cancer. Binding of bexarotene to retinoid X receptors upregulates not only lipid metabolism but also interferes with thyroid hormone synthesis, resulting in hyperlipidemia and central hypothyroidism.[27] Hypercholesterolemia is the second most common side effect of bexarotene (reported in 48% of treated patients), and it is important to check baseline lipid levels and thyroid function in patients before bexarotene therapy. Dietary modifications are recommended if triglyceride levels are 200 to 400 mg/dL, and omega-3 fatty acids with fibrates or nicotinic acid should be started for levels of 400 to 1000 mg/dL. Lipid levels should be monitored on therapy because triglyceride levels greater than 1000 mg/dL increase the risk of acute pancreatitis.[28,29] The British Association of Dermatologists has recommended starting prophylactic levothyroxine and fenofibrate for all patients receiving bexarotene because a significant proportion of patients develop central hypothyroidism and hypertriglyceridemia.[30]

Despite these measures, in some patients with genetic polymorphisms of apolipoprotein genes such as APOA5, APOC3, and APOE, there is a higher likelihood to develop severe hypertriglyceridemia, which can require combination treatment with omega-3 fatty acids and fenofibrate.[31] One study showed that patients carrying at least one minor allele were less likely to develop severe hypertriglyceridemia, which makes screening of APOA5 and APOC3 genotypes a useful tool to identify the best candidates for bexarotene therapy.[32] The long-term significance of drug-induced hypercholesterolemia is unclear; however, atorvastatin has been successfully used to treat bexarotene-associated hypercholesterolemia in patients at the University of Texas MD Anderson Cancer Center (MDACC).[33]

Mitotane, an analog of the insecticide dichlorodiphenyltrichloroethane, is used in treatment of adrenocortical carcinoma as adjuvant therapy and has a potential side effect of hypercholesterolemia. Possible mechanisms include inhibition of sterol-O-acyl transferase 1 (SOAT 1), which is important for adrenal cytotoxicity, resulting in an increase in lipid-mediated endoplasmic reticulum stress and apoptosis in adrenocortical carcinoma cells.[34] Another study also showed that mitotane directly interacts with lipid membranes and alters membrane properties depending on lipid composition.[35]

A study from MDACC showed that mitotane increases high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels.[36] Patients with adrenocortical carcinoma usually have a poor prognosis, making the clinical significance of mild to moderate elevation of cholesterol uncertain. However, in long-term survivors on

adjuvant mitotane therapy, hyperlipidemia can lead to early development of atherosclerotic disease.

mTOR inhibitors have metabolic side effects that include hypercholesterolemia and hypertriglyceridemia. Possible mechanisms include rapamycin-induced reduction of gene expression of lipogenesis enzymes, reduction in lipoprotein lipase activity, and increase in adipose tissue fatty-acid release by increasing the action of hormone-sensitive lipase and reduction of LDL-apoB100 catabolism.[37–39] In addition, mTOR inhibitors reduce LDL-receptor expression, resulting in reduced LDL uptake and then in reduction in lipid clearance from the bloodstream.[40]

Another mTOR inhibitor that is widely used for treatment of patients with progressive pancreatic neuroendocrine tumors, advanced renal cell cancer, and breast cancer, as well as for antirejection agent for transplantation is everolimus. Hyperglycemia is a common side effect of everolimus, and this medication is also used in the management of patients with insulinoma-induced hypoglycemia.[41]

Before starting mTOR inhibitor therapy, baseline fasting glucose, LDL cholesterol, and triglyceride levels should be checked. The lipid profile should be monitored with every treatment cycle. The goals of lipid-reducing therapy are targeting fasting LDL cholesterol of 190 mg/dL or less and triglycerides of 300 mg/dL or less in patients with a life expectancy longer than 1 year. Therapeutic lifestyle changes are the first appropriate approach for patients with hyperlipidemia. If these fail to reduce LDL cholesterol to 190 mg/dL or less, pravastatin is used as first-line therapy followed by fluvastatin or rosuvastatin 5 to 20 mg/day in patients with poor tolerance or inadequate response; atorvastatin and simvastatin are contraindicated because enzymatic induction of cytochrome P450 interferes with the metabolism and potentially reduces the activity of mTOR inhibitors, especially everolimus. Statin monitoring under mTOR inhibitor therapy is the same as in nononcologic contexts. The goals of LDL cholesterol reduction vary with patients' cardiovascular risk factors. Fibrate, omega-3 acid esters, niacin, and combination therapy are the treatment options for hypertriglyceridemia. Efficacy should be assessed on lipid profile after 2 months' treatment, repeated every 3 months until lipid targets are reached, and then repeated twice yearly. In uncontrollable hypertriglyceridemia exceeding 1000 mg/dL, mTOR inhibitor treatment should be interrupted, and specialist opinion should be sought.[5,42]

Dyslipidemia is also caused by other chemotherapeutic agents, including capecitabine. Transient dyslipidemia has been reported with paclitaxel and other platinum-based chemotherapy.[43,44] Neoadjuvant chemotherapy exerted an adverse temporary effect on lipid levels (manifested as increased triglyceride and LDL cholesterol levels and decreased HDL cholesterol levels) during the chemotherapy periods. However, this influence was not sustained because the lipid profiles levels were generally restored to baseline levels 6 months after chemotherapy completion.[45]

In addition to dyslipidemia, case reports have also described a new complication of cancer therapy, which is acquired generalized lipodystrophy as a complication of immunotherapy including pembrolizumab and nivolumab.[46,47] Although the mechanism is unclear, there is evidence of fat destruction in lipodystrophy, which may involve antiadipocyte antibodies.

WATER AND ELECTROLYTE DISORDERS

Serum osmolality is tightly regulated by hypothalamic osmoreceptor-controlled antidiuretic hormone secretion from cells in the paraventricular and supraoptic nuclei, the hypothalamic thirst center, and the kidneys. Disruption of these regulators leads to disturbance in free water clearance and subsequent abnormalities in serum sodium levels.

Syndrome of Inappropriate Antidiuretic Hormone Secretion and Hyponatremia

Hyponatremia, defined as serum sodium below 130 mEq/L, is a relatively common electrolyte abnormality in patients with cancer, and the incidence of this condition varies; it can be as high as 76% in patients with certain malignancies.[48] The development of hyponatremia in patients with cancer is a poor prognostic indicator and associated with an increase in 90-day mortality rate,[49] poor performance status,[50] and increased length of stay.[51]

Causes of hyponatremia in patients with cancer are categorized based on the patient's volume status. In hypervolemic patients, causes include heart failure from malignant pericardial disease or anthracycline-induced cardiac dysfunction, liver failure caused by metastatic liver disease or hepatotoxicity from chemotherapy, or kidney failure caused by nephrotoxicity from chemotherapy or malignancy-related nephrotic syndrome. In hypovolemic patients, treatment-related vomiting and diarrhea, platinum-based tubular damage resulting in renal salt wasting or intracranial tumor–related cerebral salt wasting could contribute to hyponatremia.[52]

Of the various causes, in euvolemic patients, the syndrome of inappropriate antidiuretic hormone secretion (SIADH) is one of the most common underlying causes. SIADH is a diagnosis of exclusion after ruling out hypothyroidism and adrenal insufficiency as underlying causes. In patients with cancer, SIADH is most commonly caused by ectopic production of

arginine vasopressin (AVP) by a variety of tumors. Small cell lung cancer (SCLC) cells are the only known tumor type to produce AVP in tumor cell lines, and 70% of patients with SCLC are found to have elevated AVP levels.[53] Less frequently, SIADH has also been associated with several other cancers, including head and neck cancer, gastrointestinal cancers, gynecologic malignancies, and hematologic malignancies (including Hodgkin and non-Hodgkin lymphoma, multiple myeloma [MM], chronic lymphocytic leukemia, and malignant histiocytosis).[54]

Anticancer drugs can also cause SIADH through a variety of mechanisms. Chemotherapy-induced lysis of antidiuretic hormone (ADH)–containing cancer cells leads to severe hyponatremia at the time of chemotherapy induction. Cyclophosphamide increases AVP secretion and its effect on the kidney, and aggressive hydration to prevent cyclophosphamide-induced hemorrhagic cystitis can worsen hyponatremia. Vincristine- and vinblastine-induced neurotoxicity alter the delicate regulation of AVP secretion in the hypothalamic pituitary axis. Cisplatin treatment increases ADH production and renal response to ADH with hyponatremia caused by renal salt wasting syndrome.[55]

Other key factors causing SIADH in patients with cancer include symptoms such as nausea or pain and use of medications such as narcotics, nicotine, antidepressants such as selective serotonin reuptake inhibitors, thiazide diuretics, antipsychotics, and antiepileptics.[55]

Symptoms of hyponatremia include headache, lethargy, nausea, vomiting, drowsiness, and in extreme cases, seizures and obtundation. There are certain essential criteria that must be met for diagnosis of SIADH in a clinically euvolemic patient with normal adrenal and thyroid function. These include elevated urine osmolality (>100 mOsm/kg), which is typically higher than plasma osmolality, and urine sodium greater than 30 mEq/L in a patient with normal sodium intake.[48]

Standard treatment of hyponatremia includes fluid restriction based on urine solute content and increase in oral salt intake in the form of salt tablets in asymptomatic patients. In the presence of severe symptoms (seizures or obtundation), hypertonic saline infusions (3%) are used with close and frequent monitoring of sodium levels. Demeclocycline (600–1200 mg/day) can also be used in cases when hyponatremia does not respond to strict fluid restriction. Vasopressin receptor (V2) antagonists (tolvaptan and conivaptan) have been approved for treatment of patients with clinically significant hypervolemic or euvolemic hyponatremia associated with heart failure or SIADH.[56] It is important to avoid fluid restriction after patients are started on these agents to prevent rapid overcorrection. Other less commonly used treatment options include f loop diuretics with sodium supplementation, urea, lithium, and fludrocortisone.[57]

Treatment of hyponatremia in patients with cancer poses a unique challenge, especially in patients in whom the underlying stimulus cannot be removed. In addition, fluid restriction may not be an option in patients with cancer who need aggressive hydration to prevent chemotherapy-induced toxicities. Clinical factors need to be taken into careful consideration to determine what treatment option is best for the patient.

Diabetes Insipidus and Hypernatremia

Hypernatremia, defined as a serum sodium greater than 145 mEq/L, occurs in patients with cancer either because of lack of ADH production caused by pituitary surgery or inflammation from medication side effects, resistance of ADH response at the level of the kidney, or reduced free water intake for patients on parenteral or tube feeding regimens. Central diabetes insipidus can occur after surgery for brain tumors and occasionally in cases of tumors near the sella or the hypothalamus that invade the neurohypophysis or disrupt the pituitary stalk. Central diabetes insipidus caused by treatment with immune checkpoint inhibitors has been described in case reports but remains very rare.[58,59] These cases are often recognized by a clinical presentation of polyuria or polydipsia and are usually treated with vasopressin to control the symptoms and correct the associated hypernatremia.

Nephrogenic diabetes insipidus can also occur in patients with cancer, and multiple antineoplastic agents have been described in association with this syndrome. Ifosfamide is well known to induce damage to the proximal renal tubule and, to a lesser extent, the distal renal tubule, and thereby induce nephrogenic diabetes insipidus. There are case reports of nephrogenic diabetes insipidus occurring with bendamustine and streptozocin.[60,61]

Hypernatremia is also classified based on volume status. In hypovolemic patients, the caused can be diuretics, diarrhea, vomiting, or decreased free water intake, and treatment includes hydration with normal saline. In patients with euvolemic hypernatremia, treatment includes hypotonic fluids and vasopressin for patients with central diabetes insipidus and diuretics and nonsteroidal antiinflammatory drugs for patients with nephrogenic diabetes insipidus. For patients with hypervolemic hypernatremia, treatment is free water administration with loop diuretics to help with natriuresis.[57]

DISORDERS OF BONE AND BONE MINERAL METABOLISM

Osteoporosis

Normal bone remodeling requires a delicate balance between bone formation by osteoblasts and bone

resorption by osteoclasts. Antineoplastic therapy may affect this balance by increasing the activity of osteoclasts eg, interleukin-2) or from direct toxic effects on osteoblast function. Hormones and cytokines (ie, parathyroid hormone [PTH], PTH-related peptide, and interleukin-1) can also affect overall bone turnover.

Bone mineral loss is one of the side effects of cancer treatment. Hormone-suppressive therapies, chemotherapeutics, and corticosteroids can cause osteoporosis in patients with cancer.[62] Additionally, bone loss is of big concern in patients with transplant or MM and those receiving radiation therapy or multikinase inhibitors. Improved oncologic treatments and patient longevity have focused attention on skeletal health in patients with cancer, leading to emergence of cancer treatment-induced bone loss with growing evidence about the protective effect of bisphosphonates and denosumab therapy in this setting.[63]

Patients with breast cancer are at high risk for osteoporosis after hormone-suppressive therapy.[64] Whereas aromatase inhibitors, including anastrozole and letrozole, decrease bone density and increase the rate of fractures in postmenopausal women, tamoxifen, a selective estrogen receptor modulator, has a similar effect in premenopausal women. This is in sharp contrast to the positive effect on bone (both bone mineral density [BMD] and fracture rates) seen with tamoxifen in postmenopausal women (Fig. 60–1). In the ATAC (Arimidex [anastrozole], Tamoxifen, Alone or in Combination) trial, 9366 postmenopausal women with invasive operable breast cancer who had completed primary therapy were randomly assigned to receive anastrozole, tamoxifen, or both. More fractures were seen in patients who received anastrozole than those who received tamoxifen.[65] It has been shown that fracture risk in postmenopausal women during aromatase inhibitor treatment, in real-life conditions, was more than 40% compared with tamoxifen, corroborating previous randomized controlled trial (RCT) results.[66]

Patients with breast cancer and patients with prostate cancer are at risk for two types of bone diseases: fragility fractures related to osteoporosis and skeletal-related events. Patients should undergo BMD testing before treatment with aromatase inhibitors, and annual follow-up should be conducted thereafter. Antiresorptive therapy is usually added if a patient's bone density is within the osteoporotic range (T score ≤–2.5) before treatment or if a significant decline in BMD was seen during follow-up because studies have shown significant benefit of antiresorptive therapy in this setting.[66]

Osteoporosis can also occur in patients with prostate cancer with hypogonadism secondary to androgen deprivation therapy (ADT) or treatment with gonadotropin-releasing hormone (GnRH) agonists, nonsteroidal antiandrogens, bilateral orchiectomy, or androgen blockers.[67] Hypogonadism can also causes

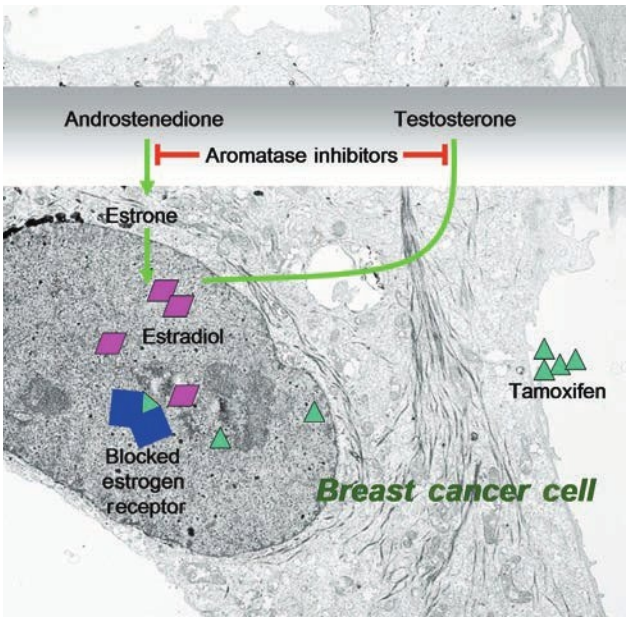


FIGURE 60–1 Mechanism of action of selective estrogen receptor modulators and aromatase inhibitors. Aromatase inhibitors, including anastrozole and letrozole, inhibit conversion of androstenedione or testosterone to estrone, which causes a decrease in bone mineral density. Tamoxifen, a selective estrogen receptor modulator, has a positive effect on bone.

muscle loss (sarcopenia), leading to increased falls and fractures.[68] Bone-seeking radiopharmaceuticals such as radium-223 dichloride should not be used with abiraterone and prednisone because of the high incidence of fracture and death.[69,70]

Patients with prostate cancer should be evaluated with BMD testing before starting ADT. Patients with fragility fractures or osteoporosis should be offered antiresorptive treatment and nonpharmacologic approaches such as exercise, along with calcium and vitamin D supplementation.[71]

Antineoplastic agents can cause chemotherapy-associated osteoporosis.

Prolonged therapy with oral methotrexate for acute lymphoblastic leukemia causes distal extremity pain, severe osteoporosis, and associated fractures, with significant improvement after cessation of methotrexate therapy.[72] Other agents reported to reduce bone density include cisplatin and carboplatin. In addition, many chemotherapy protocols include corticosteroids, which are known to decrease bone density and increase the risk of fractures.

Patients who have undergone bone marrow transplantation have been reported to have low bone mass. The reduced bone density is likely to be secondary to the long-term side effects of bone marrow radiation, chemotherapy, corticosteroids, and hypogonadism.

Bone is the predominant organ involved in MM and usually causes osteolytic bone disease in the axial and longitudinal skeleton, increasing the susceptibility to pathologic fractures. Bisphosphonates such as zoledronic acid and pamidronate reduce the proportion of patients with MM who experience skeletal morbidity.[73] It has been noted that combined treatment with a transforming growth factor β inhibitor (1D11) and bortezomib (a component of most MM first-line treatment regimens) improves bone architecture in a mouse model of myeloma-induced bone disease. However further studies are needed to validate that effect in humans.[74]

Osteoblasts and osteoclasts are under the influence of many hormonal and signaling pathways, including tyrosine kinase receptors for platelet-derived growth factor (platelet-derived growth factor [PDGF] receptors α and β) and c-Abl. Activation of the PDGF pathway improves BMD in ovariectomized rats and accelerates fracture healing. The absence of c-Abl is associated with impaired osteoblast maturation, leading to an osteoporosis phenotype.[75] Multikinase inhibitors, such as sorafenib, sunitinib, and imatinib, inhibit pathways that affect bone remodeling. Inhibition of bone resorption appears to be a class effect and is likely contributed by TKI effects on the hematopoietic and mesenchymal stem cells.[76,77] More studies are needed to determine the effects of TKIs on bone and bone mineral metabolism and the clinical implications of that effect. After 2 to 4 years of treatment with imatinib in patients with CML, a significant increase in the volume of the trabecular bone in the iliac crest has been observed.[78] Preosteoblast cells exposed to imatinib undergo suppression of PDGF-induced PI3 kinase/Akt activation with upregulation of genes associated with osteoblast differentiation and bone formation. In subsequent prospective investigation, imatinib-treated patients have also been confirmed to manifest a decrease in calcium levels with an associated increase in PTH levels unrelated to vitamin D deficiency or chronic renal insufficiency.[79,80]

The goals of management with regard to skeletal health are to prevent fragility fractures in patients without bone metastasis and to prevent symptomatic skeletal events (SSEs), which include pathologic fractures and spinal compression. Fragility fractures and SSE are both correlated with worse overall survival.[70]

Role of Antiresorptive Therapy in Prevention and Treatment of Cancer-Induced Bone Loss

There is significant benefit of antiresorptive therapy in setting of cancer-induced bone loss (CIBL). For example, in patients with breast cancer treated with aromatase inhibitors who are at high risk of fracture, treatment with bisphosphonate lowered fracture risk by 30% compared with patients who were not treated.[66] Bisphosphonates and denosumab are also beneficial in reducing the risk of bone loss and fractures in patients with prostate cancer treated with ADT.[81]

In addition, adjuvant bisphosphonates may have benefits on disease-free survival, especially with regard to bone recurrences, in postmenopausal women with nonmetastatic breast cancer.

A systematic review and meta-analysis of RCTs in patients with prostate and breast cancer showed that denosumab, when administered at dose of dose of 60 mg every 6 months led to a reduction of the BMD loss up to 36 months both at the lumbar and femoral levels and a BMD increase at both 24 and 36 months. There was also a reduction in the number of new vertebral and femoral fractures at 24 and 36 months.[82]

Bisphosphonates may have benefit in chemotherapy-induced bone loss. There is evidence that adding zoledronic acid to cisplatin ameliorated cisplatin-induced bone and muscle abnormalities in young mice.[83] For glucocorticoid-induced osteoporosis, denosumab was superior to bisphosphonates in its effects on lumbar spine and total hip BMD with no difference in the incidence of infections or adverse events. However, studies were underpowered to detect differences in the risk of fracture.[84]

Antiresorptive therapies have limitations because they lead to a low turnover state in which bone formation decreases with the decrease in bone-remodeling activity. Other drugs are currently widely used for the management of nonmalignant bone disease but are not specifically recommended in the oncologic setting; these include calcitonin (the clinical investigation of which in cancer patients has been very limited) and teriparatide, a recombinant human PTH analog. Teriparatide has been associated with an increased risk of osteosarcoma in patients receiving bone radiotherapy and is contraindicated for the treatment of CIBL.[85,86]

Osteomalacia and Rickets

Osteomalacia is characterized by hypomineralization of the bone matrix. In children, abnormal mineralization and maturation of the growth plate at the epiphysis is called rickets. Nutritional deficiency (especially vitamin D deficiency) and renal wasting of phosphorus leading to hypocalcemia or hypophosphatemia are among the common causes of osteomalacia. Other contributing factors include drugs such as anticonvulsants or aluminum and systemic acidosis. Antineoplastic agents can also cause or worsen osteomalacia.

Cisplatin and ifosfamide-induced tubular damage lead to renal phosphate wasting, hypophosphatemia, and rickets. Although renal and skeletal consequences of ifosfamide therapy have been well described in

children, only four adult patients with osteomalacia have been reported.[87] Another antineoplastic agent, the estrogen derivative estramustine, used in prostate cancer metastatic to bone, can cause hypocalcemia, hypophosphatemia, secondary hyperparathyroidism, and osteomalacia with normal vitamin D levels.[88]

Tumor-induced osteomalacia (TIO) is a rare paraneoplastic metabolic syndrome that is characterized by severe hypophosphatemia, hyperphosphaturia, and osteomalacia secondary to renal loss of phosphate. It is caused by overproduction of fibroblast growth factor 23 (FGF23) from tumors of mesenchymal origin. However, it has been also reported in patients with solid malignancies, including breast cancer.[89]

Treatment of patients with TIO consists of surgical resection of the tumor, though locating the responsible tumor is often challenging. Before surgery or when surgery is not indicated, medical treatment with phosphate repletion and active vitamin D is needed. Use of a monoclonal antibody against FGF23 (burosumab) is still under review for TIO, though it is FDA approved for X-linked hypophosphatemia rickets. Data on management of TIO in the metastatic setting are scarce. In these cases, treatment of cancer can potentially lead to the normalization of the electrolytic disturbances and reduction of the activity of FGF23. The use of antiresorptive therapy in patients with bone metastases can potentially trigger FGF23 overexpression, and further studies are needed are to evaluate the use of antiresorptive therapy in this setting.[89]

Hypercalcemia

Calcium homeostasis is normally maintained by the interplay of PTH, calcitonin, phosphorus, and vitamin D metabolites in several target organs, including bones, parathyroid glands, intestines, and kidneys. In patients with cancer, multiple factors can affect this delicate balance, including nutritional status, medications, and tumor secretion of cytokines, hormones, or other humoral factors.

Hypercalcemia can occur in 20% to 30% of all patients with malignancy.[90] Recent studies report a lower incidence, probably reflecting better cancer care. A retrospective study used the Oncology Services Comprehensive Electronic Records warehouse of electronic health records to evaluate the prevalence of hypercalcemia of malignancy in the United States. It estimated the prevalence of hypercalcemia of malignancy to affect approximately 2% of patients with cancer. The rates were highest for patients with MM (7.5%–10.2%) and lowest for those with prostate cancer (1.4%–2.1%).[91] In addition to MM, squamous carcinoma, renal cell carcinoma, non–small cell lung carcinoma, breast carcinoma, leukemia, and non-Hodgkin lymphoma are among the most common malignancies associated with hypercalcemia. Retinoic acid derivatives have been reported to induce hypercalcemia and are used for treatment of patients with acute promyelocytic leukemia.[92]

Evaluation should include PTH level to differentiate between PTH-dependent or -independent hypercalcemia. PTH level more than 20 in setting of hypercalcemia is considered unsuppressed and should raise suspicion for hyperparathyroidism. For patients with low PTH, further evaluation is needed and should include PTH-related peptide, 25 hydroxy-vitamin D, and 1,25 hydroxy- vitamin D.[93] Hyperparathyroidism occurs 2.5 to 3 times more often in patients treated with low-dose (2.0–7.5 Gy) external radiation to the head and neck area than in the age-matched control population. Hyperparathyroidism after high-dose irradiation is uncommon. Radiation exposure from radioactive iodine treatment has also been reported in association with hyperparathyroidism.[94]

Management of hypercalcemia includes fluid resuscitation, calcitonin (4–8 U/kg intramuscularly or subcutaneously every 12 hours) and intravenous (IV) zoledronic acid at a dose of 5 mg. Denosumab can has been shown to be effective in cases of hypercalcemia that is refractory to bisphosphonate treatment. Denosumab is administered subcutaneously (120 mg every 4 weeks, with loading doses on days 8 and 15). Steroids can be beneficial in hypercalcemia caused by increased levels of 1,25-dihydroxy vitamin D.[95]

Hypocalcemia

Many factors can increase a cancer patient's risk of hypocalcemia. These factors include the patient's nutritional status, antineoplastic agents used, and type of surgical procedures performed eg, neck dissection). Cytotoxic chemotherapy can result in tumor lysis syndrome and its resultant hypocalcemia, as commonly seen in treatment of hematologic malignancies. Hyperphosphatemia, hyperkalemia, hypocalcemia, and hyperuricemia can occur after induction chemotherapy; it is of vital importance to prevent the complications of tumor lysis by hydration, alkaline diuresis, inhibition of uric acid synthesis, and administration of oral calcium or aluminum-based compounds to bind intestinal phosphate and enhance calcium absorption. IV calcium administration can potentially cause calcium phosphate precipitation in the presence of severe hyperphosphatemia and should be used with extreme caution. Dialysis may be needed in cases of symptomatic hypocalcemia and with refractory hypophosphatemia with and elevated calcium phosphorus product greater than 70 mg^2/dL.[4,96]

Cisplatin has been associated with hypocalcemia. One proposed mechanism of cisplatin's ability to induce hypocalcemia is through hypomagnesemia

resulting in decreased PTH secretion.[97] Other theories include inhibition of 1,25-dihydroxy-vitamin D formation by hypomagnesemia or cisplatin inhibition of mitochondrial function in the proximal renal tubule. Other agents reported to induce hypocalcemia include dactinomycin, carboplatin, doxorubicin, and cytarabine. Hypocalcemia has been seen after administration of bisphosphonates (zoledronic acid and pamidronate) or denosumab (a monoclonal antibody that inhibits receptor activator of nuclear factor-κB ligand [RANKL]), both used to reduce skeletal complications in treatment and prevention of advanced malignancies involving the bone.[98] Serum calcium levels and 25-hydroxy-vitamin D levels should be checked before and during therapy with bisphosphonates or denosumab.[99]

More recently, there are emerging data regarding immunotherapy-induced hypoparathyroidism resulting in hypocalcemia. There have been case reports describing hypoparathyroidism caused by combination anti–PD1 and CLA4 in two patients with malignant melanoma. Both patients manifest with acute severe symptomatic hypocalcemia. The exact pathophysiology remains unknown but may be caused by immune-mediated destruction of calcium-sensing receptor or inflammation mediated. Because immunotherapy is being commonly used in treatment of various malignancies, clinicians should be aware of the potential risk for hypocalcemia.[100,101]

Hypomagnesemia

Hypomagnesemia is common in patients with cancer. This may be caused by gastrointestinal (diarrhea) magnesium losses, malnutrition, decreased dietary intake, and certain chemotherapeutic agents. Hypomagnesemia is a well-known side effect in patients receiving platinum-based chemotherapy. Cisplatin has toxic effects on the kidneys, causing morphologic changes and necrosis in the proximal tubule, a major site of magnesium reabsorption. Hypomagnesemia is a frequent complication of cisplatin chemotherapy, affecting up to 90% of patients; 10% of these patients have symptoms of muscle weakness, tremulousness, and dizziness. A study showed that premedication with magnesium reduced cisplatin-induced nephrotoxicity in patients with thoracic cancers.[102]

Carboplatin, a second-generation platinum compound, was developed to reduce the side effects of cisplatin. However, hypomagnesemia has been seen with increasing frequency and severity at higher doses of carboplatin.

Oxaliplatin, a third-generation platinum derivative that has become an integral part of various chemotherapy protocols, particularly in advanced CRC, has dose-limiting cumulative sensory neurotoxicity like cisplatin. Oxaliplatin chelates to calcium and decreases magnesium levels. Hypomagnesemia was seen in 11% of patients with advanced epithelial ovarian cancer treated with oxaliplatin in a phase II trial.[103] Oxaliplatin is considered to carry a lower risk for hypomagnesemia than cisplatin and carboplatin.

Cetuximab and panitumumab, monoclonal antibodies against the epithelial growth factor receptor (EGFR), are used to treat metastatic colon cancer and can cause supplement-resistant hypomagnesemia. Because EGFR is common in the loop of Henle, cetuximab and panitumumab block reabsorption of magnesium in the kidneys. Magnesium levels should be checked before and during cetuximab or panitumumab therapy and should be treated. Interestingly, a recent meta-analysis showed that metastatic cancer colon patients who developed hypomagnesemia because of anti-EGFR monoclonal antibodies demonstrated better progression-free survival, overall survival, and objective response rate than those who did not develop hypomagnesemia because of therapy.[104]

Erlotinib, which is a TKI that acts on the EGFR receptor, was found in mouse model to cause mild hypomagnesemia, oxidative stress, and cardiac dysfunction. Further studies are needed to investigate if a similar effect is produced in humans.[105]

PITUITARY AND HYPOTHALAMIC DISORDERS

Hypothalamic–pituitary damage leading to hormonal deficiencies can occur in patients treated with cranial or craniospinal irradiation or intracranial surgery. Cranial radiation therapy is often used to treat leukemia and lymphoma, nonpituitary brain tumors, pituitary tumors, nasopharyngeal carcinoma, and skull base tumors.[106] The hypothalamus appears to be more radiosensitive than the pituitary gland and may be damaged by low radiation doses (<40 Gy), but high radiation doses are likely to damage both hypothalamic and pituitary functions. Deficiency in one or more pituitary hormones occurs after irradiation (>40 Gy) of the hypothalamic–pituitary area in about 90% of patients 5 years after radiation treatment (Fig. 60–2).[107]

Ipilimumab, an immunoglobulin G1 antibody that blocks CTLA-4, is used in the treatment of melanoma, renal cell carcinoma, CRC, and non–small cell lung cancer. In a retrospective review of patients with metastatic melanoma treated with ipilimumab, 11% developed autoimmune hypophysitis, with increased risk seen in older men.[108] In comparison, hypophysitis is rare with other immune checkpoint inhibitors, with only a handful of cases reported with anti–PD-1 or PD-L1 monotherapy (Table 60–2).[109] Combination

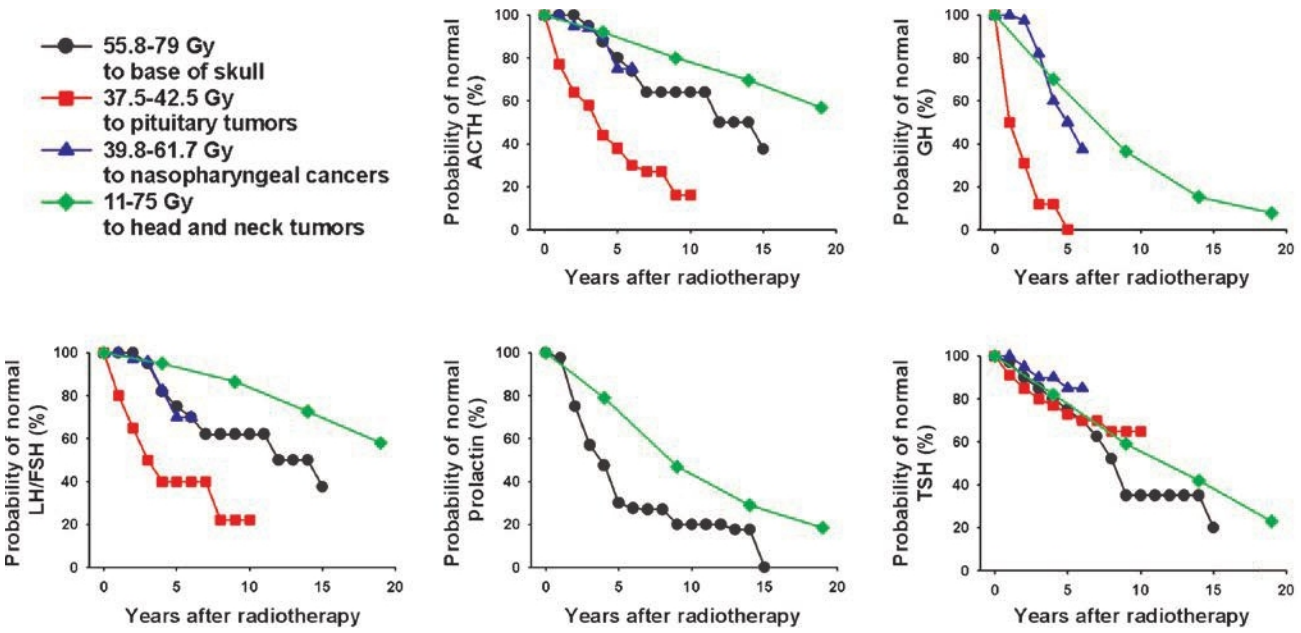


FIGURE 60–2 **Probability of normal pituitary hormone secretion over time after irradiation of the hypothalamic–pituitary area. The data are from four studies: Pai et al,[124] in which 55.8 to 79 Gy was administered to the base of the skull; Shalet et al,[107] in which pituitary tumors were treated with 37.5 to 42.5 Gy; Appelman-Dijkstra et al,[123] in which nasopharyngeal carcinoma was treated with 39.8 to 61.7 Gy; and Samaan et al,[125] in which 11 to 75 Gy was administered to treat head and neck tumors. ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.**

TABLE 60–2 Novel Immunotherapeutic Agents with Endocrine Adverse Effects

Drug	Type	Mechanism	Endocrine Adverse Effects
Ipilimumab Tremelimumab	IgG1 monoclonal antibody	Block CTLA-4 receptor	Hypophysitis Thyroiditis Graves disease Primary adrenal insufficiency
Pembrolizumab Nivolumab	IgG4 monoclonal antibody	Block PD-1 receptor	Hypothyroidism Thyroiditis Hypophysitis Autoimmune diabetes Primary adrenal insufficiency Lipodystrophy
Atezolizumab Durvalumab Avelumab	IgG1 monoclonal antibody	Bind PD-L1 and block its binding to PD-1 receptor	Hypothyroidism Thyroiditis Autoimmune diabetes

CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; Ig, immunoglobulin; PD, programmed cell death protein 1; PD-L1, programmed death ligand 1.

therapy with anti–CTLA-4 and anti–PD-1 increases antitumor efficacy but also the frequency of irAEs, including hypophysitis.[110]

The typical clinical presentation includes headache, fatigue, and nausea. Magnetic resonance imaging may reveal pituitary enlargement. Visual deficits are uncommon because the degree of enlargement tends to be mild. Adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), and gonadotropin deficiencies are the most common hormonal deficiencies at presentation.[111] Diabetes insipidus, GH deficiency, and hyperprolactinemia are very rarely seen in immune checkpoint inhibitor–induced hypophysitis.[112] After cessation of the drug, pituitary morphology returns to normal (Fig. 60–3), but recovery of anterior pituitary hormone function is variable.[113] Adrenal axis recovery has only rarely been reported; thyroidal and gonadal axis recovery is more common.[114]

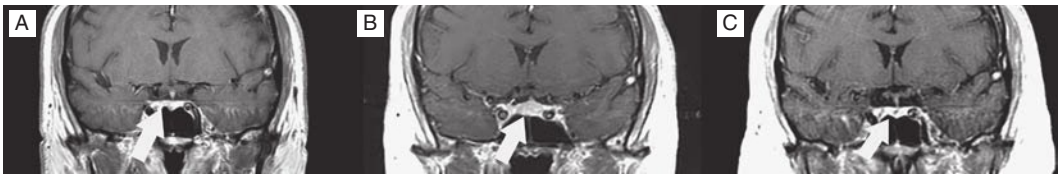


FIGURE 60–3 Magnetic resonance images of a patient before (A), during (B), and 8 weeks after (C) ipilimumab therapy.

Secondary Adrenal Insufficiency

Prolonged glucocorticoid treatment is the most common cause of adrenal dysfunction in patients with cancer. Secondary (central) adrenal insufficiency may develop up to 2 years after discontinuation of glucocorticoids and can persist for months. Irradiation of the hypothalamic–pituitary region causes ACTH deficiency with resultant secondary adrenal insufficiency in 19% to 42% of patients. The median time to development of adrenal insufficiency after radiation therapy is 5 years, but onset can occur in as little as 2 years.

Prolonged therapy with busulfan was initially reported to cause a reversible clinical syndrome resembling central adrenal insufficiency as evidenced by metyrapone testing. No recent reports have corroborated this finding. Long-term intrathecal opioid therapy for intractable nonmalignant pain resulted in central adrenal insufficiency in 15% of patients tested for insulin-induced hypoglycemia.[115]

Megestrol acetate is an appetite stimulant, but prolonged use can lead to a Cushing-like syndrome, and sudden withdrawal after prolonged treatment may result in adrenal insufficiency. Megestrol shows glucocorticoid-like effects with an acute suppressive effect on the hypothalamic–pituitary axis and can lead to central adrenal insufficiency.[116,117]

Secondary adrenal insufficiency can be diagnosed by a variety of tests with varying sensitivity and specificity, but in our practice, we frequently use a combination of basal (8:00 AM) serum cortisol and ACTH measurement as well as1-µg cosyntropin stimulation testing. Rarely, insulin-induced hypoglycemia is used to assess the overall cortisol and GH response to hypoglycemia when evaluating patients for panhypopituitarism.

Growth Hormone Deficiency

GH deficiency is frequently noted after cranial irradiation. In children, isolated GH deficiency can occur after low radiation doses, but high doses may produce panhypopituitarism. Hypopituitarism appears to be dose dependent. At low doses (20–24 Gy), the only effect may be an altered pulsatile secretory pattern. At doses higher than 30 Gy, deficient GH secretion and growth retardation are observed in more than one third of patients (Fig. 60–4). Children who receive cranial irradiation require long-term follow-up.[118]

GH deficiency is also common in adults who have undergone cranial radiation therapy. Manifestations may include decreased bone and muscle mass, fatigue, impaired sense of well-being, lowered exercise capacity,



FIGURE 60–4 A patient with short stature caused by growth hormone deficiency resulting from radiation treatment of a brain tumor.

increased volume of adipose tissue, altered myocardial function, higher occurrence of atherosclerotic plaques, and increased risk for cardiovascular diseases. GH replacement in these patients can restore normal adipose tissue composition, bone metabolism, quality of life, sense of well-being, lipid profile, and cardiac function.[119] Despite the apparent benefits, data on the effect of GH replacement in long-term cancer survivors are still lacking. GH replacement is contraindicated in all patients with an active malignant condition, but it can be initiated in an adult in whom malignant disease has been absent for at least 5 years. Another treatment reported to result in GH deficiency is long-term intrathecal opioids. Patients receiving this treatment have about a 15% elevation in the risk of developing GH deficiency.[115]

Central Hypothyroidism

Cranial and craniospinal radiation therapy can cause immediate and long-term effects with alterations in the hypothalamic and pituitary regulation of TSH, resulting in secondary and tertiary hypothyroidism, especially with doses of 40 Gy or higher. In one study, central hypothyroidism was detected 1 year after the end of radiation treatment in 6% of patients.[120] In that study, 15% to 20% of patients who had undergone cranial irradiation had diminished TSH secretion 5 years after the end of treatment, and approximately 35% of those patients had it after 10 years. Because of the combined effect of irradiation on the thyroid gland and the hypothalamic–pituitary axis, we suggest measuring serum free thyroxine and TSH concentrations yearly or sooner if the patient is having symptoms suggestive of hypothyroidism and to replace thyroid hormone when necessary.

Chemotherapy may enhance the deleterious effect of radiation. Children with brain tumors (not involving the hypothalamic–pituitary axis) who receive vincristine, carmustine, lomustine, or procarbazine in combination with brain irradiation have a 35% incidence of hypothyroidism compared with a 10% incidence in children who undergo brain irradiation alone.[121]

Bexarotene was found to cause central hypothyroidism in 40% of patients with CTCL.[29] Reversible, retinoid X receptor–mediated suppression of TSH secretion is one explanation for this side effect. Bexarotene patients often require higher levothyroxine dosing compared with patients with other causes of hypothyroidism because of bexarotene-related increase in thyroid hormone metabolic clearance.[122]

Hypogonadotropic Hypogonadism

Brain surgery and irradiation of the skull carry the potential for hypothalamic–pituitary damage, including hypogonadotropic hypogonadism.



FIGURE 60–5 Loss of axillary hair in a patient who developed secondary hypogonadism after cranial irradiation.

Hypogonadism occurs within 7 years after cranial irradiation for nonpituitary neoplasia in 25% of patients. Hypogonadism is transient in the presence of hyperprolactinemia and is treated with antidopaminergic therapy.[123] Hyperprolactinemia is the most commonly reported hormonal abnormality in patients who have undergone head and neck irradiation, occurring in more than 66% of patients.[124,125] Hyperprolactinemia inhibits gonadotropin secretion from the pituitary gland and decreases the responsiveness of the pituitary gland to GnRH, causing secondary hypogonadism. In children, inadequate sexual development, delayed puberty, and absent menarche are significant problems, whereas in adults, gonadotropin deficiency may cause sex steroid hormone deficiency, infertility, and loss of axillary and pubic hair (Fig. 60–5). Sex steroid hormone deficiency lowers libido and may have deleterious effects on bone and lipid metabolism.

Early or even precocious puberty has also been reported in patients with acute lymphoblastic leukemia treated with combined chemotherapy and cranial irradiation and in patients with brain tumors treated with cranial irradiation. This phenomenon occurs more often in girls along with coexisting GH deficiency. In a recent study of male cancer survivors (excluding those who had undergone treatment that may have otherwise affected gonadal function), chronic opioid therapy, given in morphine-equivalent daily doses of at least 200 mg/day, was associated with secondary hypogonadism.[126]

THYROID DISORDERS

Thyroid Neoplasms

Ionizing radiation is implicated in the etiology of thyroid cancer. Irradiation of the thyroid, especially in children and young adults (eg, young patients with Hodgkin disease), increases the risk of papillary thyroid carcinoma.[127]

Hyperthyroidism

Radiation-induced hyperthyroidism has been described but is far less common than radiation-induced hypothyroidism. In a 2018 report from the Childhood Cancer Survivor Study, the incidence of hyperthyroidism was found to be significantly higher in patients who received radiation therapy with an elevated risk lasting more than 25 years after exposure.[128] External and internal high-dose radiation is associated with development of Graves disease after exposure. Patients with lymphoma treated with radiation constitute the largest number of patients who have developed Graves disease after radiation therapy. Patients treated with radiation for nasopharyngeal, breast, or laryngeal carcinomas may also develop Graves disease. Radiation-induced silent thyroiditis with transient thyrotoxicosis has also been reported. Thyroiditis-induced thyrotoxicosis occurs within a few months of radiation therapy in most cases; hypothyroidism occurs several months later.

Cytokines have also been reported to lead to Graves disease. IFN is known to induce the production of autoantibodies and can lead to autoimmune thyroid disease, such as autoimmune primary hypothyroidism, transient thyrotoxicosis, or more rarely, Graves disease. Women have a higher risk than men of developing autoimmune thyroid disease upon starting IFN treatment.[129] It is important to distinguish the cases in which IFN induces transient thyrotoxicosis followed by hypothyroidism from the cases in which IFN induces Graves disease. Thyroid scans showing increased homogeneous uptake in the presence of hyperthyroidism are highly suggestive of Graves disease and warrant treatment with antithyroid medications (eg, methimazole).

Targeted therapies can also be linked to hyperthyroidism. The anti–CTLA-4 agents ipilimumab tremelimumab and anti-CD52 antibody alemtuzumab are associated with painful thyroiditis and Graves disease.[130] Pembrolizumab treatment caused hyperthyroidism in 1 of 135 patients in a safety study.[131] Interleukin-2 (denileukin diftitox) treatment alone causes transient hyperthyroidism followed by hypothyroidism, which may last months in about 50% of patients with disruption of self-tolerance postulated as a mechanism.[132]

Hypothyroidism

Multiple factors increase the risk for hypothyroidism during the course of cancer treatment, including certain systemic therapies, high doses of radiation to the head and neck, combined radiation and surgical treatments (eg, thyroid resection during laryngectomy or disruption of the vascular supply to the thyroid), time interval since radiation therapy, and failure to shield midline structures during radiation (Table 60–3).

Radiation can induce primary hypothyroidism when given in doses higher than 25 Gy to the region near the thyroid gland with a dose-related risk (Fig. 60–6). Cumulative incidence of hypothyroidism after thyroid irradiation is estimated to be 20% to 30%, with the greatest risk in the first 5 years after treatment, but elevated risk persists up to 20 years later.[133,134]

A significant number of patients develop subclinical hypothyroidism (elevated TSH with normal thyroxine levels), not overt hypothyroidism, when less than 40 Gy of radiation is administered. Subclinical hypothyroidism (20%) is more frequent than overt hypothyroidism (5%) 5 years after chemotherapy and radiation therapy.[135]

The use of iodine-131 (^{131}I) may result in thyroid dysfunction. The use of ^{131}I-metaiodobenzylguanidine in treatment of metastatic pheochromocytoma carries the possibility of inducing primary hypothyroidism and requires routine use of potassium perchlorate to block the thyroid ^{131}I uptake.

IFN therapy is associated with primary hypothyroidism in about 10% of treated patients, especially those with pretreatment antithyroid antibodies, and is not dose related.[136] The absence of thyroid autoantibodies at the end of IFN treatment was found to be a protective factor against development of thyroiditis up to 6 years after treatment, whereas positivity for thyroid antibodies at high titers at the end of IFN treatment was significantly related to chronic subclinical hypothyroidism.

Patients treated with multiple antineoplastic agents (with or without radiation) also have a higher-than-normal incidence of primary hypothyroidism. Fifteen percent of patients who received a combination of cisplatin, bleomycin, dactinomycin, vinblastine, and etoposide developed elevated TSH levels with normal free triiodothyronine (T_3) and free thyroxine (T_4), compatible with subclinical primary hypothyroidism, in contrast to the control group.[137]

Targeted therapy has also been linked to development of a variety of thyroid abnormalities. For example, autoimmune thyroid disease has been seen in 23% of patients receiving alemtuzumab.[138] Thyroid dysfunction is a known potential adverse effect of TKIs, specifically those that target angiogenic receptors such as sunitinib, sorafenib, and vandetanib. Reported rates

TABLE 60–3 Antineoplastic Agents Associated with Hypothyroidism

Therapy Type	Drug	Effect on the Thyroid
Synthetic retinoid	Bexarotene	Central hypothyroidism Increased dose requirement in patients on thyroid hormone replacement
Steroidogenesis inhibitor and adrenolytic	Mitotane	Central hypothyroidism
Immune checkpoint inhibitors	Anti–CTLA-4 Tremelimumab Ipilimumab	Central hypothyroidism in the setting of hypophysitis Thyroiditis with transient thyrotoxicosis followed by primary hypothyroidism Primary hypothyroidism
	Anti–PD-1 Pembrolizumab Nivolumab	Thyroiditis with transient thyrotoxicosis followed by primary hypothyroidism Central hypothyroidism in the setting of in hypophysitis
	Anti–PD-L1 Atezolizumab Durvalumab Avelumab	Primary hypothyroidism Thyroiditis with transient thyrotoxicosis followed by primary hypothyroidism
Nonspecific immunomodulatory cytokines	IL-2 IL-α	Thyroiditis with transient thyrotoxicosis followed by primary hypothyroidism Primary hypothyroidism
CD52 monoclonal ab	Alemtuzumab	Subacute thyroiditis Primary hypothyroidism
Tyrosine kinase inhibitors	Sunitinib	Destructive thyroiditis Primary hypothyroidism
	Sorafenib	Primary hypothyroidism May lead to increased or decreased dose requirement in patients on thyroid hormone replacement
	Imatinib	Increased dose requirement in patients on thyroid hormone replacement
Estrogen-containing drugs		Increased dose requirement in patients on thyroid hormone replacement
Selective estrogen receptor modulator	Raloxifene	Interferes with GI absorption of thyroid hormone

CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; GI, gastrointestinal; IL, interleukin; PD, programmed cell death protein 1; PD-L1, programmed death ligand 1.



FIGURE 60–6 Mapping of radiation ports on a patient with squamous cell cancer of the head and neck. The patient developed primary hypothyroidism 2 years after radiation therapy.

of thyroid dysfunction on sorafenib range from 21% to 68%, but fewer patients may require thyroid hormone replacement (6% in one prospective study).[139,140] Sorafenib-related thyroiditis has been suggested as a mechanism of thyroid dysfunction in some of the patients, but it is unclear if thyroid dysfunction represents an autoimmune process or a manifestation of vascular endothelial growth factor blockade affecting the thyroid blood supply. Sorafenib also frequently affects the thyroid hormone replacement dose requirement in patients with preexisting hypothyroidism.[141,142]

Similarly, thyroid dysfunction has been well documented in patients receiving sunitinib, with reported rates of 20% to 85%.[143] Some patients were reported to present with thyrotoxic phase preceding hypothyroidism supporting destructive thyroiditis as a cause. However, some patients became athyrotic on sunitinib after having normal thyroid function at baseline.[144] Another study showed that thyroid size was reduced to 59%

after 12 months of sunitinib use in patients with renal cell carcinoma.[145] Impaired iodine uptake and inhibition of peroxidase activity were also suggested as potential mechanisms to explain hypothyroidism.[146,147]

Thyroid dysfunction is a significant adverse effect of ICIs. Treatment with anti–PD-1 antibody confers a higher risk of hypothyroidism than with anti–PD-L1 and anti–CTLA-4 antibodies.[148] Combination therapy with two immune checkpoint inhibitors increases the risk of thyroid dysfunction as compared with monotherapy.

Primary hypothyroidism has been reported to occur in 8.3% of patients receiving pembrolizumab, with a median time to onset being 3.5 months (range, 0.7 weeks–19 months).[149] Ipilimumab-induced activation of T-cells results in not only antitumor activity but also immune infiltration of endocrine glands. The major endocrine glands affected by ipilimumab are the pituitary and thyroid glands. Although hypophysitis can involve central hypothyroidism as discussed earlier, ipilimumab-induced thyroiditis leads to primary hypothyroidism.[150] Primary and central hypothyroidism can present concomitantly. Because the timing of the onset of thyroid dysfunction varies widely, patients who have received immune checkpoint inhibitor therapy should be monitored closely for changes in thyroid function during treatment and in short- to medium-term follow-up.[151]

Abnormalities in Thyroid Hormone–Binding Proteins

Thyroid hormones are preferentially bound to thyroid hormone–binding globulin (TBG) (65%–70%), transthyretin (15%–20%), and albumin (10%–15%). Multiple factors in patients with malignancies, including changes in sex hormone levels, glucocorticoids, narcotics, nutritional status, and some antineoplastic agents, affect the levels of these binding proteins and the subsequent levels of bound thyroid hormones. Overall, the level of total T_3 and T_4 may be affected, but in general, the levels of free (biologically active) hormones are normal. The effect on TBG synthesis or clearance is usually reversible. Not only are estrogens known to increase TBG and total thyroid hormone levels, but tamoxifen also causes elevated plasma concentrations of TBG in postmenopausal women with breast cancer after 6 months of therapy. Letrozole, a nonsteroidal aromatase inhibitor, when given at 2.5 mg/day, was associated with a statistically significant decrease in total T_4 but not total T_3 levels.[152]

Glucocorticoids are frequently used in combination with chemotherapy and are known to suppress TSH secretion and inhibit TBG synthesis. L-Asparaginase can inhibit the synthesis of albumin and TBG, which affects serum thyroid hormone levels. 5-Fluorouracil increases total T_3 and T_4 levels and maintains a normal free thyroxine index, suggesting that this agent increases serum thyroid hormone–binding proteins, resulting in normal thyroid function.[153]

Mitotane increases the levels of hormone-binding globulins, but the increase in TBG is less remarkable than mitotane's effect on corticosteroid-binding globulin.

ADRENAL DISORDERS

Diagnosis of adrenal insufficiency in patients with advanced malignancy can be difficult. The symptoms of fatigue, weakness, loss of appetite, weight loss, nausea, hypotension, hyponatremia, and so on can be similar to progressive disease or secondary to cancer therapy. Treatment involves administration of glucocorticoids and mineralocorticoids.

Primary Adrenal Insufficiency

Adrenal glands are a common site for metastatic disease in patients with advanced malignancies of the kidney, lung, breast, or colon; non-Hodgkin lymphoma; and melanoma. Patients with bilateral adrenal metastases can develop adrenal insufficiency because of infiltration of the adrenal gland. There have been several reports of adrenal insufficiency as the presenting symptom of an occult malignancy.[154]

Antineoplastic agents can also cause destruction of the adrenal cortex. Mitotane has selective toxicity to both normal and malignant adrenocortical cells. Active form of mitotane irreversibly binds with adrenal molecules, including cytochrome P450 (CYP) enzymes such as CYP11A1 and CYP21B, causing altered serum hormone concentrations.[155,156] It directly interacts with lipid membranes and inhibits SOAT activity, resulting in an excess of free cholesterol and other fatty acids that are toxic to the hormone-producing adrenal cells.[34,35] In addition to inhibiting steroidogenesis by multiple mechanisms, it also induces CYP3A4 expression, leading to increased steroids clearance, and causes an increase in serum levels of cortisol-binding globulin.[157] Glucocorticoid replacement therapy is needed when mitotane is used; high doses are required because of the increased levels of binding globulin and enhanced metabolic clearance of corticosteroids by mitotane.

Animal studies found cases of adrenal necrosis associated with sunitinib use, leading the FDA to recommend monitoring adrenal function in patients receiving sunitinib. However, there was no evidence of adrenal hemorrhage or clinical evidence of adrenal insufficiency in subsequent clinical safety data.[158]

Primary adrenal insufficiency, though uncommon, has also been reported with immune checkpoint inhibitors by causing direct impairment of adrenal cortex. Primary adrenal insufficiency associated with

immunotherapy may be underestimated because of concomitant treatment with corticosteroids or the coexistence of secondary adrenal insufficiency.[159] It has been described in 0.3% to 1.5% of patients treated with anti–CTLA-4 (ipilimumab and tremelimumab) in addition to case reports describing primary adrenal insufficiency with nivolumab.[110,160]

Primary adrenal insufficiency can also by caused by novel anti–prostate cancer drugs (abiraterone or novel steroid-blocking agents, eg, ODM-208). These medications cause inhibition of steroid synthesis at multiple levels (eg, cholesterol side-chain cleavage enzyme, 17-hydroxylase, and 21-hydroxylase), which results in various degrees of decreased cortisol production.[161]

Elevated ACTH with low cortisol is often diagnostic of primary adrenal insufficiency. Confirmatory testing with 250-μg cosyntropin stimulation may be needed. Treatment requires replacement of glucocorticoids with daily hydrocortisone (~30 mg in divided doses), prednisone (5 mg), or dexamethasone (0.5–1 mg). Patients with primary adrenal insufficiency also need mineralocorticoid replacement with fludrocortisone 0.1 mg/day.

GONADAL DISORDERS

Direct radiation exposure and cytotoxic chemotherapeutic agents are common causes of hypogonadism and infertility in cancer survivors, with a variety of effects on fertility and gonadal functions in the two sexes. Compromised fertility is one of the most common long-term effects of cancer therapy.[162] Childhood cancer survivors should have routine monitoring that assesses their gonadal health and fertility potential as part of survivorship care.[163]

Female Gonadal Disorders

Because oogenesis occurs during embryonic life and is quiescent, oocytes are relatively resistant to the adverse effects of cytotoxic chemotherapy. However, because of their limited number, any damage can shorten a woman's reproductive period. Granulosa cells, on the other hand, are susceptible to cytotoxic drugs, as evidenced by the results of ovarian biopsies performed after chemotherapy (Fig. 60–7). Infertility can be caused by damage to either granulosa cells or oocytes.

With advances in cancer treatment, an increasing number of women survive malignancies to face reproductive disorders. It is of vital importance to discuss fertility issues before initiating radiation or systemic chemotherapy because of the long-term risks of ovarian dysfunction and infertility. Baseline ovarian reserve can be evaluated by levels of serum anti-Mullerian hormone level, antral follicle count, follicle-stimulating hormone (FSH) levels, inhibin-B levels, and ovarian volume.[162]

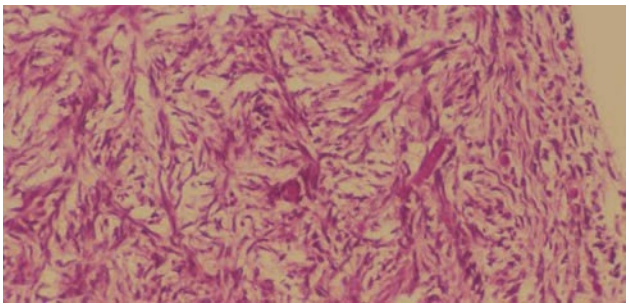


FIGURE 60–7 Hematoxylin and eosin staining of a biopsy sample showing atrophy of ovarian tissue after cytotoxic chemotherapy.

The effects of radiation treatment on the ovaries differ with patient age, radiation dose, and field of treatment. Radiation treatment that includes the pelvis increases the risk of infertility more than radiation treatment that includes only the abdomen.[164] Pregnancy rates decrease at doses between 5 and 10 Gy.[165] Fractionated radiation carries less risk for permanent sterility, and if done with appropriate shielding of the gonads, reduces the risk of ovarian failure. Before initiating pelvic irradiation, ovarian transposition (oophoropexy) via laparotomy or laparoscopy can preserve ovarian function in women younger than 40 years of age with cervical carcinoma less than 3 cm in diameter.[166] Patients require assisted fertilization after this procedure for future pregnancies.

Oocyte cryopreservation before cancer treatment has been proposed as a means of preserving fertility in women treated for cancer, but it has been less successful in humans than in animal models. The ethical issues behind these techniques are still being disputed, and there is still the concern of potential disease recurrence from residual disease in autografted ovarian tissues. Obtaining unilaminar follicles from cryopreserved, thawed tissue and growing them in vitro has been proposed to reduce the risk of recurrence.

GnRH agonists are also used to reduce ovarian susceptibility to chemotherapy based on the concept that the cytotoxic effects of chemotherapeutic agents are seen more in rapidly dividing cells than in cells at rest.[167] GnRH agonist–induced suppression of the hypothalamic–pituitary–gonadal axis has been shown in animal models to reduce cyclophosphamide-induced but not radiation-induced ovarian toxicity and has also shown encouraging results in women with breast cancer, leukemia, and lymphoma. Another study showed that GnRH agonist therapy may protect ovarian reserve but does not decrease the risk of premature ovarian failure in patients treated for lymphoma.[167] In mice, melatonin, which has antioxidant properties, has been shown to prevent primordial follicle loss in cisplatin-treated ovaries.[168]

In premenopausal women with breast cancer treated with regimens based on anthracyclines (5-fluorouracil,

epirubicin, and cyclophosphamide), the rate of chemotherapy-related amenorrhea is 93%. At the end of therapy, menstrual periods resume in 24% of patients.[169]

Alkylating agents, which are non–cell-cycle specific, are generally highly gonadotoxic. Mechlorethamine is usually used in combination with vincristine, procarbazine, and prednisone. Chlorambucil, melphalan, busulfan, and cyclophosphamide also carry a high risk of ovarian damage. Ovarian failure with alkylating agents was found to impose the highest risk with an estimated odds ratio (relative to no treatment) of 3.98.[170] Temporary amenorrhea developed in 2 of 12 female patients in whom cisplatin (0.4–0.6 g/m^2) was used in combination with bleomycin and vinblastine to treat ovarian germ cell tumors; the amenorrhea lasted from 12 to 15 months after the cessation of chemotherapy.[170]

Transient and permanent ovarian failure has been reported with etoposide use.[171]

Antimetabolites, which are cell-cycle specific, may exert few toxic effects on the ovaries. As a single agent, doxorubicin has few, if any, adverse effects on ovarian function, although a synergistic effect of the combination of doxorubicin and cyclophosphamide is a concern.

Vinblastine has been known to cause reversible and dose-related amenorrhea when combined with alkylating agents.[172]

Male Gonadal Disorders

Spermatogenesis occurs continuously and germ cells and spermatogonia, and in contrast to Leydig or Sertoli cells, sperm are much more sensitive to cytotoxic agents. If sufficient germ cells remain after cytotoxic chemotherapy, resumption of spermatogenesis usually occurs; the longer the duration of azoospermia, the lower the likelihood of spermatogenesis recovery.[173]

Radiation damage to the gonads is dose dependent. Low-dose testicular irradiation leads to a transient suppression of sperm counts with recovery time proportional to the radiation dose.[174] However, permanent infertility can occur with fractionated radiation doses of more than 2 Gy (Fig. 60–8), whereas clinically significant Leydig cell impairment occurs rarely with doses of less than 20 Gy.[175]

Therapy with alkylating agents such as cyclophosphamide or chlorambucil causes reversible but prolonged azoospermia. Chlorambucil causes azoospermia at cumulative doses of 400 to 800 mg, with recovery taking 3 to 4 years after a mean total dose of about 750 mg/m^2.[176] Cyclophosphamide affects spermatogenesis more than Leydig cell function, causing reduced sperm count with normal testosterone levels.

Antineoplastic agents causing azoospermia in humans can be classified in four groups. The first group consists of chemotherapeutics that cause prolonged azoospermia, which include chlorambucil, cyclophosphamide, procarbazine, melphalan, and cisplatin. In the second group, chemotherapy agents such as carmustine and lomustine cause azoospermia in adults treated with chemotherapy before puberty. In the third group, agents such as busulfan, ifosfamide, nitrogen mustard, and dactinomycin cause prolonged azoospermia when given with other sterilizing agents. The agents in the fourth group, which include doxorubicin, thiotepa, cytosine arabinoside, and vinblastine, have additive and temporary effects on azoospermia when combined with any of the agents from the other three groups.[177]

Multiple methods of preventing or reversing infertility in men treated for cancer have been suggested. In rats, suppression of testosterone production with use of GnRH agonists or antagonists before or after cytotoxic therapy can preserve fertility; although this approach does not protect survival of stem cells in the testes, it enhances the ability of the testes to maintain differentiation of type A spermatogonia.[178] Semen cryopreservation before starting gonadotoxic therapy followed by assisted fertilization is another strategy to preserve fertility in men with cancer.

SURVEILLANCE FOR COMPLICATIONS IN CANCER SURVIVORS

Primary care physicians and oncologists should be aware of the long-term consequences of cancer therapy for early detection and management of treatment-related side effects because many of the complications occur years after treatment and can have subtle clinical presentations.

Diabetes and Metabolic Disorders

For long-term cancer survivors who were treated with streptozocin, L-asparaginase, partial pancreatectomy, or immunotherapy, screening for delayed development of diabetes mellitus is recommended because they are at risk of development of 1 I diabetes, which can present as either new-onset diabetes or sudden worsening of previously well-controlled type 2 diabetes.

Recent data indicate that survivors of childhood cancer are at particularly increased risk of diabetes mellitus and metabolic syndrome and thus increased cardiovascular risk. Risk is even increased in patients exposed to abdominal or total-body irradiation.[179] According to 2013 Children's Oncology Group guidelines, these patients should have a fasting blood glucose or hemoglobin A1c checked every 2 years or more frequently if clinically indicated and clinicians should have a low threshold for performing oral glucose tolerance testing in suspected cases.

New data are emerging about increased diabetes risk in survivors of cancer colon for up to 5 years after the diagnosis.[180] Similarly, increased diabetes risk was also reported as a complication of hormonal therapy in breast cancer survivors (hazard ratio, 2.40; 95% confidence interval, 1.26–4.55; P =.008) with more risk reported with aromatase inhibitors than tamoxifen.[181] Thus, active screening and counseling regarding modifiable risk factors may be warranted in this high-risk group. Preventive strategies aimed at lifestyle modifications may minimize the risk.

Pituitary Dysfunction

In children with a history of cranial irradiation or craniospinal irradiation, the growth rate should be assessed at 6-month intervals. A more detailed evaluation, including measurement of the levels of GH and insulinlike growth factor 1 (IGF-1), thyroid function tests, and bone age assessments, should be performed when there is evidence of an abnormal growth pattern. The T_4 and TSH measurements should be performed annually for the first 5 years and less frequently thereafter. Central hypogonadism (or luteinizing hormone [LH] or FSHD) may emerge decades after cranial radiation and occurs in at least 35% of patients with an increased risk after doses greater than 30 Gy. Interestingly, a study of childhood brain tumor survivors showed that 12.2% of the patients had precocious puberty, indicating activation rather than reduction of pituitary function.[182] Discussions of fertility options, including oocyte or sperm cryopreservation, should be discussed early on to help keep the highest chances of fertility.

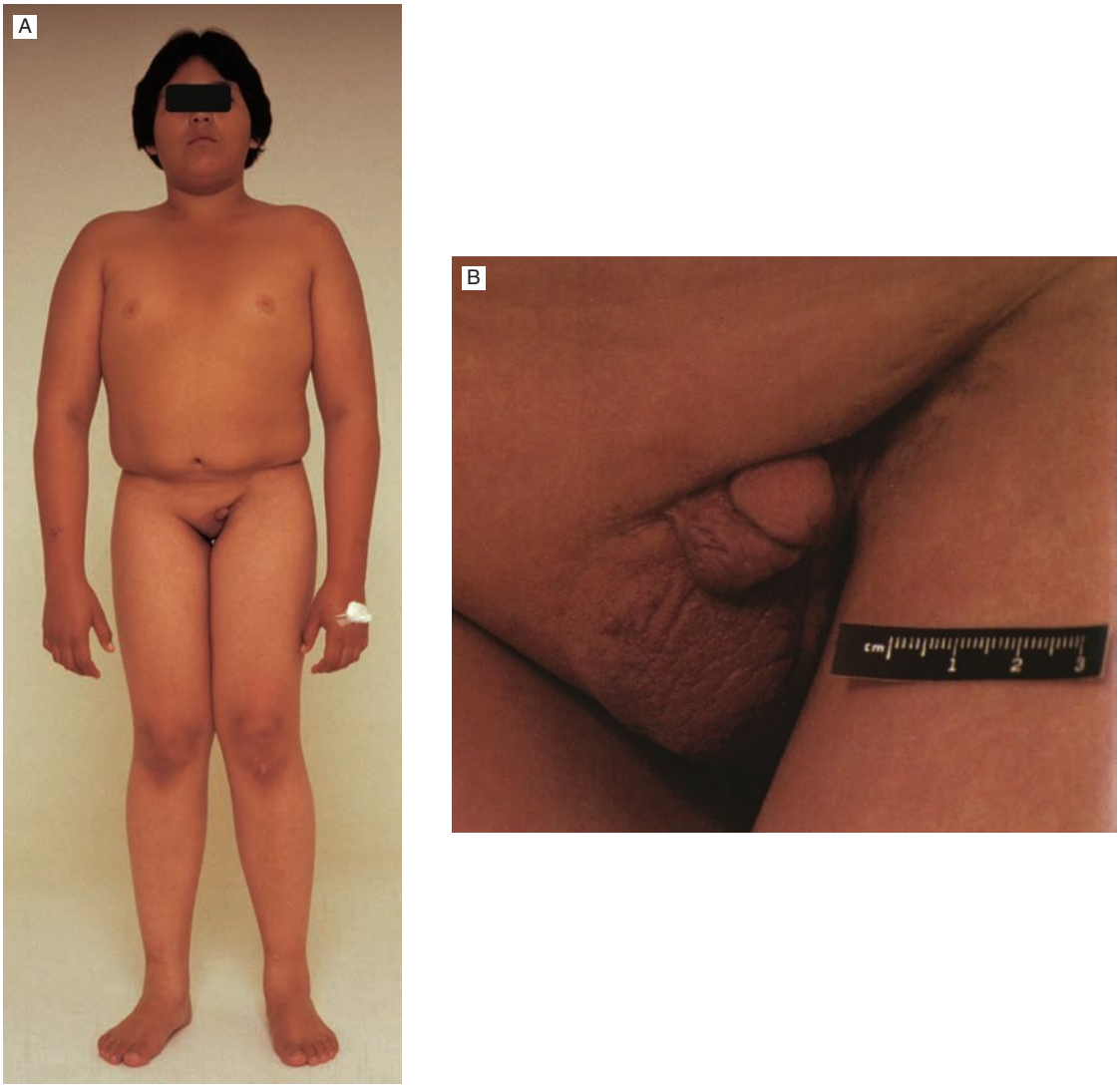


FIGURE 60–8 **A young male patient after therapeutic irradiation of the left testicle for a testicular tumor. Note the loss of body hair, hypogonadal facial puffiness, decreased muscle mass, and increased body fat (A). The left testicle was small and firm (B). The patient was infertile.**

In adults who have undergone cranial irradiation with more than 20 Gy, clinical monitoring with measurement of serum cortisol, ACTH, free T_4, IGF-1 (if the patient is a candidate for GH replacement), prolactin, LH, FSH, and serum testosterone and documentation of menstrual history should be undertaken annually for 15 years and then every 2 years for another 15 years.[123] The 1-µg cosyntropin stimulation test has been proposed to screen central adrenal insufficiency in cancer survivors who received more than 30 Gy of radiation to hypothalamic and pituitary areas.[183]

Thyroid Disorders

Careful physical examination should be performed annually for recipients of head and neck radiation to detect thyroid nodules, and if any are detected, a more detailed examination should be performed using ultrasound and, if necessary, fine-needle aspiration biopsy. Because multitarget TKIs can cause thyroid dysfunction, thyroid hormone levels should be checked before treatment begins. During treatment, thyroid hormone levels should be checked periodically to adjust thyroxine replacement. Multitarget TKIs can cause new-onset hypothyroidism or increase the levothyroxine requirements in patients on chronic thyroid hormone replacement.

Bone Health

In survivors of childhood malignancies, bone mass may be assessed in the early 30s, an age at which peak bone mass has been attained in most people. It is also important to consider the possibility of bone loss in androgen- or estrogen-deficient adults. If bone mass is normal, no further evaluation is needed beyond the usual recommendations for prevention of osteoporosis. In those with low bone mass, an active program of calcium and vitamin D supplementation, exercise, and occasionally, medical therapy (bisphosphonates or recombinant PTH) should be combined with assessment of bone mass every 12 to 18 months.

Patients who have been treated with chemotherapeutic agents that cause hypophosphatemia, hypomagnesemia, or hypocalcemia, such as ifosfamide, platinum compounds, fludarabine, or estramustine, are particularly at risk for osteomalacia and should undergo an evaluation of serum calcium, phosphorus, magnesium, alkaline phosphatase, and vitamin D metabolite levels. Those who have been treated with aromatase inhibitors should have BMD measurements before and during treatment and should be given calcium and vitamin D. Patients can be given bisphosphonates if deemed necessary.

MD ANDERSON PRACTICE TIPS

- Most endocrine glands are controlled by feedback systems. In a functional endocrine system, extreme hormone levels (deficiency or excess) should lead to extreme responses by negative feedback. Example, we see elevated TSH when the free T_4 levels are low. Abnormality in the feedback signal helps distinguish between primary and secondary endocrine dysfunction. Some hormones are secreted with circadian rhythmicity such as cortisol and testosterone with highest levels in the morning. For proper assessment, testing should be done at the appropriate time to include the complete axis. For example, cortisol along with ACTH should be done at 8 am.
- Many drugs can interfere with endocrine testing, resulting in an incorrect diagnosis. Steroids are frequently used in oncologic practice and can interfere with cortisol testing both as a result of endogenous hormone suppression and assay interference. Hence, cortisol testing is not recommended when the patient is being treated with steroids. The medications have to be held for an appropriate duration of time before testing.
- It is important to check C-peptide and glucose levels in patients with new-onset hyperglycemia and any signs and symptoms of insulin deficiency such as weight loss, polyuria, or polydipsia while on immune checkpoint inhibitor therapy and send urgent referral to endocrinology service for evaluation and management.
- It is important to screen patients for underlying adrenal insufficiency before initiating treatment for hypothyroidism in patients with immunotherapy-induced hypophysitis and multiple hormone deficits. If a patient has both secondary adrenal insufficiency and secondary hypothyroidism, steroid replacement therapy should be initiated first to prevent adrenal crisis that can occur with increased metabolism from initiating thyroid hormone.
- Bone targeting therapies such as bisphosphonates and denosumab can cause severe hypocalcemia in the setting of vitamin D deficiency. Hence, it is always recommended that the patient be screened for vitamin D deficiency and treated appropriately while receiving these agents.
- Patients with radiation-induced bone loss often have a delayed manifestation of bone loss, which can occur several years after completing radiation treatment. This is especially seen in women with gynecologic cancers who have had pelvic irradiation, which puts them at higher risk to develop sacral insufficiency fractures.

REFERENCES

1. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2014;370(11):997-1007.
2. Flinn IW, Kahl BS, Leonard JP, et al. Idelalisib, a selective inhibitor of phosphatidylinositol 3-kinase-delta, as therapy for previously treated indolent non-Hodgkin lymphoma. *Blood*. 2014;123(22):3406-3413.
3. Burt MG, Drake SM, Aguilar-Loza NR, et al. Efficacy of a basal bolus insulin protocol to treat prednisolone-induced hyperglycaemia in hospitalised patients. *Intern Med J*. 2015;45(3):261-266.
4. Brady V, Thosani S, Zhou S, et al. Safe and effective dosing of basal-bolus insulin in patients receiving high-dose steroids for hyper-cyclophosphamide, doxorubicin, vincristine, and dexamethasone chemotherapy. *Diabetes Technol Ther*. 2014;16(12):874-879.
5. Dhital SM, Shenker Y, Meredith M, Davis DB. A retrospective study comparing neutral protamine hagedorn insulin with glargine as basal therapy in prednisone-associated diabetes mellitus in hospitalized patients. *Endocr Pract*. 2012;18(5):712-719.
6. Wallace MD, Metzger NL. Optimizing the treatment of steroid-induced hyperglycemia. *Ann Pharmacother*. 2018;52(1):86-90.
7. Busaidy NL, Farooki A, Dowlati A, et al. Management of metabolic effects associated with anticancer agents targeting the PI3K-Akt-mTOR pathway. *J Clin Oncol*. 2012;30(23):2919-2928.
8. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet*. 2008;372(9637):449-456.
9. Andre F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. *N Engl J Med*. 2019;380(20):1929-1940.
10. Juric D, Janku F, Rodon J, et al. Alpelisib plus fulvestrant in PIK3CA-altered and PIK3CA-wild-type estrogen receptor-positive advanced Breast cancer: a phase 1b clinical trial. *JAMA Oncol*. 2019;5(2):e184475.
11. Mayer IA, Prat A, Egle D, et al. A phase II randomized Study of neoadjuvant letrozole plus alpelisib for hormone receptor-positive, human Epidermal growth factor receptor 2-negative breast cancer (NEO-ORB). *Clin Cancer Res*. 2019;25(10):2975-2987.
12. Panigrahi M, Swain TR, Jena RK, Panigrahi A. L-asparaginase-induced abnormality in plasma glucose level in patients of acute lymphoblastic leukemia admitted to a tertiary care hospital of Odisha. *Indian J Pharmacol*. 2016;48(5):595-598.
13. Lowas SR, Marks D, Malempati S. Prevalence of transient hyperglycemia during induction chemotherapy for pediatric acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2009;52(7):814-818.
14. Raja RA, Schmiegelow K, Albertsen BK, et al. Asparaginase-associated pancreatitis in children with acute lymphoblastic leukaemia in the NOPHO ALL2008 protocol. *Br J Haematol*. 2014;165(1):126-133.
15. Schein PS, O'Connell MJ, Blom J, et al. Clinical antitumor activity and toxicity of streptozotocin (NSC-85998). *Cancer*. 1974;34(4):993-1000.
16. Nakamura K, Kawasaki E, Imagawa A, et al. Type 1 diabetes and interferon therapy: a nationwide survey in Japan. *Diabetes Care*. 2011;34(9):2084-2089.
17. Yamazaki M, Sato A, Takeda T, Komatsu M. Distinct clinical courses in type 1 diabetes mellitus induced by peg-interferon-alpha treatment for chronic hepatitis C. *Intern Med*. 2010;49(5):403-407.
18. Verges B, Walter T, Cariou B. Endocrine side effects of anti-cancer drugs: effects of anti-cancer targeted therapies on lipid and glucose metabolism. *Eur J Endocrinol*. 2014;170(2):R43-R55.
19. Agostino NM, Chinchilli VM, Lynch CJ, et al. Effect of the tyrosine kinase inhibitors (sunitinib, sorafenib, dasatinib, and imatinib) on blood glucose levels in diabetic and nondiabetic patients in general clinical practice. *J Oncol Pharm Pract*. 2011;17(3):197-202.
20. Zezza M, Kosinski C, Mekoguem C, et al. Combined immune checkpoint inhibitor therapy with nivolumab and ipilimumab causing acute-onset type 1 diabetes mellitus following a single administration: two case reports. *BMC Endocr Disord*. 2019;19(1):144.
21. Kotwal A, Haddox C, Block M, Kudva YC. Immune checkpoint inhibitors: an emerging cause of insulin-dependent diabetes. *BMJ Open Diabetes Res Care*. 2019;7(1):e000591.
22. Stamatouli AM, Quandt Z, Perdigoto AL, et al. Collateral damage: insulin-dependent diabetes induced with checkpoint inhibitors. *Diabetes*. 2018;67(8):1471-1480.
23. Akturk HK, Kahramangil D, Sarwal A, et al. Immune checkpoint inhibitor-induced type 1 diabetes: a systematic review and meta-analysis. *Diabet Med*. 2019;36(9):1075-1081.
24. Trinh B, Donath MY, Laubli H. Successful treatment of immune checkpoint inhibitor-induced diabetes with infliximab. *Diabetes Care*. 42. United States2019. p. e153-e4.
25. Ferrari S, Pieretti F, Verri E, et al. Prospective evaluation of renal function in pediatric and adult patients treated with high-dose ifosfamide, cisplatin and high-dose methotrexate. *Anticancer Drugs*. 2005;16(7):733-738.
26. Shen Y, Wang C, Ren Y, Ye J. A comprehensive look at the role of hyperlipidemia in promoting colorectal cancer liver metastasis. *J Cancer*. 2018;9(16):2981-2986.
27. Lilley JS, Linton MF, Fazio S. Oral retinoids and plasma lipids. *Dermatol Ther*. 2013;26(5):404-410.
28. Klor HU, Weizel A, Augustin M, et al. The impact of oral vitamin A derivatives on lipid metabolism—what recommendations can be derived for dealing with this issue in the daily dermatological practice? *J Dtsch Dermatol Ges*. 2011;9(8):600-606.
29. Duvic M, Martin AG, Kim Y, et al. Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. *Arch Dermatol*. 2001;137(5):581-593.
30. Scarisbrick JJ, Morris S, Azurdia R, et al. U.K. consensus statement on safe clinical prescribing of bexarotene for patients with cutaneous T-cell lymphoma. *Br J Dermatol*. 2013;168(1):192-200.
31. Cabello I, Servitje O, Corbella X, et al. Omega-3 fatty acids as adjunctive treatment for bexarotene-induced hypertriglyceridaemia in patients with cutaneous T-cell lymphoma. *Clin Exp Dermatol*. 2017;42(3):276-281.
32. Cabello I, Alia P, Pintó X, et al. Association of APOA5 and APOC3 Genetic polymorphisms with severity of hypertriglyceridemia in patients with cutaneous T-cell lymphoma treated with bexarotene. *JAMA Dermatol*. 2018;154(12):1424-1431.
33. Talpur R, Ward S, Apisarnthanarax N, et al. Optimizing bexarotene therapy for cutaneous T-cell lymphoma. *J Am Acad Dermatol*. 2002;47(5):672-684.
34. Sbiera S, Leich E, Liebisch G, et al. Mitotane inhibits sterol-O-Acyl transferase 1 triggering lipid-mediated endoplasmic reticulum stress and apoptosis in adrenocortical carcinoma cells. *Endocrinology*. 2015;156(11):3895-3908.
35. Scheidt HA, Haralampiev I, Theisgen S, et al. The adrenal specific toxicant mitotane directly interacts with lipid membranes and alters membrane properties depending on lipid composition. *Mol Cell Endocrinol*. 2016;428:68-81.
36. Shawa H, Deniz F, Bazerbashi H, et al. Mitotane-induced hyperlipidemia: a retrospective cohort study. *Int J Endocrinol*. 2013;2013:624962.
37. Hoogeveen RC, Ballantyne CM, Pownall HJ, et al. Effect of sirolimus on the metabolism of apoB100- containing lipoproteins in renal transplant patients. *Transplantation*. 2001;72(7):1244-1250.

38. Brown NF, Stefanovic-Racic M, Sipula IJ, Perdomo G. The mammalian target of rapamycin regulates lipid metabolism in primary cultures of rat hepatocytes. *Metabolism*. 2007;56(11):1500-1507.
39. Morrisett JD, Abdel-Fattah G, Hoogeveen R, et al. Effects of sirolimus on plasma lipids, lipoprotein levels, and fatty acid metabolism in renal transplant patients. *J Lipid Res*. 2002;43(8):1170-1180.
40. Ma KL, Ruan XZ, Powis SH, et al. Sirolimus modifies cholesterol homeostasis in hepatic cells: a potential molecular mechanism for sirolimus-associated dyslipidemia. *Transplantation*. 2007;84(8):1029-1036.
41. Morviducci L, Rota F, Rizza L, et al. Everolimus is a new anticancer molecule: metabolic side effects as lipid disorders and hyperglycemia. *Diabetes Res Clin Pract*. 2018;143:428-431.
42. Bouillet B, Buffier P, Smati S, et al. Expert opinion on the metabolic complications of mTOR inhibitors. *Ann Endocrinol (Paris)*. 2018;79(5):583-590.
43. Geva S, Lazarev I, Geffen DB, Ariad S. Hypertriglyceridemia in patients with metastatic breast cancer and treatment with capecitabine. *J Chemother*. 2013;25(3):176-180.
44. Wang G, Su C, Yin T. Paclitaxel and platinum-based chemotherapy results in transient dyslipidemia in cancer patients. *Mol Clin Oncol*. 2017;6(2):261-265.
45. Tian W, Yao Y, Fan G, et al. Changes in lipid profiles during and after (neo)adjuvant chemotherapy in women with early-stage breast cancer: a retrospective study. *PLoS One*. 2019;14(8):e0221866.
46. Haddad N, Vidal-Trecan T, Baroudjian B, et al. Acquired generalized lipodystrophy under immune checkpoint inhibition. *Br J Dermatol*. 2020;182(2):477-480.
47. Falcao CK, Cabral MCS, Mota JM, et al. Acquired lipodystrophy associated with nivolumab in a patient with advanced renal cell carcinoma. *J Clin Endocrinol Metab*. 2019;104(8):3245-3248.
48. Kitchlu A, Rosner MH. Hyponatremia in patients with cancer. *Curr Opin Nephrol Hypertens*. 2019;28(5):433-440.
49. Doshi SM, Shah P, Lei X, et al. Hyponatremia in hospitalized cancer patients and its impact on clinical outcomes. *Am J Kidney Dis*. 2012;59(2):222-228.
50. Sengupta A, Banerjee SN, Biswas NM, et al. the incidence of hyponatraemia and its effect on the ECOG performance status among lung cancer patients. *J Clin Diagn Res*. 2013;7(8):1678-1682.
51. Berardi R, Caramanti M, Castagnani M, et al. Hyponatremia is a predictor of hospital length and cost of stay and outcome in cancer patients. *Support Care Cancer*. 2015;23(10):3095-3101.
52. Onitilo AA, Kio E, Doi SA. Tumor-related hyponatremia. *Clin Med Res*. 2007;5(4):228-237.
53. List AF, Hainsworth JD, Davis BW, et al. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in small-cell lung cancer. *J Clin Oncol*. 1986;4(8):1191-1198.
54. Sorensen JB, Andersen MK, Hansen HH. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in malignant disease. *J Intern Med*. 1995;238(2):97-110.
55. Verzicco I, Regolisti G, Quaini F, et al. Electrolyte Disorders Induced by Antineoplastic Drugs. *Front Oncol*. 2020;10:779.
56. Elhassan EA, Schrier RW. Hyponatremia: diagnosis, complications, and management including V2 receptor antagonists. *Curr Opin Nephrol Hypertens*. 2011;20(2):161-168.
57. Khan MI, Dellinger RP, Waguespack SG. Electrolyte disturbances in critically ill cancer patients: an endocrine perspective. *J Intensive Care Med*. 2018;33(3):147-158.
58. Zhao C, Tella SH, Del Rivero J, et al. Anti-PD-L1 treatment induced central diabetes insipidus. *J Clin Endocrinol Metab*. 2018;103(2):365-369.
59. Deligiorgi MV, Siasos G, Vergadis C, Trafalis DT. Central diabetes insipidus related to anti-programmed cell-death 1 protein active immunotherapy. *Int Immunopharmacol*. 2020;83:106427.
60. Derman BA, Jain M, McAninch EA, Gashti C. Bendamustine-induced nephrogenic diabetes insipidus. *Clin Nephrol*. 2017;87 (2017)(1):47-50.
61. Delaney V, de Pertuz Y, Nixon D, Bourke E. Indomethacin in streptozocin-induced nephrogenic diabetes insipidus. *Am J Kidney Dis*. 1987;9(1):79-83.
62. Drake MT. Osteoporosis and cancer. *Curr Osteoporos Rep*. 2013;11(3):163-170.
63. Fukumoto S, Matsumoto T. [Cancer treatment-induced bone loss (CTIBL)]. *Gan To Kagaku Ryoho*. 2018;45(12):1685-1689.
64. Spangler L, Yu O, Loggers E, Boudreau DM. Bone mineral density screening among women with a history of breast cancer treated with aromatase inhibitors. *J Womens Health (Larchmt)*. 2013;22(2):132-140.
65. Baum M, Budzar AU, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet*. 2002;359(9324):2131-2139.
66. Pineda-Moncusí M, Garcia-Giralt N, Diez-Perez A, et al. Increased fracture risk in women treated with aromatase inhibitors versus tamoxifen: beneficial effect of bisphosphonates. *J Bone Miner Res*. 2019;35(2):291-297.
67. Smith MR. Androgen deprivation therapy for prostate cancer: new concepts and concerns. *Curr Opin Endocrinol Diabetes Obes*. 2007;14(3):247-254.
68. Smith MR, Boyce SP, Moyneur E, et al. Risk of clinical fractures after gonadotropin-releasing hormone agonist therapy for prostate cancer. *J Urol*. 2006;175(1):136-9; discussion 9.
69. Saad F, Carles J, Gillessen S, et al. Radium-223 in an international early access program (EAP): effects of concomitant medication on overall survival in metastatic castration-resistant prostate cancer (mCRCP) patients. *J Clin Oncol*. 2015;33(15 suppl):5034.
70. Matsushima H. [Bone and calcium metabolism associated with malignancy. Bone management of prostate cancer in the novel anti-androgen era.]. *Clin Calcium*. 2018;28(11):1535-1544.
71. Gralow JR, Biermann JS, Farooki A, et al. NCCN Task Force report: bone health in cancer care. *J Natl Compr Canc Netw*. 2013;11(suppl 3):S1-S50; quiz S1.
72. D'Angelo P, Conter V, Di Chiara G, et al. Severe osteoporosis and multiple vertebral collapses in a child during treatment for B-ALL. *Acta Haematol*. 1993;89(1):38-42.
73. Rosen LS, Gordon D, Kaminski M, et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. *Cancer*. 2003;98(8):1735-1744.
74. Nyman JS, Merkel AR, Uppuganti S, et al. Combined treatment with a transforming growth factor beta inhibitor (1D11) and bortezomib improves bone architecture in a mouse model of myeloma-induced bone disease. *Bone*. 2016;91:81-91.
75. Li B, Boast S, de los Santos K, Schieren I, et al. Mice deficient in Abl are osteoporotic and have defects in osteoblast maturation. *Nat Genet*. 2000;24(3):304-308.
76. Alemán JO, Farooki A, Girotra M. Effects of tyrosine kinase inhibition on bone metabolism: untargeted consequences of targeted therapies. *Endocr Relat Cancer*. 2014;21(3): R247-R259.
77. Wang L, Wang Y, Chen A, et al. Effects of a checkpoint kinase inhibitor, AZD7762, on tumor suppression and bone remodeling. *Int J Oncol*. 2018;53(3):1001-1012.
78. Biver E. [Bone effects of bisphosphonates and denosumab treatments in breast or prostate cancer]. *Rev Med Suisse*. 2019;15(647):824-830.
79. O'Sullivan S, Horne A, Wattie D, et al. Decreased bone turnover despite persistent secondary hyperparathyroidism during

prolonged treatment with imatinib. *J Clin Endocrinol Metab*. 2009;94(4):1131-1136.
80. Berman E, Girotra M, Cheng C, et al. Effect of long term imatinib on bone in adults with chronic myelogenous leukemia and gastrointestinal stromal tumors. *Leuk Res*. 2013;37(7):790-794.
81. Joseph JS, Lam V, Patel MI. Preventing osteoporosis in men taking androgen deprivation therapy for prostate cancer: a systematic review and meta-analysis. *Eur Urol Oncol*. 2019;2(5):551-561.
82. Galvano A, Scaturro D, Badalamenti G, et al. Denosumab for bone health in prostate and breast cancer patients receiving endocrine therapy? A systematic review and a meta-analysis of randomized trials. *J Bone Oncol*. 2019;18:100252.
83. Essex AL, Pin F, Huot JR, et al. Bisphosphonate treatment ameliorates chemotherapy-induced bone and muscle abnormalities in young mice. *Front Endocrinol (Lausanne)*. 2019;10:809-.
84. Saag KG, Wagman RB, Geusens P, et al. Denosumab versus risedronate in glucocorticoid-induced osteoporosis: a multicentre, randomised, double-blind, active-controlled, double-dummy, non-inferiority study. *Lancet Diabetes Endocrinol*. 2018;6(6):445-454.
85. Subbiah V, Madsen VS, Raymond AK, et al. Of mice and men: divergent risks of teriparatide-induced osteosarcoma. *Osteoporos Int*. 2010;21(6):1041-1045.
86. Handforth C, D'Oronzo S, Coleman R, Brown J. Cancer treatment and bone health. *Calcif Tissue Int*. 2018;102(2):251-264.
87. Church DN, Hassan AB, Harper SJ, et al. Osteomalacia as a late metabolic complication of ifosfamide chemotherapy in young adults: illustrative cases and review of the literature. *Sarcoma*. 2007;2007:91586.
88. Stava CJ, Jimenez C, Hu MI, Vassilopoulou-Sellin R. Skeletal sequelae of cancer and cancer treatment. *J Cancer Surviv*. 2009;3(2):75-88.
89. Savva C, Adhikaree J, Madhusudan S, Chokkalingam K. Oncogenic osteomalacia and metastatic breast cancer: a case report and review of the literature. *J Diabetes Metab Disord*. 2019;18(1):267-272.
99. Stewart AF. Clinical practice. Hypercalcemia associated with cancer. *N Engl J Med*. 2005;352(4):373-379.
91. Gastanaga VM, Schwartzberg LS, et al. Prevalence of hypercalcemia among cancer patients in the United States. *Cancer Med*. 2016;5(8):2091-2100.
92. Yamamoto T, Tashiro H, Sugao T, et al. [Hypercalcemia due to the administration of all-trans retinoic acid for acute promyelocytic leukemia: report of two cases]. *Nihon Naika Gakkai Zasshi*. 2010;99(4):828-830.
93. Zagzag J, Hu MI, Fisher SB, Perrier ND. Hypercalcemia and cancer: differential diagnosis and treatment. *CA Cancer J Clin*. 2018;68(5):377-386.
94. Ito K, Tsuchiya T, Sugino K, Murata M. [An evaluation of the incidence of hyperparathyroidism after 131I treatment for Basedow disease (part II)]. *Kaku Igaku*. 1996;33(7):737-742.
95. Goldner W. Cancer-related hypercalcemia. *J Oncol Pract*. 2016;12(5):426-432.
96. Mirrakhimov AE, Voore P, Khan M, Ali AM. Tumor lysis syndrome: a clinical review. *World J Crit Care Med*. 2015;4(2):130-138.
97. Liamis G, Milionis HJ, Elisaf M. A review of drug-induced hypocalcemia. *J Bone Miner Metab*. 2009;27(6):635-642.
98. Jones SG, Dolan G, Lengyel K, Myers B. Severe increase in creatinine with hypocalcaemia in thalidomide-treated myeloma patients receiving zoledronic acid infusions. *Br J Haematol*. *Br J Haematol*. 2002;119(2):576-577.
99. Body JJ, Bone HG, de Boer RH, et al. Hypocalcaemia in patients with metastatic bone disease treated with denosumab. *Eur J Cancer*. 2015;51(13):1812-1821.
100. Win MA, Thein KZ, Qdaisat A, Yeung SJ. Acute symptomatic hypocalcemia from immune checkpoint therapy-induced hypoparathyroidism. *Am J Emerg Med*. 2017;35(7):1039.e5-.e7.
101. Trinh B, Sanchez GO, Herzig P, Laubli H. Inflammation-induced hypoparathyroidism triggered by combination immune checkpoint blockade for melanoma. *J Immunother Cancer*. 2019;7(1):52.
102. Yoshida T, Niho S, Toda M, et al. Protective effect of magnesium preloading on cisplatin-induced nephrotoxicity: a retrospective study. *Jpn J Clin Oncol*. 2014;44(4):346-354.
103. Sundar S, Symonds RP, Decatris MP, et al. Phase II trial of oxaliplatin and 5-fluorouracil/leucovorin combination in epithelial ovarian carcinoma relapsing within 2 years of platinum-based therapy. *Gynecol Oncol*. 2004;94(2):502-508.
104. Hsieh MC, Wu CF, Chen CW, et al. Hypomagnesemia and clinical benefits of anti-EGFR monoclonal antibodies in wild-type KRAS metastatic colorectal cancer: a systematic review and meta-analysis. *Sci Rep*. 2018;8(1):2047.
105. Mak IT, Kramer JH, Chmielinska JJ, et al. EGFR-TKI, erlotinib, causes hypomagnesemia, oxidative stress, and cardiac dysfunction: attenuation by NK-1 receptor blockade. *J Cardiovasc Pharmacol*. 2015;65(1):54-61.
106. Darzy KH. Radiation-induced hypopituitarism after cancer therapy: who, how and when to test. *Nat Clin Pract Endocrinol Metab*. 2009;5(2):88-99.
107. Shalet SM, Clayton PE, Price DA. Growth and pituitary function in children treated for brain tumours or acute lymphoblastic leukaemia. *Horm Res*. 1988;30(2-3):53-61.
108. Faje AT, Sullivan R, Lawrence D, et al. Ipilimumab-induced hypophysitis: a detailed longitudinal analysis in a large cohort of patients with metastatic melanoma. *J Clin Endocrinol Metab*. 2014;99(11):4078-4085.
109. Robert C, Ribas A, Wolchok JD, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. *Lancet*. 2014;384(9948):1109-1117.
110. Iglesias P. Cancer immunotherapy-induced endocrinopathies: clinical behavior and therapeutic approach. *Eur J Intern Med*. 2018;47:6-13.
111. Kassi E, Angelousi A, Asonitis N, et al. Endocrine-related adverse events associated with immune-checkpoint inhibitors in patients with melanoma. *Cancer Med*. 2019;8(15):6585-6594.
112. Dillard T, Yedinak CG, Alumkal J, Fleseriu M. Anti-CTLA-4 antibody therapy associated autoimmune hypophysitis: serious immune related adverse events across a spectrum of cancer subtypes. *Pituitary*. 2010;13(1):29-38.
113. Chodakiewitz Y, Brown S, Boxerman JL, et al. Ipilimumab treatment associated pituitary hypophysitis: clinical presentation and imaging diagnosis. *Clin Neurol Neurosurg*. 2014;125:125-130.
114. Faje A. Immunotherapy and hypophysitis: clinical presentation, treatment, and biologic insights. *Pituitary*. 2016;19(1):82-92.
115. Abs R, Verhelst J, Maeyaert J, et al. Endocrine consequences of long-term intrathecal administration of opioids. *J Clin Endocrinol Metab*. 2000;85(6):2215-2222.
116. Meacham LR, Mazewski C, Krawiecki N. Mechanism of transient adrenal insufficiency with megestrol acetate treatment of cachexia in children with cancer. *J Pediatr Hematol Oncol*. 2003;25(5):414-417.
117. Raedler TJ, Jahn H, Goedeken B, et al. Acute effects of megestrol on the hypothalamic-pituitary-adrenal axis. *Cancer Chemother Pharmacol*. 2003;52(6):482-486.
118. Toogood AA. Endocrine consequences of brain irradiation. *Growth Horm IGF Res*. 2004;14(suppl A):S118-S124.
119. Díez JJ, Sangiao-Alvarellos S, Cordido F. Treatment with growth hormone for adults with growth hormone deficiency syndrome: benefits and risks. *Int J Mol Sci*. 2018;19(3):893

120. Schmiegelow M, Feldt-Rasmussen U, Rasmussen AK, et al. A population-based study of thyroid function after radiotherapy and chemotherapy for a childhood brain tumor. *J Clin Endocrinol Metab*. 2003;88(1):136-140.
121. Ogilvy-Stuart AL, Shalet SM, Gattamaneni HR. Thyroid function after treatment of brain tumors in children. *J Pediatr*. 1991;119(5):733-737.
122. Sherman SI. Etiology, diagnosis, and treatment recommendations for central hypothyroidism associated with bexarotene therapy for cutaneous T-cell lymphoma. *Clin Lymphoma*. 2003;3(4):249-252.
123. Appelman-Dijkstra NM, Malgo F, Neelis KJ, et al. Pituitary dysfunction in adult patients after cranial irradiation for head and nasopharyngeal tumours. *Radiother Oncol*. 2014;113(1):102-107.
124. Pai HH, Thornton A, Katznelson L, et al. Hypothalamic/pituitary function following high-dose conformal radiotherapy to the base of skull: demonstration of a dose-effect relationship using dose-volume histogram analysis. *Int J Radiat Oncol Biol Phys*. 2001;49(4):1079-1092.
125. Samaan NA, Schultz PN, Yang KP, et al. Endocrine complications after radiotherapy for tumors of the head and neck. *J Lab Clin Med*. 1987;109(3):364-372.
126. Rajagopal A, Vassilopoulou-Sellin R, Palmer JL, et al. Hypogonadism and sexual dysfunction in male cancer survivors receiving chronic opioid therapy. *J Pain Symptom Manage*. 2003;26(5):1055-1061.
127. Nikiforov YE. RET/PTC rearrangement in thyroid tumors. *Endocr Pathol*. 2002;13(1):3-16.
128. Inskip PD, Veiga LHS, Brenner AV, et al. Hyperthyroidism after radiation therapy for childhood cancer: a report from the Childhood Cancer Survivor Study. *Int J Radiat Oncol Biol Phys*. 2019;104(2):415-424.
129. Prummel MF, Laurberg P. Interferon-alpha and autoimmune thyroid disease. *Thyroid*. 2003;13(6):547-551.
130. Hamnvik OP, Larsen PR, Marqusee E. Thyroid dysfunction from antineoplastic agents. *J Natl Cancer Inst*. 2011;103(21):1572-1587.
131. Hamid O, Robert C, Daud A, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N Engl J Med*. 2013;369(2):134-144.
132. Ho VT, Zahrieh D, Hochberg E, et al. Safety and efficacy of denileukin diftitox in patients with steroid-refractory acute graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. *Blood*. 2004;104(4):1224-1226.
133. Jereczek-Fossa BA, Alterio D, Jassem J, et al. Radiotherapy-induced thyroid disorders. *Cancer Treat Rev*. 2004;30(4):369-384.
134. Sklar C, Whitton J, Mertens A, et al. Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the Childhood Cancer Survivor Study. *J Clin Endocrinol Metab*. 2000;85(9):3227-3232.
135. Demirkaya M, Sevinir B, Saglam H, et al. Thyroid functions in long-term survivors of pediatric Hodgkin's lymphoma treated with chemotherapy and radiotherapy. *J Clin Res Pediatr Endocrinol*. 2011;3(2):89-94.
136. Dalgard O, Bjoro K, Hellum K, et al. Thyroid dysfunction during treatment of chronic hepatitis C with interferon alpha: no association with either interferon dosage or efficacy of therapy. *J Intern Med*. 2002;251(5):400-406.
137. Stuart NS, Woodroffe CM, Grundy R, Cullen MH. Long-term toxicity of chemotherapy for testicular cancer—the cost of cure. *Br J Cancer*. 1990;61(3):479-484.
138. Coles AJ, Compston DA, Selmaj KW, et al. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. *N Engl J Med*. 2008;359(17):1786-1801.
139. Tamaskar I, Bukowski R, Elson P, et al. Thyroid function test abnormalities in patients with metastatic renal cell carcinoma treated with sorafenib. *Ann Oncol*. 2008;19(2):265-268.
140. Miyake H, Kurahashi T, Yamanaka K, et al. Abnormalities of thyroid function in Japanese patients with metastatic renal cell carcinoma treated with sorafenib: a prospective evaluation. *Urol Oncol*. 2010;28(5):515-519.
141. Schneider TC, Abdulrahman RM, Corssmit EP, et al. Long-term analysis of the efficacy and tolerability of sorafenib in advanced radio-iodine refractory differentiated thyroid carcinoma: final results of a phase II trial. *Eur J Endocrinol*. 2012;167(5):643-650.
142. Hoftijzer H, Heemstra KA, Morreau H, et al. Beneficial effects of sorafenib on tumor progression, but not on radioiodine uptake, in patients with differentiated thyroid carcinoma. *Eur J Endocrinol*. 2009;161(6):923-931.
143. Wolter P, Stefan C, Decallonne B, et al. The clinical implications of sunitinib-induced hypothyroidism: a prospective evaluation. *Br J Cancer*. 2008;99(3):448-454.
144. Desai J, Yassa L, Marqusee E, et al. Hypothyroidism after sunitinib treatment for patients with gastrointestinal stromal tumors. *Ann Intern Med*. 2006;145(9):660-664.
145. Kitajima K, Takahashi S, Maeda T, et al. Thyroid size change by CT monitoring after sorafenib or sunitinib treatment in patients with renal cell carcinoma: comparison with thyroid function. *Eur J Radiol*. 2012;81(9):2060-2065.
146. Mannavola D, Coco P, Vannucchi G, et al. A novel tyrosine-kinase selective inhibitor, sunitinib, induces transient hypothyroidism by blocking iodine uptake. *J Clin Endocrinol Metab*. 2007;92(9):3531-3534.
147. Wong E, Rosen LS, Mulay M, et al. Sunitinib induces hypothyroidism in advanced cancer patients and may inhibit thyroid peroxidase activity. *Thyroid*. 2007;17(4):351-355.
148. Barroso-Sousa R, Barry WT, Garrido-Castro AC, et al. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis. *JAMA Oncol*. 2018;4(2):173-182.
149. Chalan P, Di Dalmazi G, Pani F, et al. Thyroid dysfunctions secondary to cancer immunotherapy. *J Endocrinol Invest*. 2018;41(6):625-638.
150. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363(8):711-723.
151. Jannin A, Penel N, Ladsous M, et al. Tyrosine kinase inhibitors and immune checkpoint inhibitors-induced thyroid disorders. *Crit Rev Oncol Hematol*. 2019;141:23-35.
152. Bajetta E, Zilembo N, Dowsett M, et al. Double-blind, randomised, multicentre endocrine trial comparing two letrozole doses, in postmenopausal breast cancer patients. *Eur J Cancer*. 1999;35(2):208-213.
153. Ferster A, Glinoer D, Van Vliet G, Otten J. Thyroid function during L-asparaginase therapy in children with acute lymphoblastic leukemia: difference between induction and late intensification. *Am J Pediatr Hematol Oncol*. 1992;14(3):192-196.
154. Carvalho F, Louro F, Zakout R. Adrenal insufficiency in metastatic lung cancer. *World J Oncol*. 2015;6(3):375-377.
155. Paragliola RM, Torino F, Papi G, et al. Role of Mitotane in adrenocortical carcinoma—review and state of the art. *Eur Endocrinol*. 2018;14(2):62-66.
156. Lindhe O, Skogseid B, Brandt I. Cytochrome P450-catalyzed binding of 3-methylsulfonyl-DDE and o,p'-DDD in human adrenal zona fasciculata/reticularis. *J Clin Endocrinol Metab*. 2002;87(3):1319-1326.
157. van Seters AP, Moolenaar AJ. Mitotane increases the blood levels of hormone-binding proteins. *Acta Endocrinol (Copenh)*. 1991;124(5):526-533.

158. Goodman VL, Rock EP, Dagher R, et al. Approval summary: sunitinib for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumors and advanced renal cell carcinoma. *Clin Cancer Res*. 2007;13(5):1367-1373.
159. Min L, Ibrahim N. Ipilimumab-induced autoimmune adrenalitis. *Lancet Diabetes Endocrinol*. 2013;1(3):e15.
160. Trainer H, Hulse P, Higham CE, et al. Hyponatraemia secondary to nivolumab-induced primary adrenal failure. *Endocrinol Diabetes Metab Case Rep*. 2016;2016.
161. Ferraldeschi R, Sharifi N, Auchus RJ, Attard G. Molecular pathways: inhibiting steroid biosynthesis in prostate cancer. *Clin Cancer Res*. 2013;19(13):3353-3359.
162. Bedoschi G, Navarro PA, Oktay K. Chemotherapy-induced damage to ovary: mechanisms and clinical impact. *Future Oncol*. 2016;12(20):2333-2344.
163. Roeca C, Dovey S, Polotsky AJ. Recommendations for assessing ovarian health and fertility potential in survivors of childhood cancer. *Maturitas*. 2019;122:57-59.
164. Sudour H, Chastagner P, Claude L, et al. Fertility and pregnancy outcome after abdominal irradiation that included or excluded the pelvis in childhood tumor survivors. *Int J Radiat Oncol Biol Phys*. 2010;76(3):867-873.
165. Green DM, Kawashima T, Stovall M, et al. Fertility of female survivors of childhood cancer: a report from the childhood cancer survivor study. *J Clin Oncol*. 2009;27(16):2677-2685.
166. Le Bouedec G, Rabishong B, Canis M, et al. [Ovarian transposition by laparoscopy in young women before curietherapy for cervical cancer]. *J Gynecol Obstet Biol Reprod (Paris)*. 2000;29(6):564-570.
167. Recchia F, Saggio G, Amiconi G, et al. Gonadotropin-releasing hormone analogues added to adjuvant chemotherapy protect ovarian function and improve clinical outcomes in young women with early breast carcinoma. *Cancer*. 2006;106(3):514-523.
168. Demeestere I, Brice P, Peccatori FA, et al. Gonadotropin-releasing hormone agonist for the prevention of chemotherapy-induced ovarian failure in patients with lymphoma: 1-year follow-up of a prospective randomized trial. *J Clin Oncol*. 2013;31(7):903-909.
169. Berliere M, Dalenc F, Malingret N, et al. Incidence of reversible amenorrhea in women with breast cancer undergoing adjuvant anthracycline-based chemotherapy with or without docetaxel. *BMC Cancer*. 2008;8:56.
170. Meirow D, Nugent D. The effects of radiotherapy and chemotherapy on female reproduction. *Hum Reprod Update*. 2001;7(6):535-543.
171. Choo YC, Chan SY, Wong LC, Ma HK. Ovarian dysfunction in patients with gestational trophoblastic neoplasia treated with short intensive courses of etoposide (VP-16-213). *Cancer*. 1985;55(10):2348-2352.
172. van Beek RD, van den Heuvel-Eibrink MM, Laven JS, et al. Anti-Mullerian hormone is a sensitive serum marker for gonadal function in women treated for Hodgkin's lymphoma during childhood. *J Clin Endocrinol Metab*. 2007;92(10):3869-3874.
173. Sieniawski M, Reineke T, Nogova L, et al. Fertility in male patients with advanced Hodgkin lymphoma treated with BEACOPP: a report of the German Hodgkin Study Group (GHSG). *Blood*. 2008;111(1):71-76.
174. Shanei A, Baradaran-Ghahfarokhi M. Evaluation of testicular dose and associated risk from common pelvis radiation therapy in Iran. *Phys Med*. 2014;30(8):867-870.
175. Howell SJ, Shalet SM. Effect of cancer therapy on pituitary-testicular axis. *Int J Androl*. 2002;25(5):269-276.
176. Cheviakoff S, Calamera JC, Morgenfeld M, Mancini RE. Recovery of spermatogenesis in patients with lymphoma after treatment with chlorambucil. *J Reprod Fertil*. 1973;33(1):155-157.
177. Meistrich ML. Effects of chemotherapy and radiotherapy on spermatogenesis in humans. *Fertil Steril*. 2013;100(5):1180-1186.
178. Meistrich ML, Shetty G. Suppression of testosterone stimulates recovery of spermatogenesis after cancer treatment. *Int J Androl*. 2003;26(3):141-146.
179. Friedman DN, Tonorezos ES, Cohen P. Diabetes and metabolic syndrome in survivors of childhood cancer. *Horm Res Paediatr*. 2019;91(2):118-127.
180. Singh S, Earle CC, Bae SJ, et al. Incidence of diabetes in colorectal cancer survivors. *J Natl Cancer Inst*. 2016;108(6):djv402.
181. Hamood R, Hamood H, Merhasin I, Keinan-Boker L. Diabetes after hormone therapy in breast cancer survivors: a case-cohort study. *J Clin Oncol*. 2018;36(20):2061-2069.
182. Clement SC, Schouten-van Meeteren AY, Boot AM, et al. Prevalence and risk factors of early endocrine disorders in childhood brain tumor survivors: a nationwide, multicenter study. *J Clin Oncol*. 2016;34(36):4362-4370.
183. Patterson BC, Truxillo L, Wasilewski-Masker K, et al. Adrenal function testing in pediatric cancer survivors. *Pediatr Blood Cancer*. 2009;53(7):1302-1307.

This page intentionally left blank

61 Oncologic Emergencies

Sai-Ching Jim Yeung
Ellen F. Manzullo
Patrick Chaftari

KEY CONCEPTS

- Oncologic emergencies can result from either the cancer or its treatment. This chapter discusses some selected emergencies.
- Nervous system emergencies include spinal cord compression, increased intracranial pressure, leptomeningeal disease, seizures, and altered mental status.
- Superior vena cava (SVC) syndrome, hyperviscosity syndrome, hyperleukocytosis, venous thromboembolism, hemorrhage, and disseminated intravascular coagulopathy are the vascular and hematologic emergencies discussed.
- Urologic emergencies such as hemorrhagic cystitis and obstructive uropathy are discussed.
- Pulmonary problems such as airway obstruction, massive hemoptysis, toxic lung injuries, pneumonitis, and pulmonary fibrosis can be caused by cancer or cancer treatments.
- Several classic metabolic oncologic emergencies include syndrome of inappropriate antidiuretic hormone secretion, tumor lysis syndrome, and hypercalcemia of malignancy.
- Gastrointestinal bleeding in patients with cancer and typhlitis in patients with neutropenic fever are potentially serious complications.
- Immune checkpoint inhibitors may cause immune-related adverse effects (irAEs) in practically any organ system. Urgent skin irAEs include grade 3 and 4 inflammatory dermatitis or rash, bullous dermatosis, drug reaction with eosinophilia and systemic symptoms, and Stevens-Johnson syndrome or toxic epidermal necrolysis. Gastrointestinal irAEs are common. The main pulmonary irAE is pneumonitis. Endocrine irAEs affect the thyroid, adrenal, and pituitary glands as well as the pancreatic islets (type 1 diabetes), which may be associated with acute diabetic ketoacidosis. Myocarditis is rare but may be life threatening. Pneumonitis may be associated with poor overall survival.

INTRODUCTION

Oncologic emergencies can result from either the cancer or its treatment. Patients with cancer often have immunologic, metabolic, and hematologic defects, which can lead to complex emergency conditions when they present to an emergency or urgent care center. In addition, emergencies resulting from comorbid conditions also occur in patients with cancer. It is important for practitioners who treat patients with cancer to be aware of the various oncologic emergencies so they can be recognized and treated promptly. This chapter discusses some selected emergencies, including their signs and symptoms, causes, and management.

NEUROLOGIC EMERGENCIES

Spinal Cord Compression

Spinal cord compression is a serious complication of cancer, affecting about 2.5% of patients with cancer overall.[1] It is not immediately life threatening unless it involves the first three cervical vertebrae, but compression of the spinal cord at lower levels of the spine leads to significant morbidity. The spinal cord is compressed by the cervical vertebrae in 10%, thoracic vertebrae in 70%, and lumbar vertebrae in 20% of patients. In 10% to 38% of cases, spinal cord compression occurs at multiple levels.[2] Compression is predominantly caused by metastatic tumors, with lung, breast, and prostate cancer accounting for 50% of cases. Other

tumors that commonly metastasize to the spine are multiple myeloma, renal cell carcinoma, melanoma, lymphoma, sarcoma, and gastrointestinal (GI) cancers. The mechanisms by which tumors can appear in the spine are hematogenous spread of tumor cells to the vertebral bodies, metastasis to the posterior spinal elements, epidural metastasis, and direct extension of paraspinal tumors. Spinal cord compression is caused by epidural metastases in about 75% and vertebral bony collapse in about 25% of cases.

The most common symptom of spinal cord compression is back pain, occurring in more than 90% of patients. Depending on the location of the tumor in the spinal canal, the pain can be unilateral or bilateral following dermatomal patterns. Patients typically report that their pain is exacerbated by coughing or a supine position. Motor weakness is the second most common complaint after pain; difficulty walking, buckling of the legs, and a feeling of heaviness in the legs are all frequent symptoms. Weakness of the upper extremities may be present when the spinal cord is compressed at the cervical levels. Some patients may have ataxia, which is caused by compression of the spinocerebellar tracts. The patient may have sensory symptoms, including numbness or tingling, which can progress proximally. Preexisting peripheral neuropathy must be differentiated from spinal cord compression by recognizing acute worsening and new distribution pattern of numbness or tingling. The last symptoms to appear are autonomic symptoms, such as an inability to urinate (urinary retention), and constipation. It is important to remember that the patient may present with intractable pain only, so a high level of suspicion for spinal cord compression is important in treating patients with cancer.

The physical examination usually reveals tenderness to percussion over the affected level of the spine, but the spine might not be tender if there is no bone involvement. Other possible findings are bladder distention, decreased rectal sphincter tone, and muscle weakness. The patient may have pain at a referred site; for instance, patients with T4 compression may have breast pain or chest pain, and those with L1 compression may have sacroiliac pain. Sensory changes are more difficult to diagnose than motor deficits and can either precede or accompany motor deficits. The patient might have decreased sensation in the lower extremities, which may ascend to the level of spinal cord involvement with dorsal column deficits, including loss of light touch sensation, vibration, and proprioception. When the cauda equina is compressed, the sensory changes are dermatomal with loss of sensation in the perineal area, posterior thigh, or lateral leg, depending on the spinal nerves involved.

Other than cancer, causes of spinal cord compression include degenerative spinal stenosis, spondylolisthesis (osteoarthritis), degenerative disk disease, spinal abscess, hematoma or bleeding, hemangioma, chordoma, meningioma, and neurofibroma. Magnetic resonance imaging (MRI) is the imaging technique of choice today for suspected spinal cord compression (Fig. 61–1).

Patients who are not able to undergo MRI (eg, patients with cerebral aneurysm clips, certain models of cardiac pacemakers, or magnetic implants) can undergo computed tomography (CT) myelogram, although this technique is more time consuming and tedious than MRI. Imaging study of the entire spine should be considered because spinal epidural disease is often multifocal. Findings for the whole spine can help the physician optimize the type and extent of therapy needed. For any patient with rapidly progressive neurologic symptoms, diagnostic imaging should be performed on an emergency basis.

Corticosteroid is a temporizing measure to stabilize or even improve neurologic function until definitive treatment. Conventionally, dexamethasone is initially given at 10 to 100 mg intravenously and then 4 to 24 mg intravenously or orally every 6 to 8 hours. The duration of therapy with high-dose glucocorticoids should be minimized to prevent complications of steroid use. Surgery is indicated for recurrent or progressive disease at an area with previous maximal radiotherapy, spinal mechanical instability, an unknown tissue diagnosis of malignancy, or compression of the spinal cord by bony structure or fragment. Patchell and colleagues[3] in 2005 reported the first phase III randomized clinical trial comparing the role of decompressive surgery and radiation to radiation alone. In this study, patients were initially treated with 100 mg of dexamethasone followed by 24 mg every 6 hours and then treated with radiation therapy (30 Gy in 10 fractions) alone or surgery (usually within 24 hours) followed by the same course of radiation within 2 weeks of surgery. The percentage of ambulatory patients was significantly higher in the group treated with surgery and radiation compared with radiation alone (84% vs 57%, respectively); so were their duration of ambulation (median, 122 days vs 13 days) and median survival time (126 days vs 100 days). Currently, anterior decompression with spinal stabilization is the surgery of choice, allowing removal of the affected vertebral body and stabilization above and below the vertebrae by metal hardware. For paraplegic patients with spinal cord compression, surgery with postoperative radiotherapy maximizes neurologic function and modestly prolongs survival.[4] Benefit from decompressive surgery is evident in ambulatory patients with poor prognostic factors for radiotherapy and in paralyzed patients with a single spinal area of compression, paraplegia less than 48 hours, nonradiosensitive tumors, and an expected survival period of more than 3 months. If surgery is not indicated, radiation therapy can be used for radiosensitive tumors; the most common dosage is 3000 cGy delivered in 10 fractions. The incidence of radiation-induced myelopathy

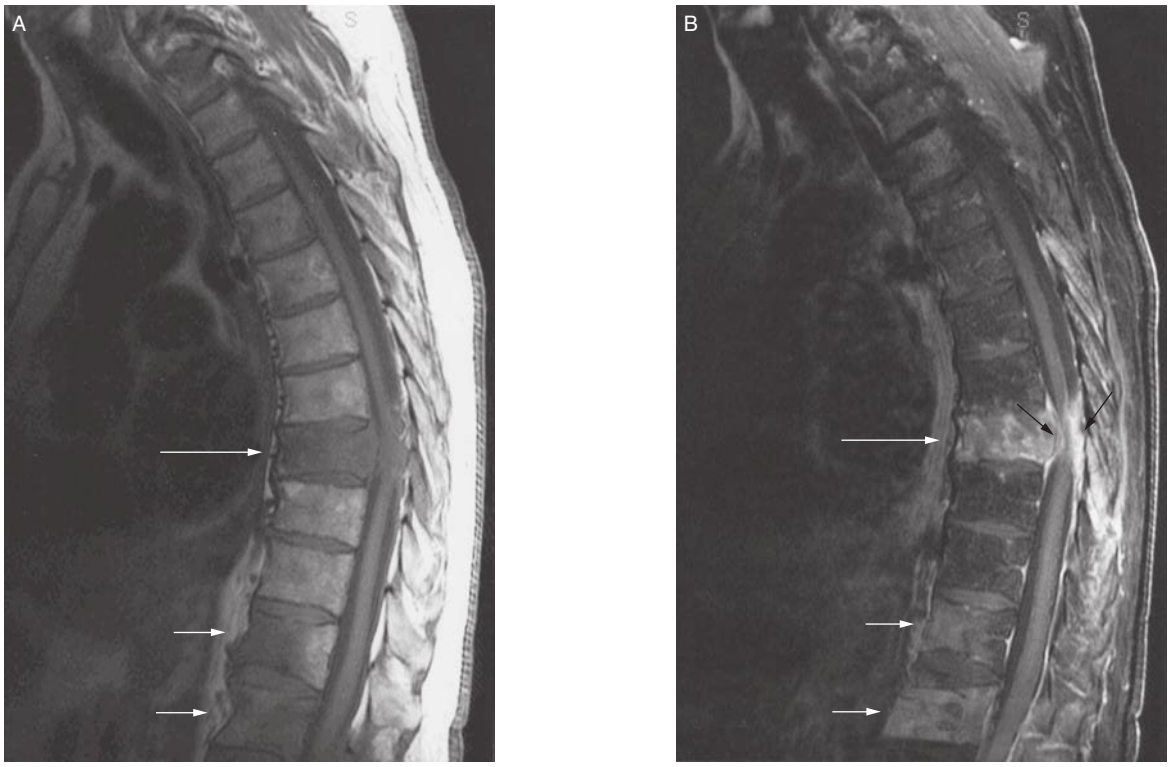


FIGURE 61–1 A. Precontrast T1-weighted magnetic resonance image (MRI) of thoracic cord compression at the T8 level produced by an epidural tumor from vertebral body metastasis (*large arrow*). *Smaller arrows* point to other sites of bony metastasis. The patient is a 67-year-old man with melanoma and back pain. B. Postcontrast T1-weighted MRI of the same patient. The epidural tumor is visualized better with contrast (*black arrows*). The white arrows are as described in A. (Used with permission from Dr. Ashok Kumar, MD Anderson Cancer Center.)

increases with increasing total dosage of radiation and can appear from months to several years after radiotherapy. Palliative radiotherapy is recommended for those with paraplegia longer than 48 hours, expected to live for fewer than 3 months, unable to tolerate surgery, and multiple areas of compression. An ambulatory patient with a stable spine may be considered for radiation treatment only. The role of chemotherapy to treat spinal cord compression is not clear. Chemotherapy is occasionally used for chemosensitive tumors, such as Hodgkin disease, non-Hodgkin lymphoma, neuroblastoma, germ cell tumors, and breast cancer. Hormonal therapy can benefit some patients with hormone-responsive tumors, such as prostate and breast cancers. One of the most important prognostic factors at diagnosis is the patient's neurologic function. Of patients who are ambulatory at the time of presentation, approximately three fourths will be able to regain their strength with treatment. In contrast, only a small percentage of patients who are paralyzed at the time of diagnosis can walk again. This difference illustrates the importance of diagnosing spinal cord compression at an early stage. A scoring system based on tumor type, interval between tumor diagnosis and spinal cord compression, other bone or visceral metastases, ambulatory status, duration of paralysis, and so on can estimate survival.[5,6] Overall, the median survival after the first episode of spinal cord compression is about 3 months.

Increased Intracranial Pressure

Increased intracranial pressure (ICP) in patients with cancer is commonly caused by hemorrhage (from thrombocytopenia or tumor bleeding), brain metastasis with vasogenic edema and mass effect, or hydrocephalus because of obstruction of the flow of cerebrospinal fluid (CSF). Increased ICP can also be caused by tumor treatments, such as radiation therapy and surgery. The normal CSF pressure is less than 10 mm Hg. As ICP increases, herniation syndromes may develop, including uncal, central, and tonsillar herniation. Uncal herniation is caused by unilateral supratentorial lesions that push brain tissue through the tentorial notch. Signs and symptoms classically include ipsilateral pupil dilation, decreased consciousness, and hemiparesis, first contralateral and then ipsilateral to the mass. A false localizing sign dubbed the Kernohan-Woltman notch phenomenon may be a source of confusion because it manifests with hemiparesis ipsilateral to the primary brain

lesion.[7] Central herniation involves bilateral supratentorial lesions that displace tissue symmetrically and bilaterally. Signs and symptoms of central herniation include decreased consciousness leading to coma and Cheyne-Stokes respiration followed by central hyperventilation, midposition unreactive pupils, and posturing. Tonsillar herniation involves increased pressure in the posterior fossa, which forces the cerebellar tonsil through the foramen magnum, thereby compressing the medulla. Signs and symptoms of tonsillar herniation include decreased consciousness and respiratory abnormalities leading to apnea. Headache is the most frequent symptom reported in increased ICP. Headache is a common symptom in any patient population, but in patients with cancer, clinicians must always maintain a high index of suspicion for increased ICP. Headaches caused by increased ICP are typically present on waking in the morning, recur throughout the day, and are increased with Valsalva maneuver; they can be associated with nausea and vomiting, altered mental status, vision changes, seizures, or focal neurologic deficits. On physical examination, the patient may have papilledema, focal neurologic deficits, or altered mental status.

The diagnosis of increased ICP can be ascertained from a CT scan of the brain. Noncontrast CT imaging is superior to MRI in detecting acute hemorrhage (Fig. 61–2).

CT scans with contrast will usually reveal cerebral metastasis and occasionally leptomeningeal disease (LMD). Contrast-enhanced MRI is more sensitive than CT in revealing cerebral tumors as small as 3 mm (Fig. 61–3), LMD (Fig. 61–4), and early strokes (Fig. 61–5). Lumbar puncture should not be used to diagnose increased ICP because it can lead to brain herniation.

The differential diagnosis of increased ICP includes bleeding, tumor edema, hydrocephalus, postradiation effects, postradiosurgery effects, brachytherapy-induced changes, benign tumor effects, subdural hematomas, meningitis, encephalitis, and abscess formation.

Brain metastases may develop in 10% to 40% of patients with cancer and may be increasing as the survival of patients with cancer is improving.[8] LMD occurs in 5% of all patients with cancer.[9,10] Two thirds to three quarters of brain metastases are recognized as multiple lesions on MRI. Lung cancer is the neoplasm that most frequently metastasizes to the brain followed by breast cancer and melanoma. Other cancers that commonly metastasize to the brain are colorectal, kidney, prostate, testicular, and ovarian cancers and sarcomas, although any systemic cancer can metastasize to the brain. Tumors most commonly metastasize to the gray–white junction where the vessels are small and narrow, trapping tumor emboli. Eighty percent of tumors metastasize to the cerebral hemispheres, 15% to the cerebellum, and 5% to the brainstem. The tumors that are often hemorrhagic include melanoma, renal cell carcinoma, and choriocarcinoma.



FIGURE 61–2 Acute intracranial hemorrhage within the right frontoparietal lobe (*arrows*) with edema (E) in a 79-year-old woman with ovarian cancer. The hemorrhage was revealed by noncontrast computed tomography imaging. This modality is superior to magnetic resonance imaging in detecting acute hemorrhage. (Used with permission from Dr. Ashok Kumar, MD Anderson Cancer Center.)

The treatment for increased ICP depends on the underlying cause. Infectious sources, such as meningitis, should be treated with antibiotics, and brain abscesses should be drained. Hydrocephalus should be treated with surgical shunting or ventriculostomy. Subdural hematomas should be either drained or, if small, monitored under the guidance of a neurosurgeon. Vasogenic edema associated with brain tumors is initially treated with oral or intravenous (IV) dexamethasone at a dosage of 16 to 28 mg/day in divided doses.[11] For patients with impending herniation, very large doses of IV dexamethasone can be used, initially 40 to 100 mg intravenously and subsequently 40 to 100 mg/day. Dexamethasone is the steroid of choice because of its lack of mineralocorticoid effect and therefore minimal effects on blood pressure and electrolytes. Steroid myopathy is a possible complication. Steroids may not be needed in asymptomatic brain lesions. If the ICP is increased by brain metastases and whole-brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS) is planned,[12] corticosteroid therapy should be started before radiation treatment to avoid further increased in ICP.

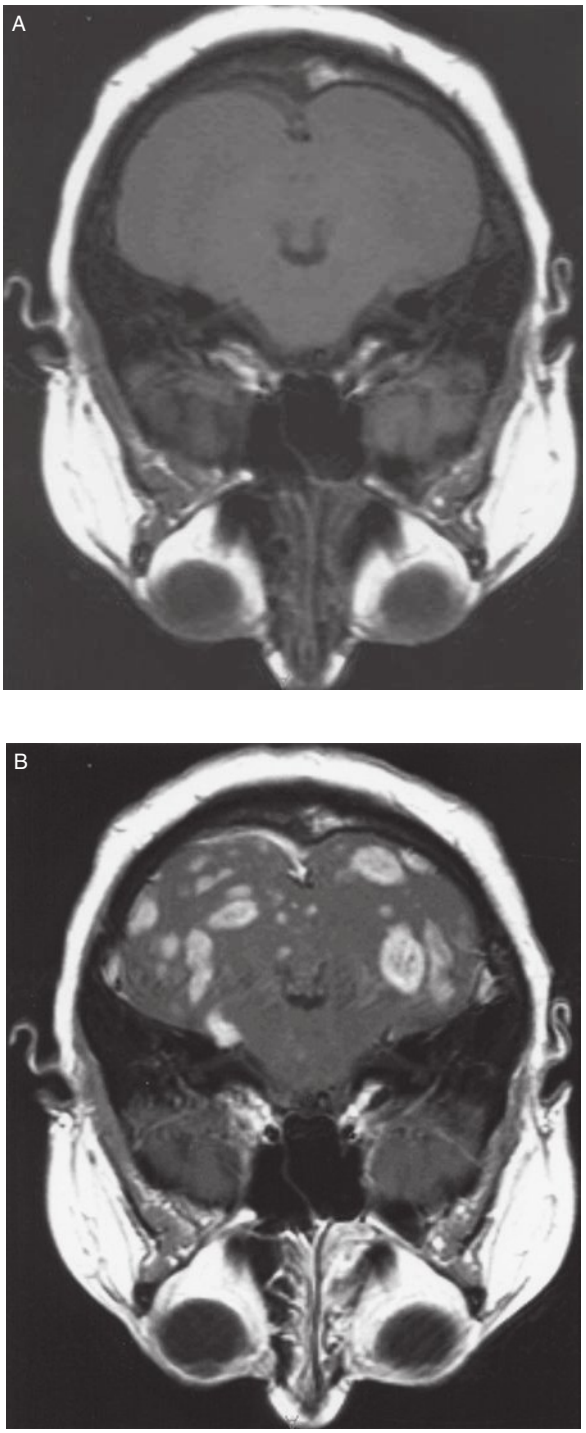


FIGURE 61–3 A. Precontrast T1-weighted magnetic resonance (images in a 40-year-old woman with breast cancer and multiple cerebellar metastases. **B.** Postcontrast images of the same patient reveal dramatic enhancement of the cerebellar metastases.

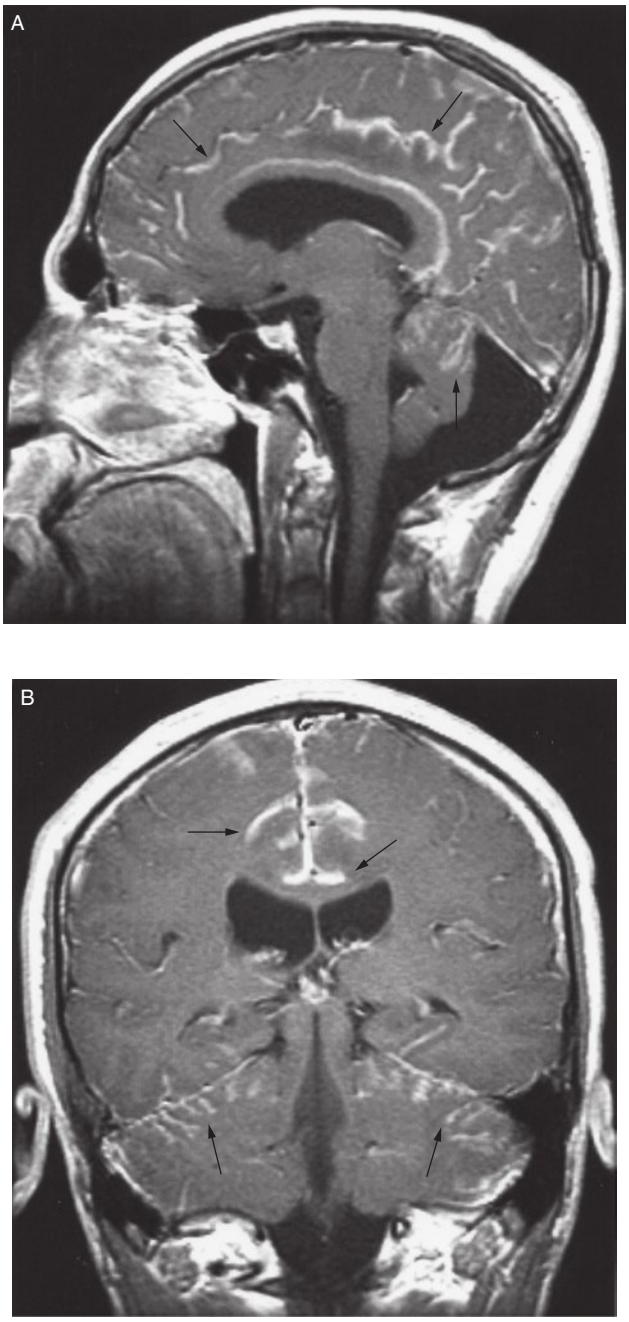


FIGURE 61–4 A. Sagittal postcontrast T1-weighted magnetic resonance image (MRI) showing subarachnoid spread of melanoma metastasis to the brain in a 29-year-old man. Abnormal enhancement of the cortical sulci (*large arrows*) and cerebellar sulci (*small arrows*) is noted. **B.** Coronal postcontrast T1-weighted MRI in the same patient. (Used with permission from Dr. Ashok Kumar, MD Anderson Cancer Center.)

For life-threatening edema, mannitol can be used to decrease ICP in patients with an intact blood–brain barrier.[11] Mannitol is a hyperosmotic agent that can draw fluid out of the brain into the circulation; its effect can be augmented by diuretics. The recommended dosage of mannitol is a 20% to 25% solution at 0.5 to 2.0 g/kg administered IV over 10 to 30 minutes. Mannitol has a rapid onset of action and lasts for hours. Hypertonic saline IV infusion is another therapy for increased ICP. Hyperventilation can be used to decrease ICP, but it

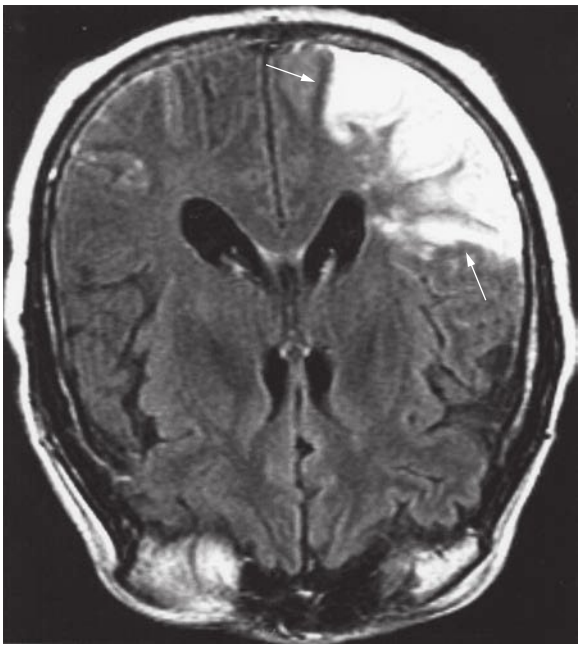


FIGURE 61–5 **Acute infarction involving the territory of the right middle cerebral artery in a 58-year-old patient with renal cell carcinoma. Magnetic resonance image (MRI; fluid-attenuated inversion recovery image) demonstrates abnormal thickening, with a T2-weighted increase in signal intensity (*arrows*) involving the right temporo-occipital lobe cortex and subcortical white matter. MRI is more sensitive than computed tomography in detecting early stroke. (Used with permission from Dr. Ashok Kumar, MD Anderson Cancer Center.)**

must be kept within the modest range of a PCO_2 of 25 to 30 mm Hg to prevent severe respiratory alkalosis.. For patients with brain lesions that are not amenable to surgery, SRS can be used in single doses as high as 1400 cGy. In a single SRS session, more than 10 brain lesions with a total volume of up to 25 mL can be treated. SRS plus WBRT may improve the overall survival in patients with brain metastasis compared with WBRT alone; however, this survival advantage may be limited to non–small cell lung cancer.[13]

Leptomeningeal Disease

LMD can involve invasion of the brain, the spinal parenchyma, the nerve roots, and blood vessels of the nervous system. LMD is commonly caused by metastatic breast and lung cancers, melanoma, non-Hodgkin lymphoma, and leukemia. Patients present with a variety of symptoms depending on the location of the leptomeninges affected, but they can include headache, altered mental status, cranial nerve palsies (in ~50% of patients), incontinence, back pain, sensory changes, seizures, isolated neurologic findings, and even a strokelike presentation.[9,14] Leptomeningeal metastases occur in 0.8% to 8% of all cases of cancer.

The diagnosis of LMD can be difficult to make. CT scans are occasionally suggestive of LMD. MRI scanning has better sensitivity than CT for detecting LMD, including leptomeningeal enhancement, hydrocephalus, and cortical nodules. However, MRI findings cannot definitively diagnose LMD because these imaging signs of inflammation of the meninges can also be found in cases of meningitis, trauma, infection, and hematoma formation. Lumbar puncture and evaluation of the CSF are the gold standard for diagnosing LMD, but multiple lumbar taps may be required to make the diagnosis because only 50% of patients have positive cytologic evidence of LMD on the first CSF evaluation. CSF findings consistent with LMD include a high opening pressure, low glucose and high protein levels, and a mononuclear pleocytosis.[9] Among patients with normal values for CSF protein, glucose, opening pressure, and cytology negative for LMD, fewer than 5% have LMD.

The treatment of patients with LMD can include chemotherapy through an implanted subcutaneous reservoir and ventricular catheter or through lumbar puncture instillation. Lumbar tap administration does not require placement of a catheter, but 10% to 15% of the subarachnoid space might be missed using this technique. Chemotherapeutic agents frequently used are methotrexate and thiotepa. Cytarabine can also be used in patients with leukemias and lymphomas, but it is generally not effective against solid tumors. Radiation therapy is commonly used for localized LMD or in areas of nerve root involvement where intrathecal chemotherapy is not likely to reach adequate concentrations.[14] Fixed neurologic deficits caused by LMD are not likely to improve with therapy, but encephalopathy may. The prognosis of patients with LMD is very poor, with a median survival time of 2 to 4 months and only a 15% to 25% chance of surviving more than 1 year.

Seizures

Seizures are the presenting symptom in 15% to 20% of patients with brain metastases. In patients with cancer presenting with seizures, metabolic, infectious, and coagulopathic causes should also be considered.[15] The initial laboratory work should include analysis of glucose level, electrolytes, blood urea nitrogen (BUN), creatinine, liver enzymes, calcium, urine analysis, lactic acid, prothrombin time (PT), activated partial thromboplastin time, and toxicology screening if indicated

Patients can have seizures during withdrawal from high-dose, short-acting benzodiazepines (eg, alprazolam), alcohol withdrawal, antibiotics (eg, the carbapenems), pain medicines (eg, meperidine), and many other medicines. The patient's family can be helpful in sorting out the etiology of seizures by providing

information about the patient's medications, social history, and preceding symptoms, such as fever or headache. CT without and with contrast is also helpful and can identify increased ICP, bleeding, or brain metastasis. Electroencephalography is also helpful in the evaluation of seizures and can determine whether an epileptic focus is present. Lumbar tap can be helpful if the seizures are believed to be secondary to infection or LMD, but this procedure should not be performed in patients with suspected increased ICP because of the risk of cerebral herniation.

Status epilepticus occurs when a patient has prolonged seizures lasting more than 30 minutes or recurrent seizures without full recovery of consciousness between seizures.[2,15,16] Initial care for patients with status epilepticus includes placing the patient in a safe environment, administering 100% oxygen by nonrebreather mask, monitoring with a continuous-pulse oximeter providing suction, and administering IV fluids (normal saline). Priority should be placed on protecting the airway and extinguishing the seizure, which can be treated initially with IV benzodiazepines (eg, diazepam, 0.2 mg/kg at 5 mg/min, up to 10 mg, or lorazepam, 0.1 mg/kg at 2 mg/min, up to 4 mg). For persistent seizures, fosphenytoin or phenytoin can be administered intravenously. Fosphenytoin can be given more rapidly and causes less hypotension than phenytoin, but continuous cardiac and blood pressure monitoring should be instituted during IV administration of 15- to 20-mg phenytoin equivalents per kilogram. Patients with persistent seizures might require intubation and sedation with phenobarbital (20 mg/kg intravenously at 100 mg/min) or other agents, such as pentobarbital or a midazolam drip. At this point, the patient requires careful monitoring and intensive care unit (ICU) care.

It is the general consensus that routine use of prophylactic antiepileptic drugs (AEDs) for patients with brain metastases who have not experienced a seizure is not indicated.[17] After seizures have been controlled, the patient should be placed on an AED. Several drugs can be used; among them are phenytoin, carbamazepine, clonazepam, gabapentin, lamotrigine, phenobarbital, primidone, topiramate, and valproate. For many of the newer AEDs, the serum drug levels do not need to be monitored. For medicines in which effective and safe levels have been defined, such as phenytoin, carbamazepine, phenobarbital, and valproate, the levels should be monitored carefully to limit toxic effects and maintain an effective preventive drug concentration.

Altered Mental Status

Altered mental status is a common neurologic complaint in patients with cancer, with metabolic encephalopathy being the most common cause.[18] Altered mental status can range from a slight decrease in normal intellectual functioning to coma. The patient's mental status may change in response to several factors, such as infections, metabolic derangements, bleeding, medications, hypoxemia, cancer therapies, paraneoplastic neurologic syndromes, and intracranial events, such as brain metastases.[19] Organ failure, whether hepatic, renal, adrenal, thyroid, or pulmonary, can also produce fluctuations in mental status. The most common metabolic deficiencies causing such alterations are hyponatremia, hypercalcemia, hypoglycemia, and vitamin B1 deficiency. The causes of altered mental status are numerous; an extensive history and physical examination can help to identify the underlying cause and determine appropriate therapy. The differential diagnosis and diagnostic evaluation are beyond the scope of this chapter, but a few entities are unique to patients with cancer.

For instance, cancer therapy is a common cause of altered mental status. Many neurologic manifestations, such as dementia, cognitive decline, and encephalopathy, can result from chemotherapy. Cancer immunotherapy can cause immune-mediated complications in the central nervous system (CNS). Table 61–1 highlights some of the common neurologic complications of chemotherapy.

Radiation therapy can also cause complications, among them leukoencephalopathy, radiation necrosis, and decreased memory and mental functioning. (The preceding section on increased ICP provides a fuller discussion of the cognitive side effects of radiation therapy.) Other possible causes of cognitive decline are narcotics (commonly prescribed for pain), infections (pneumonia, sepsis, urinary tract infection), and cerebral infarction.

CARDIAC EMERGENCIES

Cardiac Tamponade

Tumors involving the heart are much more frequently metastatic than primary. The tumors that most often metastasize to the heart are lung, breast, and GI tract cancers; leukemia; lymphoma; melanoma; and sarcoma. Metastatic involvement of the heart has also been noted in patients with leukemia and lymphoma. Certain therapies can also affect the myocardium and cause pericardial disease, such as cyclophosphamide and ifosfamide at high doses, all-*trans* retinoic acid (ATRA), and doxorubicin. Cardiac tamponade occurs when pericardial fluid accumulates and presses on the heart, increasing diastolic pressure in the ventricles and thereby decreasing stroke volume. The patient develops decreased cardiac output and systemic arterial pressure and can present with a shocklike syndrome. Most patients with pericardial

Table 61–1 Neurologic Complications of Chemotherapya

Chemotherapy	Seizure	Neuropathy or Sensory Changes	Encephalopathy	Cerebellar Symptoms	Vascular Events or Stroke	Cognitive or Dementia Nerve Palsy	Cranial	Visual Changes or Loss	Myelopathy	Other
BCNU	+		+		+	+	+	+		
Busulfan	+									
Cisplatin	+	+	+		+					Ototoxicity
Cytosine arabinoside		+	+	+		+			+	
Dacarbazine	+									
Docetaxel		+								
Doxorubicin								+		
Etoposide	+									
Fludarabine			+							
5-Fluorouracil			+	+						
Gemcitabine		+								
Ifosfamide	+	+	+	+						
Interferon	+		+			+				
Interleukin-2			+							
L-Asparaginase	+		+		+					
Methotrexate	+		+	+	+	+	+		+	
Paclitaxel	+									Gait abnormality
Procarbazine		+	+	+						
Tamoxifen			+					+		
Taxol		+								
Teniposide		+								
Thalidomide		+								
Thiotepa									+	
Vincristine	+	+		+		+	+	+		Vertigo, autonomic neuropathy
Vinorelbine		+								

[a]Not including immune-related adverse effects after cancer immunotherapy (eg, immune checkpoint inhibitors, chimeric antigen receptor T-cells).

effusions report no symptoms, but patients with cardiac tamponade present with shortness of breath, cough, hoarseness, epigastric pain, or chest pain that is made worse by lying down or leaning forward. On examination, the patient typically has distended neck veins, low systemic blood pressure, and decreased heart sounds (Beck's triad) with a low pulse pressure. Patients can also have a pericardial rub. The presence of pulsus paradoxus, which is an inspiratory decline in systolic blood pressure of more than 10 mm Hg, should be ruled out. Pulsus paradoxus can also occur in chronic obstructive pulmonary disease, pulmonary embolism (PE), right ventricular infarction, and shock. Chest radiographs often reveal a "water bottle" configuration if the effusion has accumulated slowly, but the cardiac silhouette can appear normal if the effusion accumulates rapidly. Prior chest radiographs can be useful in determining changes in the size of the cardiac silhouette. The electrocardiogram (ECG) might reveal electrical alternans (a variation of voltage in individual QRS complexes) and low-voltage or ST-segment and T-wave changes. Transthoracic echocardiography is the best test to determine whether tamponade exists. If cardiac tamponade is present, echocardiography can help determine whether the effusion is localized or loculated, and it can also aid in planning pericardiocentesis. On echocardiograms, tamponade can be evidenced by collapse of the right ventricle and atria in diastole (Fig. 61–6).

Treatment of patients with tamponade includes the administration of oxygen, IV fluids, and vasopressors if necessary. Pericardiocentesis can be performed under ultrasound guidance and is relatively safe. At MD Anderson Cancer Center (MDACC), a drainage catheter is commonly placed in patients with tamponade, with drainage performed daily. When the total volume of fluid drained is less than 50 mL/day, the catheter can be removed. A pericardial window can also be created to prevent reaccumulation of fluid. Radiation therapy and chemotherapy can also be used to prevent reaccumulation of fluid, as can sclerosis of the pericardial sac.

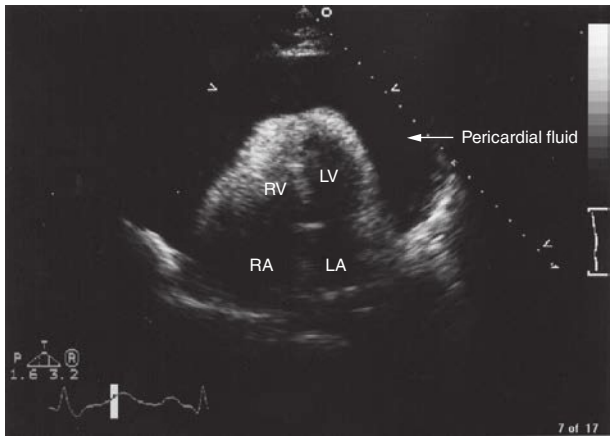


FIGURE 61–6 Two-dimensional echocardiogram in the apical four-chamber view demonstrating a large pericardial effusion. The right ventricle is not well visualized because of acoustic shadowing, which commonly occurs with large effusions. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (Used with permission from Dr. Joseph Swafford, MD Anderson Cancer Center.)

Superior Vena Cava Syndrome

Superior vena cava (SVC) syndrome is characterized by low blood flow from the SVC to the right atrium. Malignancy is by far the most common cause of SVC syndrome, although nonmalignant causes, such as indwelling central venous catheters, aneurysms, and goiters, can also cause this syndrome. Lung cancer is the most common malignant neoplasm causing SVC syndrome, but lymphoma, breast and GI cancers, sarcomas, melanomas, prostate cancer, and any mediastinal tumor can also cause this disorder. Among mechanisms that can lead to this syndrome are extrinsic compression by tumor, intrinsic compression by tumor or clot, or fibrosis. Patients may present with headache; dizziness; confusion; swelling of the upper extremities, face, and neck; shortness of breath; and dysphagia. Physical examination often reveals engorgement of veins and collaterals in the upper extremities caused by elevated pressure in the venous system.

Diagnosis of SVC syndrome requires imaging. Routine chest radiographs often reveal mediastinal widening, a right-sided chest mass, or a mediastinal mass. CT scanning of the chest using IV contrast is an excellent means of delineating the cause of the obstruction and any associated finding (Fig. 61–7). MRI, Doppler ultrasound, and radionuclide venography can be used to exclude the presence of a clot.

The treatment of SVC syndrome depends on the nature of the obstruction. Patients might respond to elevation of the head, corticosteroids if the ICP is increased, and occasionally diuretics. If thrombosis is present, local lytic therapy or anticoagulation can be used. It is important to obtain a tissue specimen of the tumor if its type is not known, so that it can be treated adequately. For patients with tumors that are chemosensitive, such as small cell lung cancer, chemotherapy can be instituted. Patients with non–small cell lung cancer often respond to radiation therapy. Intravascular stenting is effective and can provide prompt symptom relief.[20]

Myocardial Ischemia

Patients with cancer may present to the emergency center with myocardial ischemia.[21] A full discussion of ischemic heart disease is beyond the scope of this chapter, but there are special considerations in patients with cancer that should be mentioned.

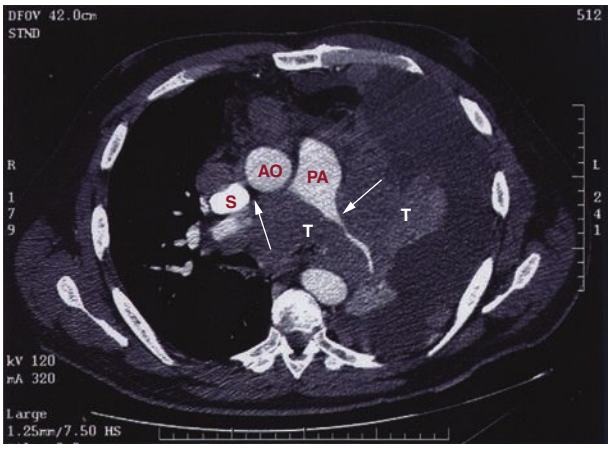


FIGURE 61–7 **Computed tomography scan revealing superior vena cava (SVC) syndrome from extrinsic compression of the SVC in a patient with non–small cell lung cancer. The *large arrow* indicates compression of the left pulmonary artery; the *small arrow* indicates obliteration of the right pulmonary artery. AO, aorta; PA, main pulmonary artery; S, superior vena cava; T, tumor. (Used with permission from Joel Dunnington, MD Anderson Cancer Center.)**

Many patients with cancer have thrombocytopenia caused by chemotherapy, radiation therapy, or bone marrow infiltration with tumor. Despite platelet counts in the single or double digits, these patients can still present with acute cardiac syndrome. Although the practitioner might feel uncomfortable giving aspirin to these patients, cardiologists at MDACC have found that patients with platelet counts less than 50,000/μL who have cardiac ischemia and are treated with aspirin have a better 24-hour survival rate than those who are not given aspirin.[22]

Certain chemotherapeutic agents can predispose patients to myocardial ischemia, including 5-fluorouracil (5-FU) and presumably capecitabine, which is a metabolite of 5-FU.[23] Radiation therapy can also be a predisposing factor for coronary artery disease. It is important to consider myocardial ischemia in patients who have undergone any of these therapies, especially those who otherwise have no risk factors for ischemic heart disease.

The cardiac markers troponin, creatine phosphokinase (CPK), and CPK-MB (creatine phosphokinase myocardial band) are useful in diagnosing myocardial infarction. Cardiac troponins are more sensitive and specific markers for ischemic heart disease than CPK-MB, which can be influenced by skeletal muscle injury; however, cardiac troponin levels can also be raised by chronic renal insufficiency, cardiomyopathy with severe congestive heart failure, myocarditis, and PE. For patients with PE, increased cardiac troponin is associated with increased right ventricular dilation (right ventricular–to–left ventricular ratio >1.2) and increased severity of hemodynamic consequences.[24] In patients with small increases of troponin, PE can be the cause rather than ischemic heart disease; this possibility should be considered in patients presenting with chest pain.

HEMATOLOGIC EMERGENCIES

Hyperviscosity Syndrome

Hyperviscosity syndrome is caused by abnormally high concentrations of paraproteins in the serum, which increase viscosity and cause red blood cell (RBC) sludging and low oxygen delivery to the tissues. This disorder occurs in 15% of patients with Waldenstrom macroglobulinemia, which is characterized by the presence of high molecular-weight (immunoglobulin [Ig] M) macromolecules and thus predisposes patients to this syndrome. Aggregation of IgG macromolecules and polymerization of IgA macromolecules, as well as purely light-chain myeloma are also capable of causing this syndrome.[25] Other conditions that can cause hyperviscosity syndrome are polycythemia vera, dysproteinemias, and occasionally leukemias.

Hyperviscosity syndrome can present with either bleeding because of abnormal platelet functioning or thrombosis caused by hyperviscosity. Visual complaints, headache, dizziness, alterations in mental status, and mucosal bleeding are all symptoms of hyperviscosity syndrome. Patients can also develop retinal hemorrhages, congestive heart failure caused by increased plasma volume, peripheral neuropathy, weakness, and fatigue.[25] Funduscopic examination can reveal venous dilatation, retinal vein occlusion, or papilledema (Fig. 61–8).

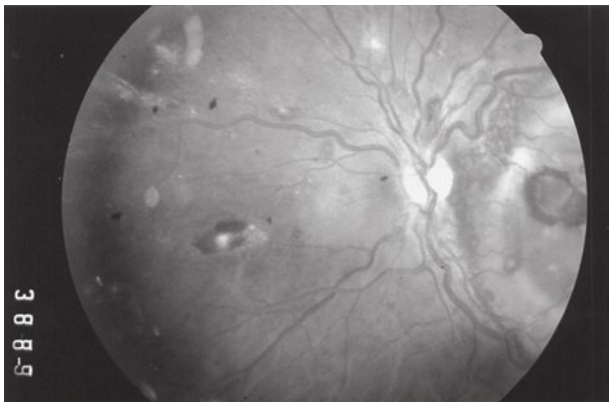


FIGURE 61–8 **Funduscopic examination revealing a Roth spot (the white-centered retinal hemorrhage). The Roth spot is the hallmark of leukemic retinopathy. (Used with permission from Dr. Bita Esmaeli, MD Anderson Cancer Center.)**

The diagnosis is made on the basis of a high serum viscosity. Normal serum viscosity ranges between 1.4 and 1.8 Ostwald units (relative to water, at 1). Patients start to develop symptoms when serum viscosity exceeds 4.0 Ostwald units.[26] The treatment for hyperviscosity syndrome includes the administration of IV fluids followed by diuresis. Plasma exchange can decrease symptoms quickly and can be followed by chemotherapy.[26]

Hyperleukocytosis

Hyperleukocytosis is typically defined as a white blood cell (WBC) count in the peripheral blood higher than 100,000/μL.[27] Acute myelogenous leukemia (AML), chronic myelogenous leukemia, and less frequently (because of the smaller size of the lymphocytes) acute and chronic lymphocytic leukemia are associated with leukostasis. From 5% to 30% of adult patients with acute leukemias present with leukostasis that requires prompt recognition and initiation of therapy to prevent respiratory failure or intracranial hemorrhage. The WBC count in patients with acute lymphocytic leukemia typically must be greater than 400,000/μL before leukostasis develops. The highest rate of mortality is in patients with AML who have high blast counts.

Symptoms of hyperleukocytosis are headache, dizziness, vertigo, shortness of breath, altered mental status, and hemoptysis. WBCs are poorly deformable and can become lodged in the microvasculature of the kidneys, lungs, brain, and other organs. The pulmonary and neurologic systems are most critically affected in hyperleukocytosis syndrome. In the lungs, WBCs can get caught in the pulmonary circulation, causing adult respiratory distress syndrome (ARDS), or can mimic PE because of WBC stasis in the pulmonary vasculature, thereby causing a ventilation/perfusion mismatch. Patients with the latter condition should not be given diuretics because they further increase stasis. Most patients with leukemia are anemic; this condition can offset the WBC elevation, so hyperviscosity is not as common in these patients. It is important not to give these patients blood transfusions unless absolutely necessary because this treatment can exacerbate hyperleukocytosis and increase the blood cell mass without changing the total blood volume. Patients can present with altered mental status, which can be caused by endothelial leakage from the small vessels of the brain or hemorrhage, but other causes of altered mental status should also be considered, including infection, LMD, and metabolic sources. Imaging studies, such as CT or MRI, as well as lumbar tap should be performed when indicated.

The treatment of patients with hyperleukocytosis involves lowering the WBC count, which can be accomplished with leukapheresis or chemotherapy. Leukapheresis can lower the WBC count by 30% to 60% from pretreatment levels. These effects can be transient; therefore, repeat leukapheresis might be necessary. Patients undergoing leukapheresis should also be monitored closely to prevent tumor lysis syndrome (TLS).

Thrombosis

Venous thromboembolism (VTE) is influenced by Virchow triad: venous stasis, higher-than-normal coagulability, and intimal injury. Patients with cancer have a high risk of VTE, and up to 15% of patients develop VTE because of hypercoagulability, the use of central venous catheters (vascular injury), and venous stasis (Virchow's triad).[28] Patients with cancer can have increased serum viscosity because of dehydration or, less frequently, hyperviscosity syndrome (described previously). Stasis and intimal injury can be caused by numerous events—for example, tumor encroachment on blood vessels or indirect effects of cancer, such as spinal cord compression, brain metastasis, dehydration, or impaired ambulation. Some chemotherapeutic cancer agents can also induce VTE; among them are tamoxifen, cisplatin, cyclophosphamide, methotrexate, and 5-FU.

Symptoms of PE include chest pain, shortness of breath, palpitations, and syncope. ECG findings can include T-wave inversion in the precordial leads, sinus tachycardia, right bundle branch block, or rightward shift of the QRS axis. Chest radiographs can be normal or might reveal a pleural effusion or elevation of the diaphragm on the involved side. Physical examination can reveal tachypnea, tachycardia, and leg edema or erythema in the case of associated deep vein thrombosis (DVT).

Diagnosis of PE can be made by spiral CT angiography (currently the most commonly used method), radionuclide perfusion/ventilation (V/Q) scan, pulmonary angiography, or MRI (Fig. 61–9).

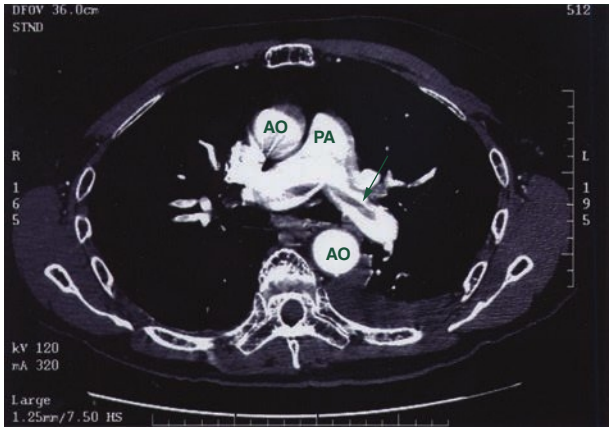


FIGURE 61–9 **Spiral computed tomography angiogram in a patient with a saddle pulmonary embolism (*arrow*). AO, aorta; PA, main pulmonary artery. (Used with permission from Joel Dunnington, MD Anderson Cancer Center.)**

Table 61–2 Heparin Dosage Schedule for Venous Thromboembolism

Low-molecular-weight heparin	
Enoxaparin	1 mg/kg SC every 12 hours or 1.5 mg/kg SC every 24 hours
Dalteparin	200 IU/kg SC every 24 hours or 100 IU/kg SC every 12 hours; maximum dosage, 18,000 IU
Tinzaparin	175 anti-Xa activity IU/kg SC every 24 hours
Unfractionated heparin	80-IU/kg IV bolus, with a maintenance IV dose of 18 IU/kg/day (adjusted to keep PTT at 1.5–2.5 times the normal range)

PTT, partial thromboplastin time; SC, subcutaneously.

Clinical suspicion based on the patient's risk factors and results of other tests can guide the clinician regarding the patient's pretest probability of PE. Spiral CT scanning and MRI can detect segmental PE but not necessarily subsegmental PE. Both of these tests are useful in that they give further information about the condition of the lung, such as whether pneumonia is present, tumor size, and impingement on the bronchial airways; this additional information is helpful in determining the cause of the patient's symptoms. Pulmonary angiography remains the gold standard in detecting PE, although it requires more dye than other contrast methods and a greater risk of renal complications. The alveolar-arterial gradient (A-a gradient) from an arterial blood gas (ABG) can serve to corroborate the diagnosis of PE. In the PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) study, ABG results were normal in 14% of patients with preexisting cardiopulmonary disease and in 38% of patients with no underlying cardiopulmonary disease despite the presence of pulmonary emboli.[29]

The diagnosis of DVT can be made by Doppler ultrasound, impedance plethysmography (IPG), venography, nuclear venogram, or magnetic resonance venography

The D-dimer test can also be used in the evaluation of VTE; normal results are associated with a significantly lower likelihood of VTE than high value, but are not helpful in patients with leukemia or lymphoma.[30] D-Dimer has a high negative predictive value for PE in patients with cancer, and a normal D-dimer can be used to exclude PE in patients with cancer. Because D-dimer is commonly high in patients with cancer, an elevated D-dimer is not useful in diagnosing VTE. The American College of Physicians guideline for PE has good sensitivity for detecting PE in patients with cancer, and using these guidelines in patients with cancer with suspected PE may reduce unnecessary imaging and laboratory tests.[31]

First-line treatment for VTE consists of either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). LMWH has the advantage that factor Xa levels usually do not have to be monitored because protein binding is low. LMWH also has a longer half-life than UFH and thus can be given less frequently (once or twice per day). The LMWHs enoxaparin, tinzaparin, and dalteparin are all different and cannot be used interchangeably. Monitoring may be required for patients with obesity and renal insufficiency because LMWH is cleared by the kidneys. When monitoring is necessary, the Xa level should be measured 4 hours after the injection, with a target level ranging from 0.6 to 1.0 IU/ mL for twice-daily dosing. For daily dosing, the Xa level should range between 1.9 and 2.0 IU/mL. For patients who will be transitioned to warfarin treatment, there should be an overlap of at least 5 days with LMWH. Although VTE can often be treated on an outpatient basis, patients not eligible for outpatient treatment are those with active bleeding, major comorbid illnesses, a history of heparin-induced thrombocytopenia, hypertensive emergencies, major surgery or trauma within the previous 2 weeks, recent GI bleeding, stroke or transient ischemic attack, severe renal dysfunction, or a platelet count below 50,000/μL. Table 61–2 shows the dosing schedule.

Most patients are treated for at least 3 to 6 months. Patients from whom the central venous catheter has been removed can undergo repeat testing using such techniques as Doppler ultrasound or nuclear venous flow study to determine whether the clot has resolved, so that cessation of anticoagulation therapy may be considered. For patients with small clots at the distal tip, manifested by the inability of the central line to work, tissue plasminogen activator can be given carefully provided that there are no contraindications.

Inferior vena cava (IVC) filters can be used for patients who cannot tolerate anticoagulation therapy or poor response or failure of optimal anticoagulation therapy. IVC filters do not decrease peripheral edema from DVT and, in fact, can serve as a nidus for further clot formation. Although IVC filters can prevent life-threatening PE, long-term complications can be significant in cancer survivors and end-stage patients with cancer may gain little benefit. Patients with massive PE may require thrombolysis or embolectomy. See Table 61–3 for a synopsis of the relative and absolute contraindications for thrombolytic therapy and Table 61–4 for thrombolytic doses.

Patients with cancer and VTE should be treated indefinitely if the cancer remains active or for at least 3 to 6 months after resolution of the VTE if the cancer is no longer active.[32] Patients who are treated with warfarin but who experience warfarin failure

Table 61–3 Absolute and Relative Contraindications to Thrombolysis

Absolute Contraindications to Thrombolysis
Major intracranial surgery or trauma within prior 2 months
Cerebrovascular hemorrhage within prior 3–6 months
Active intracranial neoplasm
Major internal hemorrhage within prior 6 months
Severe bleeding diathesis, including those associated with severe liver or renal disease
Relative Contraindications to Thrombolysis
Prolonged cardiopulmonary resuscitation
Pregnancy or postpartum period within prior 10 days
Nonhemorrhagic stroke within prior 2 months
Major trauma or surgery (excluding that of the central nervous system) within prior 10 days
Thrombocytopenia (platelet count <100,000/mm^3)
Hemorrhagic retinopathy
Allergies to thrombolytic agents
Minor surgery to noncompressible vessels within prior 10 days
Tissue biopsy within prior 10 days
Peptic ulceration within prior 3 months
Infective endocarditis or pericarditis
Uncontrolled hypertension (systolic BP ^{3}200 mm Hg or diastolic BP ^{3}110 mm Hg)
Aortic aneurysm

BP, blood pressure.
Adapted with permission from Yeung SJ, Escalante CP: Oncologic Emergencies. Hamilton, Ontario, Canada: BC Decker; 2002.

as evidenced by the recurrence or progression of clot formation can be switched to LMWH.[32] Direct oral anticoagulants (DOACs) reduce the risk of venous and arterial thromboembolism in large randomized clinical trials and provide oral alternatives for anticoagulation in patients with cancer. Apixaban, edoxaban, and rivaroxaban are efficacious in patients with cancer, but DOACs are associated with increased risk of bleeding, especially in GI tract or urinary tract patients with cancer. For starting anticoagulation using DOACs in the emergency department, rivaroxaban (15 mg orally twice daily for 21 days; then 20 mg daily) or apixaban (10 mg orally twice daily for 7 days; then 5 mg twice daily) are two options. The choice of anticoagulant for patients with cancer should consider individualized bleeding and thrombotic risks, drug interactions, and patient preferences.[33]

Aspiration mechanical thrombectomy is likely an efficacious treatment for patients with massive and submassive PE and contraindications to thrombolysis.[34] Surgical thrombectomy should be used for patients with massive PE who are hemodynamically unstable and who either have contraindications for thrombolytic therapy or have previously failed thrombolytic therapy. Catheter-based embolectomy methods and surgical thrombectomy both can improve hemodynamics, and the clinical outcomes may be comparable. The choice of therapy will need to consider the local expertise and experience, potential need for periprocedure support, and surgical risk of the patient.[35]

Table 61–4 Dosages of Thrombolytics

Streptokinase	250,000 IU IV load over 30 min; then 100,000 IU/hr for 24 hours for pulmonary embolism or 72 hours for DVT
Urokinase	4400 IU/kg IV load over 10 min; then 4400 IU/kg/hr for 12 hours
Alteplase	100 mg IV infusion over 2 hours; initiate heparin at the end of alteplase infusion

DVT, deep venous thrombosis; IV, intravenous.

Bleeding

Bleeding in patients with cancer is most commonly caused by thrombocytopenia induced by chemotherapy, marrow infiltration, disseminated intravascular coagulopathy (DIC), extensive radiation therapy, splenic sequestration, peripheral destruction, or infection. Thrombocytopenia usually manifest as mucocutaneous bleeding, such as gum oozing, epistaxis, and

gynecologic or GI bleeding. At MDACC, all patients generally receive platelet transfusions if their platelet count falls to 10,000/μL or below in patients without active bleeding or less than 50,000/μL with active bleeding. The American Society of Clinical Oncology (ASCO) recommends prophylactic platelet transfusions for patients being treated for leukemia and those receiving bone marrow transplants if their platelet counts are below 10,000/μL. A patient will also receive a platelet transfusion if an invasive procedure is planned and his or her platelet count is below 50,000/μL. Transfusion thresholds may be higher for patients with fever, hyperleukocytosis, a rapid fall in platelet count, coagulation abnormalities, or active bleeding. ASCO recommends that patients with chronic stable thrombocytopenia who are not undergoing active treatment, such as those with aplastic anemia and patients with myelodysplastic syndrome, be monitored and given platelets only for active bleeding even if their platelet counts are below 10,000/μL. For patients with solid tumors, prophylactic platelet transfusions should be given if the platelet counts are below 10,000/μL unless the tumor is necrotic or is located in the bladder and undergoing treatment; in those cases, the threshold for transfusion should be 20,000/μL. According to ASCO's guidelines, platelet counts of 50,000/μL should be sufficient for invasive procedures, such as surgery. For lumbar puncture, the platelet count should be above 20,000/μL. Patients with AML commonly receive multiple transfusions and can develop alloimmunization against human leukocyte antigens (HLAs). Approximately 25% to 35% of patients with AML will become alloimmunized and refractory to nonhistocompatible platelet transfusions, predominantly through their exposure to leukocytes. Random-donor platelets are derived from pooled platelet concentrates from whole-blood donations, whereas single-donor platelets are obtained from one donor by platelet pheresis. The likelihood of alloimmunization can be decreased by using single-donor platelets, leukocyte-depleted platelets, leukocyte filters, and ultraviolet-irradiated platelets. ASCO recommends that patients who are platelet refractory not receive platelet transfusions unless they are hemorrhaging or HLA-compatible platelets are available.[36]

DIC can cause bleeding and thrombosis. DIC should be suspected in a patient who has an unexplained elevation in PT, partial thromboplastin time (PTT), or thrombocytopenia with associated bleeding or thrombosis. Although bleeding is most often noted in patients with DIC, the thrombosis of small (and occasionally large) blood vessels leads to the most serious complications. Collaborative laboratory findings are high d-dimer and fibrin split product levels, low levels of fibrinogen and thrombin-antithrombin III, or the presence of schistocytes. It is important to remember that DIC is a clinical diagnosis based on the entire clinical scenario, and results for these laboratory tests might not be abnormal. Patients can also have mildly abnormal test results in cases of subclinical DIC; these patients should be monitored closely for conversion to overt DIC.

Tumors can cause DIC, especially adenocarcinomas of the breast, prostate, stomach, lungs, and colon. In this instance, the disorder is believed to be stimulated by mucin produced from these cancers. Leukemia, especially acute promyelocytic leukemia (APL), is associated with DIC in up to 85% of patients because of a tissue factor in APL that has procoagulant activity. Other tumors associated with DIC are melanoma, lymphoma, and ovarian and pancreatic cancers. Other causes of DIC are sepsis, acidosis, extensive burns, the use of Denver catheters or LaVeen shunts in patients with malignant ascites, hemolytic blood transfusion reactions, polycythemia rubra vera, and amniotic fluid embolism.

Patients who have both DIC and bleeding can present with oozing from multiple sites, such as arterial or venous punctures or the mucous membranes, with GI, or with epistaxis. Thrombotic complications can be visible on the skin in the form of hemorrhagic bullae, acral cyanosis, or even gangrene. Microvascular thrombosis most commonly affects the lungs, brain, and kidneys. The patient may develop shortness of breath, pleuritic chest pain, and ARDS. The kidneys can become clogged with microemboli, in which case patients often present with oliguria, anuria, hematuria, or proteinuria. The small vessels of the brain also can receive microemboli, causing strokes, seizures, altered mental status, or coma. As the patient deteriorates, hypotension, acidosis, and hypoxia can develop.

The treatment of DIC should focus on reversing the underlying cause or trigger, such as treating an underlying infection.[37] Acidosis, high catecholamine release, vasoconstriction, and corticosteroid use can exacerbate thrombosis associated with DIC. Additional therapeutic measures for thrombosis can include heparin administration at 15 U/kg/hour by continuous infusion. When the patient is bleeding, blood components (including platelets) can be transfused to correct coagulation abnormalities. Platelet transfusions are indicated to maintain platelet counts of at least 50,000/μL. Cryoprecipitate should only be used for severe hypofibrinogenemia (<50 mg/dL; <100 mg/dL if patient is actively bleeding). Cryoprecipitate can be given at 0.2 bags per kilogram of body weight, and the fibrinogen level should be tested 20 to 60 minutes after the infusion and every 6 hours thereafter until the bleeding has stopped. Fresh-frozen plasma can be transfused at 10 to 15 mg/kg to correct abnormalities in PT. Other products that might be needed are prothrombin complex, antithrombin concentrates, or washed RBCs. For patients with persistent bleeding, fibrinolytic

inhibitors, such as ε-aminocaproic acid (EACA) and tranexamic acid, can be given. EACA should always be given with heparin to prevent thrombosis; because EACA can cause hypotension, ventricular arrhythmias, and hypokalemia, it should be used with caution. Tranexamic acid is a newer fibrinolytic inhibitor that has fewer side effects and has been used successfully in DIC associated with APL.

GENITOURINARY EMERGENCIES

Hemorrhagic Cystitis

Hemorrhagic cystitis is inflammation or bleeding of the bladder; it can be caused by radiation therapy, viral infection, or chemotherapy. Radiation-induced bladder bleeding can present as early as 3 months or as late as 5 years after the termination of radiation therapy. Chemotherapeutic agents associated with hemorrhagic cystitis are cyclophosphamide and ifosfamide (because of the liver metabolites secreted during use of these compounds, namely, acrolein and chloroacetaldehyde). The mechanism by which cyclophosphamide and ifosfamide metabolites are toxic to the urinary bladder is not known, but they have been implicated as the cause of hematuria.[38] Mesna is a thiol compound that binds acrolein, chloroacetaldehyde, and other metabolites of cyclophosphamide and ifosfamide; when it is administered before the patient receives the chemotherapeutic agents, the incidence of bladder toxicity can be decreased. Forced diuresis and adequate hydration (hyperhydration) complement mesna administration.[39]

In addition to radiation therapy and chemotherapy-inducing hemorrhagic cystitis, the BK virus (a polyomavirus) can become activated in immunocompromised patients undergoing bone marrow transplantation and cause hematuria.[40]

Treatment of hemorrhagic cystitis involves gentle bladder irrigation to remove any clots and decompress the bladder. Any coagulopathy, such as thrombocytopenia, should be corrected, as should manifestations of DIC, such as low fibrinogen levels or an elevated PT or PTT. For patients with persistent bleeding, prostaglandins E_2 or F_2, 1% alum, or formalin can be instilled. Formalin instillation is painful and requires general or spinal anesthesia. To correct continued bleeding, some patients require surgery, hypogastric artery embolization, or open surgical intervention.

Urinary Tract Obstruction

Obstructive uropathy can be secondary to outflow obstruction or impingement on the ureters or kidneys; it can also be caused by tumor invasion, radiotherapy-induced changes, or indirect effects of the tumor, such as ascites, lymphadenopathy, or fibrosis. A patient who is unable to urinate should have a Foley catheter placed. In patients with benign prostatic hypertrophy (BPH) and bladder outlet obstruction, a coudé catheter can often be inserted more easily. The catheter should not be forced, and, if the bladder cannot be accessed, a suprapubic catheter may be necessary. A lack of residual urine in the absence of severe dehydration usually indicates either obstruction at a more proximal level in the urinary system or acute anuric renal failure. Patients who have residual urine may be unable to urinate because of a mechanical cause, such as BPH, urethral stricture, tumor impingement, or stone obstruction. Other possible causes of acute urinary retention are infection, spinal cord compression, viral radiculomyelitis, postsurgical effects interrupting bladder innervation, or medicines such as pain medications, anticholinergics, or antihistamines.[39] In each case, the underlying disorder should be treated. Patients with BPH can undergo a trial of α blockers, such as terazosin, prazosin, doxazosin, or finasteride, a type II 5-α–reductase inhibitor. Transurethral resection of the prostate can be considered for patients who do not respond to medical treatments.

Laboratory values are also useful in differentiating prerenal, postrenal, and renal failure. Patients with prerenal failure typically have a high ratio of BUN to creatinine of more than 20 to 1, although upper tract GI bleeding, corticosteroid use, and high protein intake can also increase the BUN-to-creatinine ratio. Acute urinary obstruction can present as flank pain, whereas chronic obstruction is often painless, with patients presenting with anuria or decreased urine output. The tumors most likely to cause ureteral obstruction are cervical, prostate, bladder, ovarian, breast, and GI cancers as well as lymphoma.[39] Patients with infected urine and obstruction may also present with symptoms of urosepsis, including fever, confusion, and a high WBC count.

CT scanning of the abdomen is good for evaluating the cause of ureteral obstruction in that it can elucidate the nature of the obstruction. Other tests that can be used are MRI, renal ultrasound, IV urography, retrograde pyelography, and radionuclide renography. Helical CT scanning of the abdomen has the added benefit of avoiding the use of IV contrast. Urinary obstruction can be managed with ureteral stents or percutaneous nephrostomy tubes with or without internal stents; the stents or tubes are typically placed under guidance by interventional radiology. Many patients with stents develop infection, which often requires hospitalization, IV antibiotics, and stent replacement. Other possible complications are stent clogging and stent migration. The "double J" stent, which is now most frequently used, is anchored in the bladder and

the renal pelvis, so that stent migration is less common than it once was. Open surgical procedures are much less frequently performed now than in the past and are generally reserved for patients in whom endourologic procedures have failed.

RESPIRATORY EMERGENCIES

Airway Obstruction

Airway obstruction can be caused by intraluminal tumor growth or compression of the airway by an extraluminal tumor. Rigid or flexible bronchoscopy can be used to both diagnose and treat airway obstruction. Patients with severe respiratory distress and airway obstruction should undergo endotracheal intubation distal to the obstruction before the obstruction is treated. After the airway has been stabilized, the obstruction can be treated. The methods that can be used to provide expedient relief of airway obstruction include laser treatment, argon plasma coagulation (APC), electrocautery, endobronchial balloon dilation, and stent placement. APC can be achieved through flexible or rigid bronchoscopy at a relatively low cost and degrades the obstructive tissue by increasing its temperature. Electrocautery is also relatively inexpensive and can provide immediate relief of the obstruction, but side effects can include fire, hemorrhage, and electric shock. Rigid bronchoscopy can be used to treat extraluminal tumors by metal or silicone stent placement; this technique is most useful for tracheal or main bronchial disease. Metal stents can promote the growth of granulomatous tissue, whereas silicone stents are more likely to develop mucous plugging and to migrate. Laser therapy can also be used for endobronchial lesions, with the possible side effects of hemorrhage, pneumothorax, and pneumomediastinum. Laser therapy is more expensive than the other techniques and requires a skilled technician. Other methods that can be used for airway obstruction are cryotherapy, brachytherapy, and photodynamic therapy, although in many cases, these do not provide rapid relief (Table 61–5).

Table 61–5 Bronchoscopic Methods of Treating Dyspnea from Tumor Obstruction

Tumor Type	Tumor Location: Intraluminal (I) or Extraluminal (E)	Rate of Relief of Dyspnea Symptoms: Immediate (I) or Delayed (D)	Complications or Disadvantages	Advantages or Uses
Argon plasma coagulation	I	I		Low cost
				Ease of use
				Rapid coagulation
Brachytherapy	I	D	Fistula	Best used in small epithelial tumors
			Hemoptysis	
Cryotherapy	I	D		Less expensive
Electrocautery	I	I	Fire	Less expensive
			Hemorrhage	
			Shock	
Laser	I	I	Bleeding	Special training; expensive equipment
			Pneumothorax	
			Pneumomediastinum	
Photodynamic therapy	I	I	Phototoxicity	
			Hemoptysis	
			Bronchial obstruction caused by debris	
Stent placement	I or E	I	Migration of stent	Used in tracheal or main bronchial disease

Hemoptysis

Massive hemoptysis is defined as bleeding into the airway at a rate of greater than 100 mL/day, although any amount of blood that compromises the airway can be considered massive. Some 5% to 14% of hemoptysis cases are massive hemoptysis.[41] Up to about one fifth of patients with lung cancer experience hemoptysis at some point, and about 3% have massive hemoptysis.[42] In addition to structural abnormalities in the lungs, bleeding can be caused by chemotherapy or other medications, sepsis, fungal infections, and thrombocytopenia. Death from this type of hemorrhage usually results from asphyxiation rather than anemia or blood loss.

The most important aspect of managing massive hemoptysis is protecting the airway. If the right lung is affected, the left lung can be selectively intubated through bronchoscopy. Use of a rigid bronchoscope allows for removal of the tumor or clots, whereas flexible bronchoscopy allows access to the more distal airways. If the left lung is affected, the right lung should not be selectively intubated because inadvertent collapse of the right upper lobe can ensue. A single-lumen endotracheal tube is easier to place than a double-lumen tube and allows a larger area for evacuation of blood and clots. The patient should lie on the side of the bleeding lung to promote aeration of the unaffected lung. Any coagulopathy should be corrected, and cough should be suppressed with codeine or other agents. If a tumor is causing the bleeding and it can be localized, the patient can undergo bronchial artery embolization or tumor resection. If the tumor is unresectable, external-beam radiation therapy can be used. If only the location of the bleeding can be determined, a solution of 1:10,000 epinephrine can be injected. Other means of halting bleeding are laser treatment, electrocautery, APC, photocoagulation, balloon tamponade, and iced-saline lavage.

Toxic Lung Injury

ARDS is a serious condition that can be a complication of infection or chemotherapy. ATRA is a chemotherapy used in APL, and it has been found to cause ARDS in 26% of patients starting 2 to 47 days after treatment. Cytarabine (Ara-C) can cause diffuse lung injury, capillary leakage, and pulmonary edema, usually after 6 days of therapy. These effects can be treated with diuresis and corticosteroids. Bleomycin can cause pulmonary fibrosis and increased sensitivity to intraoperative oxygen administration. Other chemotherapeutic agents that can cause pulmonary edema are mitomycin C, gemcitabine, cyclosporine, interferon, tumor necrosis factor (TNF), and interleukin-2.

Interstitial lung disease can be caused by bleomycin, carmustine, lomustine, busulfan, cyclophosphamide, methotrexate, doxorubicin, and actinomycin D. Bleomycin toxicity is usually dose related and most often occurs when the cumulative dose is greater than 450 units. It can be treated with corticosteroids. Busulfan's toxic effects can occur after 3 weeks of therapy, but they sometimes emerge as late as 3 years after treatment. Busulfan toxicity is associated with a high mortality rate, but corticosteroids can be used with some response. Cyclophosphamide complications present differently depending on whether they are early or late. The early-onset effect is pneumonitis, which can be treated with corticosteroids. The late-onset symptoms include a progressive fibrosis that is not responsive to steroids. Methotrexate can also produce pulmonary fibrosis, which can appear from several days to years after treatment. Interstitial lung disease (pneumonitis) from taxane toxicity is rare and usually respond to steroid therapy.[43] Tyrosine kinase inhibitors against epidermal growth factor receptor (EGFR) can cause pneumonitis, perhaps by interfering with the function of EGFR in non-neoplastic cells involved in the repair mechanisms for the lungs.[44] Immune checkpoint inhibitors (ICPis) may induce an immune-mediated pneumonitis, which is further discussed later.

Patients receiving doxorubicin and actinomycin D can present with pulmonary fibrosis characterized by a "recall" effect after radiation therapy, even in areas of the lung not exposed to radiation. Radiation can cause pneumonitis or fibrosis, the occurrence of which is most closely related to the rate of delivery of radiation. Pneumonitis is an acute-phase reaction that occurs 2 to 6 months after irradiation and may respond to corticosteroids. The late-phase response to radiation toxicity, fibrosis of the lungs, does not respond to corticosteroids.

CHEMOTHERAPY-INDUCED EXTRAVASATIONS

Extravasation injuries caused by chemotherapy can produce a variety of symptoms ranging from skin irritation to skin ulceration, tissue necrosis, nerve damage, and (rarely) loss of limbs. Vesicant chemotherapy agents, including the alkylating agents (mechlorethamine, cisplatin, mitomycin C), DNA intercalating agents (doxorubicin, daunorubicin), and plant alkaloids (vinblastine, vincristine, vinorelbine), can cause the most severe reactions. Irritant chemotherapy extravasations are generally not severe, causing only pain, erythema, and inflammation at the extravasated site.[45]

The goal is to prevent chemotherapy extravasations. The patient should be told to inform the staff of any discomfort, swelling, or erythema over the infusion site. Nursing staff should evaluate the IV infusion site carefully by administering IV fluids before chemotherapy agents are infused, and they should monitor the

patient frequently for any evidence of extravasation. IV lines should be placed carefully; areas that have a poor blood supply or overlie a joint should be avoided. If an extravasation does occur, the infusion should be stopped immediately with the catheter left in place, and the staff should attempt to withdraw any remaining chemotherapy agents. Cold compresses should then be placed on the involved site except when the agents are plant alkaloids, in which case warm compresses should be applied. Topical dimethylsulfoxide (DMSO) 99% or in a 50% solution can relieve extravasations when applied topically to the site twice daily or every 6 hours for 7 to 14 days. DMSO is commonly used to treat extravasations caused by mitomycin C and the anthracyclines. For extravasations caused by plant alkaloids (vinblastine, vincristine, vinorelbine), taxanes and epidophyllotoxins (etoposide, teniposide), a solution of 150 units of hyaluronidase in 1 to 3 mL of saline can be injected subcutaneously in and around the extravasation site in about 0.2-mL aliquots. A 0.17-mol/L solution of sodium thiosulfate can be injected into mechlorethamine-induced extravasation sites. Sodium thiosulfate is thought to work by creating an alkaline-rich site to which the vesicant binds instead of the skin. The byproduct is then excreted in the urine. There is some evidence that sodium thiosulfate can also be used for extravasations caused by carmustine, cisplatin, carboplatin, cyclophosphamide, dacarbazine, and oxaliplatin. Table 61–6 lists selected chemotherapeutic agents and their antidotes. Dexrazoxane is an antidote for anthracycline extravasation.[46] Dexrazoxane is also used to reduce the risk of cardiomyopathy induced by anthracyclines. Dexrazoxane 1000 mg/m^2 is administered IV in a limb other than the limb affected by extravasation within 5 hours of extravasation and then for 2 more consecutive days.[45]

If local measures fail to contain symptoms in all patients with anthracycline-induced extravasations, a plastic surgeon should be consulted. Surgery can consist of debridement, excision of dead tissues, and, in severe cases, skin graft placement. In patients with doxorubicin-induced extravasation, the drug remains in the tissue for a long period, perhaps being released by dying or dead cells and spreading over time. Patients who have had previous extravasation reactions can also experience a "recall reaction" when the same chemotherapy is received later, causing ulcerations or burns to reappear at the previously affected area.

METABOLIC EMERGENCIES

Syndrome of Inappropriate Antidiuretic Hormone Secretion

Hyponatremia is the most common electrolyte abnormality, present in approximately 2% of hospitalized patients. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion is a paraneoplastic syndrome in which antidiuretic hormone (ADH) is secreted inappropriately from the posterior pituitary gland despite lower serum osmolality. Typically, ADH is secreted in response to hypernatremia, hypotension, or hypoxemia to increase the permeability of the collecting ducts so that water can be reabsorbed and the blood pressure and sodium level restored to normal values. In patients with cancer, a protein similar to ADH, atrial natriuretic factor (ANF), is secreted by the cardiac atria, which increases the renal excretion of sodium. The pituitary gland does not respond to feedback from ANF. Thus, SIADH can be characterized by inappropriate ADH secretion despite normal blood volume, with hyponatremia, serum osmolality less than 260 mOsm/L, inappropriate sodium secretion in the urine of greater than 20 mEq/L, and high urine osmolality greater than 100 mOsm/kg.[47,48]

SIADH can be caused by various cancers, including small cell lung cancer, pancreatic cancer, and primary brain cancers. Other causes of SIADH are pulmonary infections, postoperative effects, CNS disorders (meningitis, stroke, hemorrhage), and chemotherapeutic agents (vincristine, cisplatin, and cyclophosphamide).

Symptoms of SIADH depend on the sodium level and the rate at which the sodium level declines. The patient can present with confusion, seizures, headache, or weight gain without edema. In evaluating hyponatremia, the patient's volume status should be addressed, and the plasma osmolality, urine osmolality, and urine sodium and chloride levels should be determined. Hyponatremia should be distinguished from pseudohyponatremia, in which plasma osmolality is normal (hyperlipidemia, hyperproteinemia) or even high (hypertriglyceridemia, hyperglycemia, and mannitol use).

Most patients with hyponatremia have low serum osmolality, which can be grouped by type: primary sodium loss, primary sodium gain, and primary water gain. Patients with sodium gain present with volume overload, which occurs in congestive heart failure, liver disease, and nephrotic syndrome. Patients with primary sodium loss present with dehydration; sodium deficits can be caused by GI loss (nausea, vomiting, diarrhea, bowel obstruction), renal loss (thiazide diuretics), and skin loss (severe burns). Patients with SIADH can also have primary water gain, although other sources of primary water gain (primary polydipsia, decreased solute intake, beer potomania, chronic renal insufficiency, adrenal or thyroid deficiency, or increased ADH secretion in response to pain, nausea, vomiting, or drugs) should be distinguished. Some patients appear to have SIADH based on laboratory test results but actually have a reset osmostat. This adjustment can occur in patients with quadriplegia,

Table 61–6 Chemotherapeutic Extravasations and Their Antidotes

Chemotherapy Agent	Irritant (I) or Vesicant (V)	Sodium Thiosulfate	DMSO	Hyaluronidase	Dexrazoxane	Cool	Warm
Carboplatin	I	+				+	
Carmustine	I OR V	+		+			Dry warm
Cisplatin	I or V	+				+	
Cyclophosphamide	I	+				+	
Dacarbazine	I or V	+					
Dactinomycin	I or V					+	
Daunorubicin	I or V		+		+	+	
Docetaxel	I					+	Warm soaks
Doxorubicin	I or V		+		+	+	
Epirubicin	I or V		+		+	+	
Etoposide	I or V			+			+
Idarubicin	I or V		+		+	+	
Ifosfamide	I					+	
Mechlorethamine	I or V	+					
Mitomycin C	V		+			+	
Oxaliplatin	I or V	+					
Paclitaxel	I or V			+			
Plicamycin	I or V						
Streptozocin	I or V						
Teniposide	I or V			+			+
Topotecan						+	
Vinblastine	I or V			+			+
Vincristine	I or V			+			+
Vindesine	I or V			+			+
Vinorelbine	I or V			+			+

DMSO, dimethylsulfoxide.

tuberculosis, psychosis, chronic illness, volume contraction, encephalitis, malnutrition, or malignancy and in older or pregnant patients. Other rare causes of euvolemic hyponatremia are an incomplete pituitary stalk and increased sensitivity to ADH secretion.

Treatment of SIADH involves restricting water to 500 to 1000 mL/day from all sources and treating the underlying disorder. If this combination is not effective, demeclocycline (600–1200 mg/day) can be used in divided doses two to four times per day. Patients whose symptoms include coma or seizure can be treated by slow infusion of 3% normal saline; care must be taken not to increase serum sodium by more than 0.5 to 1 mEq/hours. Too-rapid correction of serum sodium level can lead to central pontine myelinolysis. Vasopressin receptor antagonists is very effective in managing hyponatremia. If acute treatment of hyponatremia is needed or parenteral administration is more appropriate, conivaptan (a V_1/V_2R antagonist) can be given intravenously. Oral selective V_2R antagonists such as tolvaptan and lixivaptan can be used to manage hyponatremia chronically. In addition, urea and loop diuretics are all useful to increase free water excretion.[48]

Tumor Lysis Syndrome

TLS is a result of excessive tumor breakdown, causing hypocalcemia, hyperphosphatemia, hyperkalemia, elevated uric acid, and occasionally acute renal failure. Risk factors for TLS include high tumor burden, chronic renal insufficiency, and certain tumor types (Burkitt lymphoma, lymphoblastic lymphoma, diffuse large cell lymphoma, undifferentiated lymphoma, and leukemia). TLS usually presents during chemotherapy, but it can also occur after radiation therapy, corticosteroid treatment for sensitive tumors, or administration of hormonal agents.

Patients with TLS can present with nausea and vomiting, diarrhea, constipation, low urine output, weight gain, acute renal failure, weakness, cramps, seizures, tetany, or arrhythmias.

Prophylaxis is very important in preventing TLS and consists of IV hydration and oral allopurinol (100–600 mg/day). Alkalinizing the urine with sodium bicarbonate to maintain a urine pH greater than 7.5 decreases uric acid crystallization in the kidneys but is generally not necessary. Because allopurinol use is now common before chemotherapy, hyperphosphatemia, rather than hyperuricemia, is now the predominant cause of acute renal failure in TLS. To prevent TLS, patients with leukemia and high WBC counts should be treated with leukapheresis or hydroxyurea before chemotherapeutic agents are administered. Some patients with refractory electrolyte abnormalities might require dialysis if conservative measures fail. A newer and effective alternative to allopurinol is rasburicase. Rasburicase is a highly soluble IV recombinant form of urate oxidase that can also be used to prevent or treat hyperuricemia and does not require simultaneous urine alkalinization. Rasburicase effectively decreases levels of uric acid, xanthine, and hypoxanthine by reducing existing pools and preventing further production of uric acid. Rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency, methemoglobinemia, and pregnancy and has a known side effect of hemolytic anemia. The 2008 International Expert Panel on TLS provided rasburicase dosing guidelines based on the level of risk for TLS and uric acid levels.[49]

Hypercalcemia

Hypercalcemia is present in 10% to 20% of patients with advanced cancer. The most common cancers include squamous cell cancer of the lungs, breast cancer, multiple myeloma, and lymphoma. The two major mechanisms of hypercalcemia include the secretion of a parathyroid-related peptide and abnormal 1,25-vitamin D production (which occurs in Hodgkin disease and non-Hodgkin lymphoma).

Symptoms of hypercalcemia are altered mental status, polyuria, polydipsia, nausea, vomiting, anorexia, constipation, and seizures. Measured serum calcium levels should be adjusted according to the albumin level for accurate estimation. A low albumin level should be subtracted from 4, and the difference should be multiplied by 0.8. This product should be added to the serum calcium level to arrive at the estimated calcium. Alternatively, ionized calcium can be measured, which assesses the active calcium in the serum and is more accurate.

The choice of treatment for hypercalcemia depends on the patient's calcium level and symptoms. Calcium is a potent diuretic, and patients with mild hypercalcemia can be treated by IV fluids. Patients with a calcium level greater than 14 mg/dL should be treated with additional measures. Patients who have symptoms of hypercalcemia and a calcium level between 12 and 14 mg/dL should also receive additional treatment to lower the calcium level.

Bisphosphonates are the drugs of choice in treating hypercalcemia. Zoledronic acid 4 mg intravenously over 15 min is more convenient than pamidronate 60 to 90 mg, which is infused intravenously over 2 to 24 hours. Bisphosphonates do not work immediately but have an onset of action after 12 to 48 hours. Bisphosphonates are useful not only in reducing serum calcium levels but can also help to decrease bone pain and treat skeletal complications in patients with cancer with bone metastases. Denosumab, a monoclonal antibody against the receptor activator of nuclear factor κB ligand (RANKL), is effective for treatment of hypercalcemia of malignancy, even for bisphosphonate-refractory cases.[50] Calcitonin 4 units/kg subcutaneously can also be used to treat hypercalcemia; it has an onset of action of 2 to 4 hours, but its effects are transient because tachyphylaxis develops after 3 days. Patients may develop nausea, abdominal cramps, or hypersensitivity reactions to calcitonin, and this medication is very expensive.

Corticosteroids can be helpful in some patients with hypercalcemia—for instance, those with lymphoma and myeloma. Furosemide can be used, but only after the patient has been hydrated adequately. In acute renal failure, severe life-threatening or refractory hypercalcemia, hemodialysis can effectively decrease calcium to safe levels.[51]

GASTROINTESTINAL EMERGENCIES

Gastrointestinal Bleeding

Patients with cancer can present with GI bleeding caused by direct tumor invasion, effects of chemotherapy agents or corticosteroids, thrombocytopenia, coagulopathy, side effects of radiation therapy, or Mallory-Weiss tears from intractable nausea and vomiting. Other possible causes of GI bleeding are gastritis, peptic ulcer disease, duodenal ulcers, arteriovenous malformations, and diverticulosis. Patients who have undergone bone marrow transplantation can present with GI bleeding as a manifestation of graft-versus-host disease, which typically presents as ulcerations in the small intestine. Immune-mediated colitis from ICPi therapy may also result in hematochezia. Patients with small tumors rarely have significant bleeding, and patients with large tumors tend to ooze and bleed. However, relief of bleeding by endoscopic measures is usually temporary, and these tumors tend to bleed

repeatedly. Endoscopic interventions can include electrocoagulation, epinephrine injections, and argon plasma laser treatment. For patients with persistent bleeding, arteriography and embolization is occasionally successful. If all other interventions have failed, surgery can be considered. Patients with bleeding should have any coagulopathy corrected, including deficits in the platelet count, which should be greater than 60,000/μL. Somatostatin or vasopressin can be used to control bleeding of esophageal varices. The patient should receive either an H2 blocker or a proton pump inhibitor intravenously. Nausea should be controlled using IV antiemetics, and the patient should receive nothing by mouth. The patient should also receive maintenance IV fluid. If hypotensive, the patient should be volume resuscitated with IV crystalloid fluid, transfusion, or both.

Typhlitis

Typhlitis is a syndrome of bowel inflammation, edema, and wall thickening involving the proximal large bowel in patients with neutropenic fever. It commonly affects the cecum but can also affect the ascending colon and occasionally the transverse colon. Typhlitis can occur in conjunction with any cancer but is most common in patients with leukemia. The organisms most often isolated in cases of typhlitis are *Clostridium* spp. and gram-negative bacilli.

Patients with typhlitis present with fever, pain in the right lower quadrant of the abdomen, and sometimes diarrhea, which may be bloody. The patient with typhlitis is neutropenic, and plain abdominal x-ray films are often inconclusive. The diagnosis of typhlitis is made based on clinical suspicion and CT or MRI findings that reveal bowel inflammation, edema, wall thickening, and possibly gas formation in bowel wall (eg, pneumatosis intestinalis) or, in severe cases, intraabdominal free air (Fig. 61–10).

Typhlitis is managed by bowel rest and IV administration of broad-spectrum antibiotics, including anaerobic coverage. Patients rarely require surgery unless they develop intractable bleeding or bowel perforation or do not respond to conservative measures.

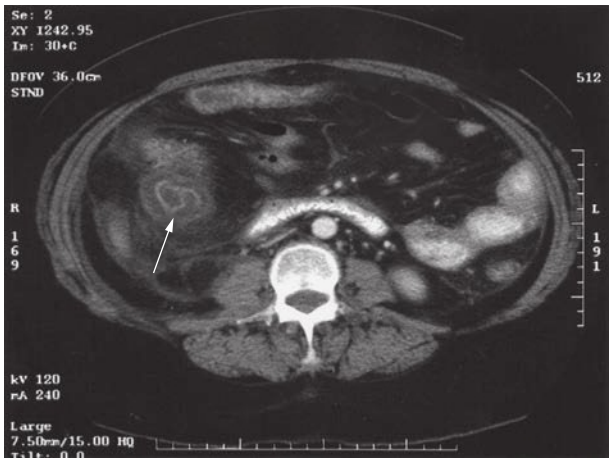


FIGURE 61–10 Inflammation of the cecum and ascending colon in a 45-year-old patient with typhlitis. The *arrow* points to inflammation and edema of the cecum. (Used with permission from Dr. Stephanie Mundy, MD Anderson Cancer Center.)

IMMUNOTHERAPY TOXICITY

The addition of ICPis to the arsenal of antineoplastic agents marked a breakthrough in cancer therapeutics. These drugs include monoclonal antibodies that target either the interaction between programmed cell death protein 1 (PD-1)on T-cells and programmed cell death ligand 1 (PD-L1) on tumor cells or immune cells in the microenvironment of the tumor (eg, nivolumab, pembrolizumab, atezolizumab, durvalumab, and avelumab), or the interaction between cytotoxic T-cell lymphocyte antigen-4 (CTLA-4) on T-cells and B7 on antigen-presenting cells (eg, ipilimumab, cemiplimab).[52]

However, these drugs unleash the immune system, and can lead to immune-related adverse events (irAEs) that practically can attack any organ system. Therefore, patients may present with a variety of symptoms depending on the organs involved and the degree of involvement. Toxicities are typically categorized into grades ranging from grade 1 to grade 4. ASCO has proposed some general recommendations for the management of irAEs irrespective of the organ involved.[53] For grade 3 irAEs, the ICPis should be withheld, and high-dose corticosteroids should be initiated (eg, prednisone 1 to 2 mg/kg/day or methylprednisolone IV 1 to 2 mg/kg/day) and then tapered over 4 to 6 weeks. If symptoms do not improve within 48 to 72 hours of corticosteroid therapy, infliximab may be considered. In general, grade 4 toxicities necessitate permanent discontinuation of ICPi therapy, except for endocrinopathies that have been controlled by hormone replacement.

Urgent skin irAEs include grade 3 and 4 inflammatory dermatitis or rash, bullous dermatosis, and severe cutaneous adverse reactions (SCARs) such as drug reaction with eosinophilia and systemic symptoms (DRESS), and Stevens-Johnson syndrome or toxic epidermal necrolysis. Rashes or inflammatory dermatitis associated with ICPis can be eczematous, lichenoid, psoriasiform, or morbilliform rashes. Possible reactions also include erythema multiforme minor, palmoplantar dysesthesia, and neutrophilic dermatoses (eg, Sweet syndrome). Grade 4 manifestations of these conditions are those that are severe, intolerable, and unmanageable with the regular interventions. They

require immediate admission with an urgent dermatology consultation. Bullous dermatosis includes bullous pemphigoid or other autoimmune and drug-related etiologies. Grade 3 and 4 bullous dermatosis involves more than 30% of the body surface area of a patient. In such cases, it is important to detect a secondary cellulitis or neutropenia, which would warrant an infectious diseases consultation. If bullous pemphigoid is diagnosed, alternative treatments such as rituximab may be explored. Grade 4 SCAR toxicity involves skin erythema and blistering or sloughing covering at least 10% of body surface area with associated signs or systemic symptoms and concerning associated blood work abnormalities (eg, liver function test elevation in DRESS). In such cases, it is important to urgently admit the patient to the ICU or burn unit. Intravenous immunoglobulin (IVIG) and cyclosporine may be considered in severe and corticosteroid-unresponsive cases.

GI irAEs are also common and include colitis and hepatitis, among others. Grade 3 colitis is characterized by an increase of seven or more stools per day over baseline, incontinence, hospitalization indicated, severe increase in ostomy output compared with baseline, or limiting self-care activities of daily living (ADLs). A grade 4 colitis is life threatening and warrants permanent discontinuation of the incriminated drug, with the possibility of early initiation of 5 to 10 mg/kg of infliximab if the symptoms are refractory to steroids within 2 to 3 days. A grade 3 hepatitis is defined by a 5- to 20-fold increase in transaminases (alanine aminotransferase or aspartate aminotransferase) from the upper limit of normal (ULN) or a 3- to 10-fold increase in the total bilirubin from the ULN. Grade 4 hepatitis on the other hand represents decompensated liver function (eg, ascites, coagulopathy, encephalopathy, coma) with more than a 20-fold increase in transaminases or more than a 10-fold increase in total bilirubin from the ULN. Both grade 3 and 4 hepatitis warrant permanent discontinuation of the ICPi; however, infliximab is typically avoided in patients with hepatitis, resorting to non–TNF-α immunosuppressants. In both grade 4 colitis and hepatitis, a corticosteroid taper may be attempted if symptoms improve to grade 1 or less.

The main pulmonary irAE is pneumonitis. A grade 3 pneumonitis typically requires hospitalization because of severe symptoms and involvement of all lung lobes or more than 50% of lung parenchyma, limiting self-care ADLs. A grade 4 toxicity represents life-threatening respiratory compromise. A grade 3 pneumonitis requires oxygen therapy, whereas in a grade 4 toxicity, urgent intervention such as intubation may be necessary. Otherwise, grades 3 and 4 pneumonitis are treated similarly with initial treatment involving permanent ICPi discontinuation and methylprednisolone 1 to 2 mg/kg/day intravenously. Empiric antibiotics for possible pneumonia may be indicated until infection has been excluded.

Endocrine irAEs affect the thyroid, adrenal, and pituitary glands as well as the pancreatic islets. Thyroid manifestations could include either hypothyroidism (primary) or hyperthyroidism. As these manifestations are common, testing for TSH and free thyroxine every 4 to 6 weeks is recommended for patients on ICPi therapy as part of routine monitoring. Grade 3 and 4 hypothyroidism is defined as having severe symptoms with medically significant or life-threatening consequences and inability to perform ADLs. Such a toxicity is treated by holding ICPi therapy and thyroid supplementation. Admission may be necessary for IV therapy if signs of myxedema exist; however, steroids have no major role in this toxicity. Most cases of thyrotoxic irAEs are caused by thyroiditis, but some can be caused by Graves disease, which is distinguished from thyroiditis by the presence of elevated thyroid-stimulating immunoglobulin. Similarly, grade 3 or 4 hyperthyroidism also presents with severe medically significant symptoms and an inability to perform ADLs. However, in addition to holding ICPi therapy, immediate therapy includes a β-blocker such as atenolol or propranolol for symptomatic relief. Severe symptoms or concern for thyroid storm warrant hospitalization and initiation of prednisone 1 to 2 mg/kg/day or equivalent tapered over 1 to 2 weeks. Other agents such as SSKI (potassium iodide) and thionamides (eg, methimazole or propylthiouracil (PTU)) can also be considered in the setting of Graves disease.

Another endocrinopathy is primary adrenal insufficiency, which typically leads to low morning cortisol, high morning ACTH, and hyponatremia and hyperkalemia with orthostasis and volume depletion caused by loss of aldosterone. Severe and significant symptoms affecting ADLs are considered grade 3 or 4 toxicities. These should be managed by holding ICPi therapy until the patient is stabilized on replacement corticosteroid hormone. At least 2 L of normal saline solution should be administered upon presentation, as well as an IV stress dose of 100 mg hydrocortisone or a 4 mg-dose of dexamethasone if the diagnosis is unclear and stimulation testing is expected. The corticosteroid dose should then be tapered to a maintenance dose over 7 to 14 days after discharge.

Hypophysitis is inflammation of the pituitary gland and can result in hypofunction of one or multiple hypothalamic–pituitary hormonal axes. Central hypothyroidism, adrenal insufficiency, diabetes insipidus, and hypogonadism are common findings. A grade 3 or 4 toxicity results in severe symptoms affecting ADLs and warrants immediate cessation of ICPi therapy until the patient is stabilized on replacement hormones. In addition, we may consider initial pulse

dose therapy with prednisone 1 to 2 mg/kg orally daily (or equivalent) tapered over at least 1 to 2 weeks. In addition to hypophysitis, ICPi therapy may result in type 1 diabetes from islet cell destruction and may be associated with acute diabetic ketoacidosis, which is a grade 3 or 4 toxicity with severe symptoms affecting ADLs or is life threatening. As for hyperglycemia, a grade 3 toxicity is also defined as having a glucose level greater than 250 to 500 mg/dL (>13.9–27.8 mmol/L), whereas a grade 4 toxicity would involve a glucose level greater than 500 mg/dL (>27.8 mmol/L). In grade 3 and 4 toxicities, ICPis must be held until glucose control is obtained on therapy with reduction of toxicity to grade 1 or less. Furthermore, insulin therapy should be initiated for all these patients.

Musculoskeletal irAEs include inflammatory arthritis, myositis, and polymyalgia-like syndrome. A grade 3 or 4 inflammatory arthritis manifests as severe pain associated with signs of inflammation, erythema, or joint swelling and can lead to irreversible joint damage. Because early recognition is critical to avoid erosive joint damage, such a toxicity warrants temporary holding of ICPi therapy with an initial oral prednisone dose of 0.5 to 1 mg/kg. Myositis is characterized by muscle inflammation with weakness and elevated muscle enzymes (CK). In addition to pain, severe myositis may be life threatening if respiratory muscles or the myocardium are involved. As such, a grade 3 or 4 toxicity, characterized by severe weakness limiting self-care ADLs, warrants immediate cessation of ICPi therapy. In addition to initiating corticosteroids, plasmapheresis, IVIG, and other immunosuppressants may be considered. Caution is advised with rechallenging, but ICPi discontinuation is typically permanent if myocardial involvement is evident. Polymyalgia-like syndrome is characterized by marked pain and stiffness in proximal upper or lower extremities and no signs of true muscle inflammation or true muscle weakness. A grade 3 or 4 toxicity manifests as severe stiffness and pain, limiting self-care ADLs. Initial management includes holding ICPi therapy and initiating 20 mg/day of prednisone or its equivalent. Admission for pain control is reasonable.

The major renal irAE is nephritis, which, although serious, may be asymptomatic. If the diagnosis is suspected, swift treatment of the autoimmunity is important. If no alternative causes of the acute kidney injury are identified, a kidney biopsy should be obtained, and the patient should be initiated on immunosuppressive treatment. A grade 3 toxicity is represented by creatinine more than three times baseline or greater than 4.0 mg/dL and warrants immediate permanent discontinuation of ICPi therapy with hospital admission. The recommended initial dosage of corticosteroid is 1 to 2 mg/kg/day of prednisone or its equivalent. A grade 4 toxicity is treated similarly but is characterized by severe life-threatening consequences and the need for dialysis. Tapering of corticosteroids can be attempted if toxicity improves to grade 1 levels.

Nervous system ICPi toxicities are of particular concern. They can be very debilitating and include a wide variety of conditions, notably myasthenia gravis (MG), Guillain-Barré syndrome (GBS), peripheral neuropathy, autonomic neuropathy, aseptic meningitis, encephalitis, and transverse myelitis. MG may be particularly difficult to differentiate from the Miller Fisher variant of GBS and from oculobulbar myositis because of overlapping symptoms. For MG and GBS, any grade toxicity requires workup and intervention given the potential of progression to respiratory compromise. Grade 3 or 4 MG is characterized by limited self-care, weakness that limits walking, any of dysphagia, facial weakness, respiratory muscle weakness, rapidly progressive symptoms, or Myasthenia Gravis Foundation of America (MGFA) severity class 3 or above. Management of patients with grade 2 MG includes pyridostigmine and corticosteroids (prednisone, 1.0–1.5 mg/kg orally daily). Grade 3 or 4 toxicity warrants permanent ICPi discontinuation and should be administered corticosteroids as well as IVIG 2 g/kg IV over 5 days (0.4 g/kg/day) or plasmapheresis for 5 days. Admission is warranted, and the patient may require ICU monitoring. Treatment of a GBS toxicity of any grade also warrants IVIG or plasmapheresis for the same duration and dose. Although corticosteroids are not recommended for idiopathic GBS, a trial of 2 to 4 mg/kg/day of methylprednisolone may be reasonable, with pulse dosing as another possibility.

Peripheral neuropathies can present as asymmetric or symmetric sensory, motor, or sensory motor deficits. Autonomic neuropathies result from damage to the nerves that control involuntary bodily functions, such as blood pressure, digestion, and bladder function. A grade 3 or 4 peripheral neuropathy leads to limited self-care weakness, limiting walking or respiratory problems (ie, leg weakness, foot drop, rapidly ascending sensory changes). If the changes are severe, they may represent GBS and should be managed as such. Otherwise, initial management of grade 3 or 4 peripheral toxicity includes permanent ICPi discontinuation with a 2- to 4-mg/kg dose of IV methylprednisolone followed by regular GBS management. A grade 3 or 4 autonomic neuropathy also warrants permanent ICPi discontinuation but with 1 g of methylprednisolone for 3 days followed by an oral corticosteroid taper.

Patients with aseptic meningitis may present with headache, photophobia, and neck stiffness. Patients are usually febrile, although they may be afebrile. Unlike encephalitis, mental status in patients with aseptic meningitis should be normal. In both conditions, it is important to rule out infectious causes. For

aseptic meningitis, a grade 3 or 4 toxicity is severe and limits self-care and is treated similarly to any grade. Management includes holding ICPi therapy and performing a lumbar puncture with the possibility of initiating empirical antiviral and antibacterial therapy pending results. If the results are negative for infection, the patient may be monitored closely without corticosteroids or may be administered oral prednisone 0.5 to 1 mg/kg or IV methylprednisolone 1 mg/kg for the management of moderate to severe symptoms. Encephalitis symptoms include confusion, altered behavior, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, and speech abnormality. A grade 3 or 4 toxicity is severe and limits self-care and is treated as any grade toxicity for encephalitis. As in aseptic meningitis, ICPi should be held ,and IV acyclovir may be administered pending polymerase chain reaction detection of herpes virus. Immediate treatment includes a trial of methylprednisolone 1 to 2 mg/kg. If the condition progresses, pulse corticosteroids and IVIG may be considered. The presence of autoimmune encephalopathy antibody warrants rituximab or plasmapheresis if there is no or limited improvement with regular treatment. Transverse myelitis typically presents with bilateral acute or subacute weakness or sensory changes, often with increased deep tendon reflexes. Treatment of all toxicity grades includes permanent ICPi discontinuation, 2 mg/kg of methylprednisolone or higher doses of 1 g/day for 3 to 5 days, and the possibility of using IVIG.

Hematologic irAEs also encompass a wide variety of conditions, including autoimmune hemolytic anemia (AIHA), acquired thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), aplastic anemia, lymphopenia, immune thrombocytopenia (ITP), and acquired hemophilia, which is discussed. AIHA symptoms include weakness, paleness, jaundice, dark-colored urine, fever, and heart murmur. A grade 3 toxicity is defined with a hemoglobin level below 8.0 g/dL, whereby transfusion is indicated. A grade 4 toxicity is characterized by life-threatening consequences and requires urgent intervention. The immediate management of both grade 3 and 4 toxicities warrant permanent ICPi discontinuation with RBC transfusion as per existing guidelines and 1 to 2 mg/kg/d of prednisone (oral or IV for grade 3; IV for grade 4). Acquired TTP is characterized by the presence of microangiopathic hemolytic anemia, thrombocytopenic purpura, fever, renal abnormalities, and neurologic abnormalities. A high index of suspicion and a timely diagnosis are crucial because delayed hematology consult is associated with increased mortality/morbidity. Grade 1 and 2 toxicities do not present with any clinical consequences. However, a grade 3 toxicity involves both laboratory findings and clinical findings such as thrombocytopenia, anemia, renal insufficiency. A grade 4 toxicity is one that presents with life-threatening consequences such as intracranial hemorrhage and renal failure. Grade 3 and 4 toxicities require immediate cessation of ICPi, initiation of plasma exchange (PEX) as per existing guidelines, and administration of 1 g of methylprednisolone IV daily for 3 days with the first dose typically immediately after PEX. HUS is characterized by a form of thrombotic microangiopathy with renal failure, hemolytic anemia, and severe thrombocytopenia. Symptoms vary but can include bloody diarrhea and high blood pressure. As in TTP, a G3 toxicity is one with clinical consequences and a G4 toxicity is a life-threatening one with consequences such as CNS thrombosis or embolism and renal failure. Both grade 3 and 4 HUS require permanent ICPi discontinuation with initiation of eculizumab therapy 900 mg weekly for four doses and 1200 mg for week 5 followed by 1200 mg every 2 weeks. RBC transfusion may be done as per existing guidelines.

Aplastic anemia is characterized by a deficiency in the production of new blood cells. During diagnostic workup, the patient should be typed and screened, and the blood bank should be notified that all transfusions need to be irradiated and filtered. A grade 3 or 4 toxicity presents with absolute neutrophil count less than 200/mm,^{3} platelet count less than 20,000/mm,^{3} reticulocyte count less than 20,000/mm,^{3} and hypocellular marrow less than 25%. ICPi therapy should be held, with a hematology consult and growth factor support. Initial treatment also includes horse antithymocyte globulin (ATG) plus cyclosporine. Lymphopenia is a specific hematologic disorder defined as an abnormally low level of lymphocytes in the peripheral smear (<1500/mm^3 for adults). Grade 3 lymphopenia is defined with a lymphocyte level of 250 to 499/mm^3 and warrants weekly complete blood count monitoring and cytomegalovirus (CMV) screening while continuing ICPi therapy. However, if the toxicity is G4 (lymphocyte count <250/mm^3), then ICPi should be discontinued, and prophylaxis should be initiated for *Mycobacterium avium complex* and *Pneumocystis jirovecii*. CMV, human immunodeficiency virus, and hepatitis screening should be done, and Epstein-Barr virus testing may be considered if signs or symptoms are consistent with lymphoproliferative disease.

ITP is another specific autoimmune disorder characterized by immunologic destruction of otherwise normal platelets. A platelet count below 50/μL is considered a grade 3 toxicity, whereas a count below 25/μL is considered grade 4. Both grade 3 and 4 toxicities require holding ICPi. Prednisone 1 to 2 mg/kg/day (oral or IV depending on symptoms) should be given,

and IVIG (1 g/kg as a one-time dose; can be repeated) may be added if a rapid rise in platelets is required.

Acquired hemophilia is a form of hemophilia caused by the development of autoantibodies (inhibitors) directed against plasma coagulation factors. The development of hemophilia A generally requires a specialist on-board with clinical and laboratory experience. A grade 3 or 4 toxicity is severe and leads to less than 1% of normal factor activity in blood or levels below 0.01 IU/mL of whole blood. ICPi should be discontinued, and the patient should be admitted. Treatment involves immunosuppressive agents and factor replacement based on Bethesda unit level of inhibitor. Prednisone is given as 1 to 2 mg/kg/day (oral or IV depending on symptoms) with or without rituximab (375 mg/m^2 weekly for 4 weeks) and/or cyclophosphamide (1–2 mg/kg/day). Bypassing agents may be used, and transfusion support is provided as required.

Cardiovascular irAEs are also of concern. These typically include VTE, which is managed in one way, and several other irAEs such as myocarditis, pericarditis, arrhythmias, impaired ventricular function with heart failure, and vasculitis, which are all managed similarly. For VTE, a grade 2 or 3 toxicity is one in which medical intervention is required. ICPi can be continued, and the patient should be managed as per CHEST, American College of Cardiology (ACC), or American Heart Association (AHA) guidelines. LMWH is the preferred agent for initial and long-term treatment, although IV heparin is an acceptable alternative for initial use, and oral anticoagulants are acceptable for the long term. A grade 4 VTE is life threatening and typically includes hemodynamic or neurologic instability and the need for urgent intervention. The management of a grade 4 toxicity also follows the aforementioned guidelines with preference for the use of LMWH but also includes permanent ICPi discontinuation with hemodynamic and respiratory support. For all other mentioned irAEs, signs and symptoms may include chest pain, arrhythmia, palpitations, peripheral edema, progressive or acute dyspnea, pleural effusion, and fatigue. A grade 3 toxicity is one that involves abnormal testing or symptoms with mild activity, whereas a grade 4 toxicity involves moderate to severe decompensation, the need for IV medication or intervention, or life-threatening conditions. All toxicity grades require workup and intervention given the possibility for cardiac compromise. In toxicities with grade greater than 1, ICPi should be permanently discontinued, and high-dose corticosteroids (1–2 mg/kg of prednisone) should be initiated rapidly (oral or IV depending on symptoms). Immediate transfer to a coronary care unit is required for patients with elevated troponin or conduction abnormalities, and management of cardiac symptoms should be according to ACC/AHA guidelines. In patients without an immediate response to high-dose corticosteroids, consider early institution of cardiac transplant rejection doses of corticosteroids (methylprednisolone 1 g every day) and the addition of mycophenolate, infliximab, or ATG. However, it is important to note that infliximab has been associated with heart failure and is contraindicated at high doses in patients with moderate to severe heart failure.

Ocular irAEs require a high level of clinical suspicion because symptoms may not always be associated with severity. These events include uveitis or iritis, episcleritis, and blepharitis and are often seen in the context of other irAEs. The workup for these disorders is the same, and patients are best treated after an ophthalmologist eye examination. Uveitis or iritis is inflammation of the middle layer of the eye (uvea or iris). A grade 3 toxicity includes posterior uveitis or panuveitis. This warrants permanent ICPi discontinuation with urgent ophthalmology referral and systemic corticosteroids and intravitreal, periocular, or topical corticosteroids. A grade 4 toxicity leads to visual deficits of 20/200 vision or worse. This also warrants permanent ICPi discontinuation with emergent ophthalmology referral. Corticosteroids should be administered systemically (IV prednisone 1–2 mg/kg or methylprednisolone 0.8–1.6 mg/kg) and intravitreal, periocular, or topical corticosteroids as per ophthalmologist opinion. In severe or refractory cases, TNF-α blockers can be considered. Episcleritis is defined as an inflammatory condition affecting the episcleral tissue between the conjunctiva and the sclera in the absence of an infection. A grade 3 toxicity is symptomatic and involves vision worse than 20/40 vision, whereas a grade 4 toxicity involves 20/200 vision or worse. Both grade 3 and 4 toxicities require permanent ICPi discontinuation, ophthalmology referral, and systemic and topical corticosteroids with cycloplegic agents. TNF-α blockers can also be considered in some cases. Blepharitis is characterized by inflammation of the eyelid that affects the eyelashes or tear production. As of yet, there is no formal grading system for blepharitis. However, treatment includes warm compresses and lubrication drops, with continuation of ICPi therapy unless the condition is persistent and serious.

It is important to have a high index of suspicion for irAEs while examining patients taking ICPis to facilitate early recognition and minimize any long-term damage. Experience and evidence are accumulating on the best possible approach to the diagnosis and management of irAEs. At this point, many recommendations are based on expert opinion, and more studies are needed in the future to determine evidence-based best practice for irAEs.

MD ANDERSON PRACTICE TIPS

- Spinal cord compression occurs at the cervical vertebrae in 10%, thoracic vertebrae in 70%, and lumbar vertebrae in 20% of cases. Up to about one third of cases have multilevel compression. Metastatic lung, breast, and prostate cancers account for 50% of cases. Early diagnosis before severe paraplegia is associated with more favorable clinical outcome.
- For life-threatening cerebral edema with increased ICP, mannitol, hypertonic saline IV infusion, and hyperventilation can be used to decrease ICP, in addition to high-dose glucocorticoids.
- Pericardial tamponade can be managed by emergent pericardiocentesis and placement of a drainage catheter followed by pericardial window, radiotherapy, chemotherapy, or sclerotherapy.
- Intravascular stenting usually can provide prompt symptom relief for SVC syndrome.
- Patients with massive PE may require thrombolysis or embolectomy.
- Interstitial lung disease (pneumonitis) from certain cytotoxic chemotherapy agents may occur. Tyrosine kinase inhibitors against EGFR can cause pneumonitis. ICPi may induce an immune-mediated pneumonitis.
- Rasburicase can effectively manage hyperuricemia in TLS but is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency,
- Beware of bullous lesions, the Nikolsky sign, and mucosal involvement in dermatologic irAEs.
- Multiple irAEs may occur concurrently. When one irAE is diagnosed, look for other irAEs.
- In patients with dyspnea or mental status change, arterial blood gases are informative in the diagnostic workup.
- Hyponatremia is a common metabolic abnormality in both hypoadrenalism and hypothyroidism.

REFERENCES

1. Loblaw DA, Laperriere NJ, Mackillop WJ. A population-based study of malignant spinal cord compression in Ontario. *Clin Oncol (R Coll Radiol)*. 2003;15(4):211-217.
2. Lin AL, Avila EK. Neurologic emergencies in the patients with cancer. *J Intensive Care Med*. 2017;32(2):99-115.
3. Patchell RA, Tibbs PA, Regine WF, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. *Lancet*. 2005;366(9486):643-648.
4. Vaillant B, Loghin M. Treatment of spinal cord tumors. *Curr Treat Options Neurol*. 2009;11(4):315-324.
5. Feng JT, Yang XG, Wang F, et al. Prognostic discrepancy on overall survival between ambulatory and nonambulatory patients with metastatic spinal cord compression. *World Neurosurg*. 2019;121:e322-e332.
6. Rades D, Motisi L, Veninga T, et al. Predictors of outcomes and a scoring system for estimating survival in patients treated with radiotherapy for metastatic spinal cord compression from small-cell lung cancer. *Clin Lung Cancer*. 2019;20(4):322-329.
7. Zhang CH, DeSouza RM, Kho JS, et al. Kernohan-Woltman notch phenomenon: a review article. *Br J Neurosurg*. 2017;31(2):159-166.
8. Fecci PE, Champion CD, Hoj J, et al. The evolving modern management of brain metastasis. *Clin Cancer Res*. 2019;25(22):6570-6580.
9. Nayar G, Ejikeme T, Chongsathidkiet P, et al. Leptomeningeal disease: current diagnostic and therapeutic strategies. *Oncotarget*. 2017;8(42):73312-73328.
10. Lukas RV, Buerki R, Mrugala MM. Management of leptomeningeal disease from solid tumors. *Oncology (Williston Park)*. 2016;30(8):724-730.
11. Moravan MJ, Fecci PE, Anders CK, et al. Current multidisciplinary management of brain metastases. *Cancer*. 2020;126(7):1390-1406.
12. Niranjan A, Monaco E, Flickinger J, Lunsford LD. Guidelines for multiple brain metastases radiosurgery. *Prog Neurol Surg*. 2019;34:100-109.
13. Khan M, Lin J, Liao G, et al. Whole brain radiation therapy plus stereotactic radiosurgery in the treatment of brain metastases leading to improved survival in patients with favorable prognostic factors. *Front Oncol*. 2019;9:205.
14. Buszek SM, Chung C. Radiotherapy in leptomeningeal disease: a systematic review of randomized and non-randomized trials. *Front Oncol*. 2019;9:1224.
15. Gonzalez Castro LN, Milligan TA. Seizures in patients with cancer. *Cancer*. 2020;126(7):1379-1389.
16. Shah VA, Suarez, J. I. Seizures and status epilepticus in critically ill cancer patients. In: Nates J, Price, K. J. eds. *Oncologic Critical Care*. Springer; 2019.
17. Mikkelsen T, Paleologos NA, Robinson PD, et al. The role of prophylactic anticonvulsants in the management of brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neurooncol*. 2010;96(1):97-102.
18. Doriath V, Paesmans M, Catteau G, Hildebrand J. Acute confusion in patients with systemic cancer. *J Neurooncol*. 2007;83(3):285-289.
19. El Majzoub I, Abunafeesa H, Cheaito R, et al. Management of altered mental status and delirium in cancer patients. *Ann Palliat Med*. 2019;8(5):728-739.
20. Karakhanian WK, Karakhanian WZ, Belczak SQ. Superior vena cava syndrome: endovascular management. *J Vasc Bras*. 2019;18:e20180062.
21. Mohanty BD, Mohanty S, Hussain Y, et al. Management of ischemic coronary disease in patients receiving chemotherapy: an uncharted clinical challenge. *Future Cardiol*. 2017;13(3):247-257.
22. Yusuf SW, Iliescu C, Bathina JD, et al. Antiplatelet therapy and percutaneous coronary intervention in patients with acute coronary syndrome and thrombocytopenia. *Tex Heart Inst J*. 2010;37(3):336-340.
23. Sara JD, Kaur J, Khodadadi R, et al. 5-fluorouracil and cardiotoxicity: a review. *Ther Adv Med Oncol*. 2018;10:1758835918780140.
24. El-Menyar A, Asim M, Nabir S, et al. Implications of elevated cardiac troponin in patients presenting with acute pulmonary embolism: an observational study. *J Thorac Dis*. 2019;11(8):3302-3314.
25. Weaver A, Rubinstein S, Cornell RF. Hyperviscosity syndrome in paraprotein secreting conditions including Waldenstrom macroglobulinemia. *Front Oncol*. 2020;10:815.
26. Gertz MA. Acute hyperviscosity: syndromes and management. *Blood*. 2018;132(13):1379-1385.
27. Giammarco S, Chiusolo P, Piccirillo N, et al. Hyperleukocytosis and leukostasis: management of a medical emergency. *Expert Rev Hematol*. 2017;10(2):147-154.
28. Bagot CN, Arya R. Virchow and his triad: a question of attribution. *Br J Haematol*. 2008;143(2):180-190.
29. PIOPED Investigators. Tissue plasminogen activator for the treatment of acute pulmonary embolism. A collaborative study by the PIOPED Investigators. *Chest*. 1990;97(3):528-533.
30. Qdaisat A, Soud RA, Wu CC, et al. Poor performance of D-dimer in excluding venous thromboembolism among patients with lymphoma and leukemia. *Haematologica*. 2019;104(6):e265-e268.
31. Qdaisat A, Yeung SJ, Variyam DE, et al. Evaluation of cancer patients with suspected pulmonary embolism: performance of the American College of Physicians guideline. *J Am Coll Radiol*. 2020;17(1 pt A):22-30.
32. Wang TF, Li A, Garcia D. Managing thrombosis in cancer patients. *Res Pract Thromb Haemost*. 2018;2(3):429-438.
33. Mosarla RC, Vaduganathan M, Qamar A, et al. Anticoagulation strategies in patients with cancer: JACC review topic of the week. *J Am Coll Cardiol*. 2019;73(11):1336-1349.
34. Pieraccini M, Guerrini S, Laiolo E, et al. Acute massive and submassive pulmonary embolism: preliminary validation of aspiration mechanical thrombectomy in patients with contraindications to thrombolysis. *Cardiovasc Intervent Radiol*. 2018;41(12):1840-1848.
35. Loyalka P, Ansari MZ, Cheema FH, et al. Surgical pulmonary embolectomy and catheter-based therapies for acute pulmonary embolism: a contemporary systematic review. *J Thorac Cardiovasc Surg*. 2018;156(6):2155-2167.
36. Schiffer CA, Anderson KC, Bennett CL, et al. Platelet transfusion for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol*. 2001;19(5):1519-1538.
37. Thachil J, Falanga A, Levi M, et al. Management of cancer-associated disseminated intravascular coagulation: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2015;13(4):671-675.
38. Matz EL, Hsieh MH. Review of advances in uroprotective agents for cyclophosphamide- and ifosfamide-induced hemorrhagic cystitis. *Urology*. 2017;100:16-19.
39. Russo P. Urologic emergencies in the cancer patient. *Semin Oncol*. 2000;27(3):284-298.
40. Aldiwani M, Tharakan T, Al-Hassani A, et al. BK virus associated haemorrhagic cystitis. A systematic review of current prevention and treatment strategies. *Int J Surg*. 2019;63:34-42.
41. Radchenko C, Alraiyes AH, Shojaee S. A systematic approach to the management of massive hemoptysis. *J Thorac Dis*. 2017;9(suppl 10):S1069-S1086.
42. Kvale PA, Selecky PA, Prakash UB, American College of Chest Physicians. Palliative care in lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest*. 2007;132(3 suppl):368S-403S.

43. Long K, Suresh K. Pulmonary toxicity of systemic lung cancer therapy. *Respirology*. 2020;25(suppl 2):72-79.
44. Higenbottam T, Kuwano K, Nemery B, Fujita Y. Understanding the mechanisms of drug-associated interstitial lung disease. *Br J Cancer*. 2004;91(suppl 2):S31-S37.
45. Kreidieh FY, Moukadem HA, El Saghir NS. Overview, prevention and management of chemotherapy extravasation. *World J Clin Oncol*. 2016;7(1):87-97.
46. Langer SW. Dexrazoxane for the treatment of chemotherapy-related side effects. *Cancer Manag Res*. 2014;6:357-363.
47. Milionis HJ, Liamis GL, Elisaf MS. The hyponatremic patient: a systematic approach to laboratory diagnosis. *CMAJ*. 2002;166(8):1056-1062.
48. Hoorn EJ, Zietse R. Diagnosis and treatment of hyponatremia: compilation of the guidelines. *J Am Soc Nephrol*. 2017;28(5):1340-1349.
49. Coiffier B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol*. 2008;26(16):2767-2778.
50. Thosani S, Hu MI. Denosumab: a new agent in the management of hypercalcemia of malignancy. *Future Oncol*. 2015;11(21):2865-2871.
51. Basok AB, Rogachev B, Haviv YS, Vorobiov M. Treatment of extreme hypercalcaemia: the role of haemodialysis. *BMJ Case Rep*. .2018;2018:bcr2017223772.
52. Yeung SJ, Qdaisat A, Chaftari P, et al. Diagnosis and management of immune-related adverse effects of immune checkpoint therapy in the emergency department. *J Am Coll Emerg Physicians Open*. 2020;1(6):1637-1659.
53. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2018;36(17):1714-1768.

62 Oncocardiology

Elie Mouhayar
Danielle El-Haddad
Peter Kim
Kara Thompson
Cezar Iliescu
Abdulrazzak Zarifa

KEY CONCEPTS

- Myocardial dysfunction related to chemotherapy can be classified as type 1 or type 2. Type 1 is typically irreversible and associated with myocyte death. Anthracyclines are the prototype drugs that cause type 1 cardiotoxicity, and this can manifest months to years later. Thus, lifelong cardiac monitoring is recommended. Type 2 myocardial dysfunction is associated with reversible myocyte contractile dysfunction. Trastuzumab is the prototype drug causing type 2 dysfunction, but other targeted agents such as tyrosine kinase inhibitors (TKIs) can also cause type 2 cardiotoxicity. Trastuzumab can be reinitiated after recovery of left ventricular (LV) systolic dysfunction. Myocardial dysfunction is less common with TKIs than with trastuzumab, but LV dysfunction reverses in only about half of these patients.
- Cancer can be associated with risks for cardiovascular ischemia beyond traditional risk factors. These risks include hypercoagulability associated with cancer, development of coronary or carotid vascular disease related to radiation therapy, tumor embolization, and arterial ischemia related to chemotherapies (L-asparaginase, cisplatin, 5-fluorouracil, capecitabine, and gemcitabine) and angiogenesis inhibitors (thalidomide and TKIs).
- QT prolongation with risk of torsades de pointes is an important consideration in patients with cancer. Many cancer drugs prolong the QT interval, and this can be exacerbated by concomitant use of antiemetics, methadone, antibiotics, antifungal agents, antiviral agents, antiarrhythmic agents, and antipsychotics, and by electrolyte abnormalities. QT prolongation is particularly prominent with vandetanib, nilotinib, vemurafenib, and arsenic.
- Pericardial effusions are common in patients with cancer. Two thirds of pericardial effusions are nonmalignant and related to loss of lymphatic drainage or certain drugs or infection or radiation. The 1-year survival rate is 55% in nonmalignant effusions and dismal, 16%, with malignant effusions.
- Hypertension is commonly caused by angiogenesis inhibitors. Onset of hypertension is typically in days to weeks and usually returns to baseline after the vascular endothelial growth factor (VEGF) inhibitor is discontinued. It is not yet clear if hypertension can be considered a marker of response to therapy.
- Atrial fibrillation is common in patients with cancer, particularly after thoracic surgery. It often requires pharmacotherapy for rate or rhythm control, and anticoagulation must be guided by the risk of bleeding versus the risk of thromboembolism.

Oncocardiology is a fast-growing medical subspecialty focused on the management of heart diseases in patients with cancer. Although cancer remains a leading cause of morbidity and mortality worldwide, the survival rate of patients with cancer has increased in the last 25 years. In the United States, the 5-year relative survival rate of patients diagnosed with cancer between 1975 and 1977 was 50%. For patients diagnosed between 1999 and 2005, the survival rate increased to 68%. The U.S. National Cancer Institute estimates that at least 13.7 million cancer survivors were alive in the United States in 2012.[1] More recent data show a continued decline in cancer-related death over the past three consecutive decades with a 27% decrease in cancer mortality between 1991 and 2016.[2]

Although survival from cancer is improving, there is evidence that cancer survivors have an increase in cardiovascular (CV) events and CV mortality compared with age-matched control participants.[3] A survey of 1807 cancer survivors with a 7-year follow-up period

found that 33% of the survivors died of heart diseases, and 51% died of cancer.[4] Cancer survivors living at least 5 years beyond diagnosis are reported to have a 3.6-fold increased risk of CV-specific mortality and up to an 18.5-fold increased incidence of CV disease risk factors such as hypertension, diabetes mellitus, and dyslipidemia compared with age-matched counterparts with no cancer history.[5–7] These increased CV risks are likely the results of normal age-related pathologies in association with direct (ie, radiation therapy, chemotherapy) and indirect (ie, deconditioning, weight gain, oncometabolites) effects of cancer therapies and may partially explain the increased incidence of certain CV syndromes in this population, including a 2-fold increase in risk of arterial ischemia and up to a 15-fold increased risk for cardiomyopathy and heart failure (HF).[8–10]

Historically, since the late 1970s, the interest in chemotherapy-induced cardiotoxicity was focused on cardiomyopathy related to a few chemotherapeutic agents. As the field of cancer therapies has expanded, so has the finding of other CV side effects such as transient left ventricular (LV) dysfunction, hypertension, cardiac arrhythmias, pericardial effusions, and arterial ischemia.

Oncocardiology has evolved to address the CV needs of these patients whose optimal outcome mandates close and collaborative efforts between cardiologists and oncologists in a multidisciplinary approach. Involvement of cardiologists in the care of patients with cancer has changed from a focus on management of CV complications of therapy to consultation in the care of these patients from the initial cancer diagnosis to survivorship as outlined in Figure 62–1.

PATHOPHYSIOLOGY

Clinical knowledge and basic science discoveries in oncocardiology have grown over the past decade. The molecular mechanisms of cardiac toxicity caused by cancer drugs is now better understood. For example, the Bruton tyrosine kinase receptor is expressed in the atria of human heart tissue.[11] This tyrosine kinase is the target of the novel drug, ibrutinib, used in certain hematologic malignancies, including chronic lymphocytic leukemia. Ibrutinib has been associated with a significant incidence of atrial arrhythmias, possibly mediated by its on-target effect but more specifically mediated by inhibiting the phosphoinositide 3-kinase (PI3K)–Akt signaling pathway.[11] Another drug, trastuzumab, targets ErbB2 in breast cancer cells and improves outcome and prolongs survival in HER2+/ErbB2 patients with breast cancer. These same receptors within the cardiac myocyte are responsible for normal cell function and myocyte repair and, when affected by ErbB2 inhibitors such as trastuzumab, can develop secondary mitochondrial dysfunction.[12] Other mechanisms of toxicities have recently been reported with older, conventional, chemotherapeutic drugs such as the anthracyclines; recently, the CV toxicity of this drug has been linked to inhibition of topoisomerase IIβ.[13] This enzyme is responsible for normal myocyte function, and its inhibition partially explains the CV toxicity associated with Adriamycin.

Other chemotherapeutic agents such as cisplatin, 5-fluorouracil (5-FU), monoclonal antibodies against VEGF (vascular endothelial growth factor [VEGF]

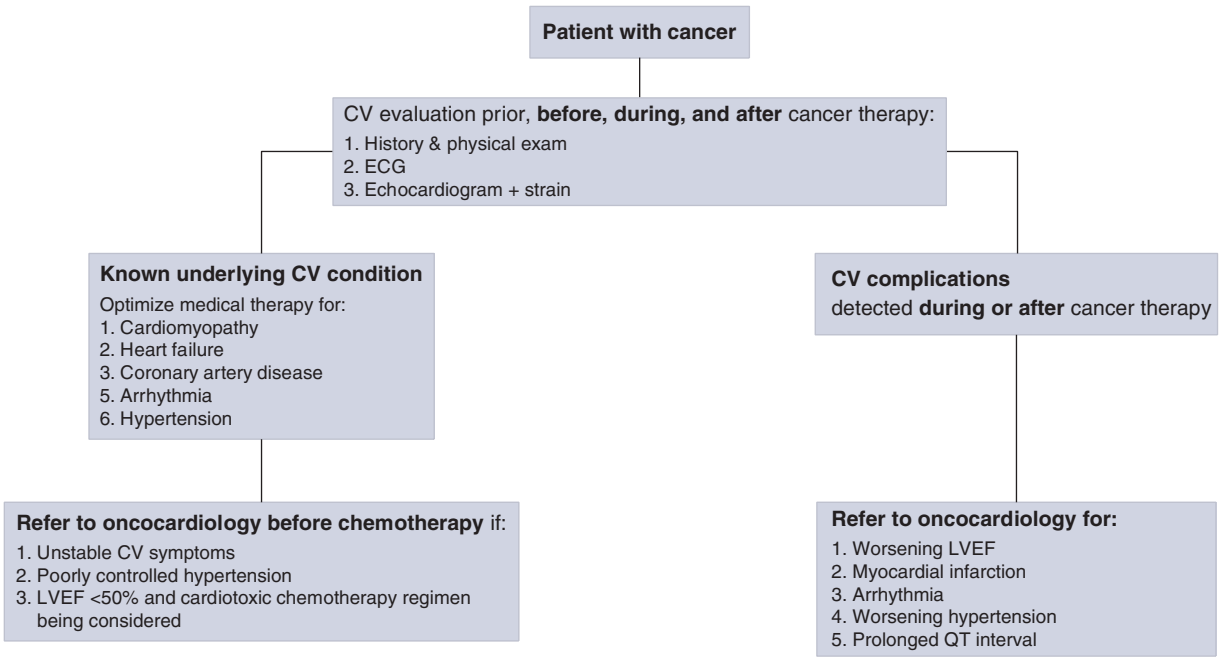


FIGURE 62–1 The general role of onco-cardiology algorithm. CV, cardiovascular; LVEF, left ventricular ejection fraction.

inhibitors), and several oral tyrosine kinase inhibitors (TKIs) (ie, ponatinib, sunitinib, sorafenib and others) are known to be associated with vascular toxicity. This toxicity is mediated via direct interference with normal physiologic endothelial function and alteration of the delicate balance of the coagulation factors, leading to a variety of vascular toxicities, including hypertension and arterial or venous thrombosis.

Certain TKIs such as crizotinib, ceritinib, and dasatinib can also cause QT prolongation because of interaction with myocardial human ether-a-go-go-related gene (hERG) Kþ channels, resulting in delayed repolarization.[14–16] They occur with variable frequency, which may be accentuated by drug interactions and genetic predispositions.[17]

Immune checkpoints inhibitors (ICIs) are a new category of targeted immunotherapy directed against mechanisms that cancer cells use to evade the immune system. They have been approved for the treatment of patients with metastatic melanoma, non–small lung carcinoma, and squamous cell carcinoma of the head and neck. They have been reported to cause myocarditis, pericarditis or pericardial effusion, cardiomyopathy, hypertension, and arrhythmia.[18,19] Data from animal models suggest that one potential mechanism of ICI-mediated cardiotoxicity involves modulation of the programmed cell death protein 1 (PD-1) pathway, which can lead to immune-mediated CV toxicity, primarily in the form of autoimmune myocarditis. Knockout of the PD-1 receptor in mice causes severe dilated cardiomyopathy characterized by high levels of immunoglobulin G autoantibodies that react specifically to cardiac troponin.[20]

Chest radiation used to treat patients with Hodgkin lymphoma, esophageal, lung, and breast cancers can cause injury to cardiac myocytes within or near the radiation field. This can result in vascular injury, direct myocyte damage, and alterations in cardiac conduction.[21] Radiation-induced arrhythmias are likely caused by microvascular damage to the sinoatrial and atrioventricular nodes, leading to bradycardia or heart block.

Infiltrative processes are another cause of cardiomyopathies commonly encountered in patients with cancer. Examples include amyloidosis and secondary hemochromatosis. In patients with myelodysplastic syndrome, myocardial iron overload develops from frequent blood transfusions (ie, >100 units).

In addition to the benefit of improving strategies to prevent drug toxicities, a better understanding of these biologic pathways that are important for cancer therapy may also provide a better understanding of certain heart diseases and their management. For example, the discovery of the key role of ERB2 in normal cardiac function and its relation to trastuzumab toxicity was followed by the discovery of the benefit of an ERB2 agonist called neuregulin-1 in the animal models of HF. Neuregulin-1 is currently being studied as a treatment of HF in humans.[22]

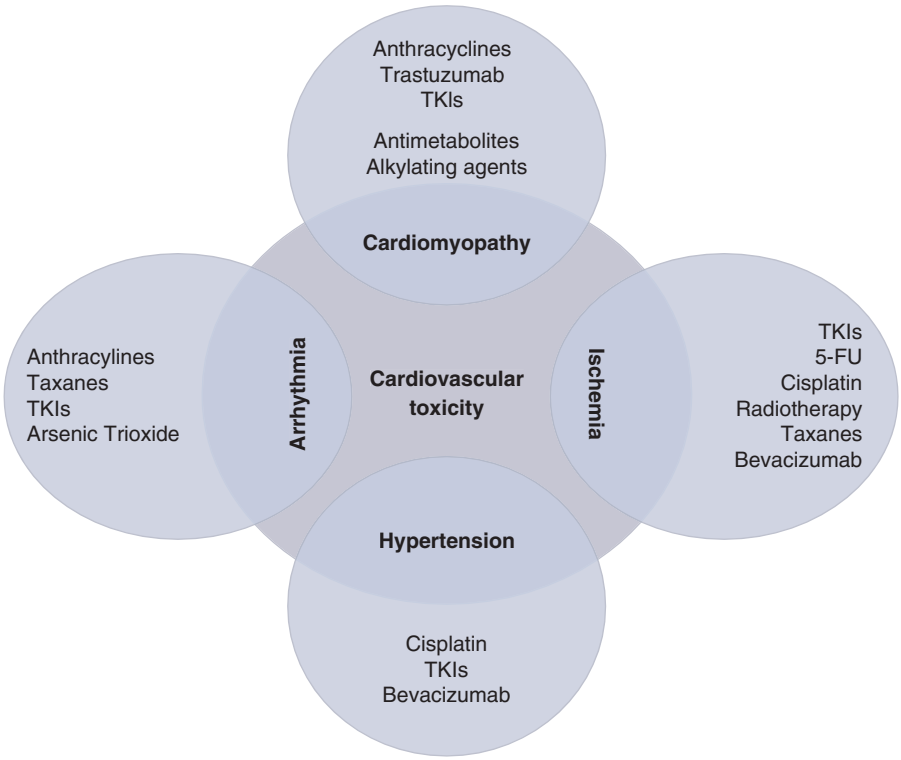


FIGURE 62–2 Cardiovascular syndromes associated with certain chemotherapy agents. 5-FU, 5-fluorouracil; TKI, tyrosine kinase inhibitor.

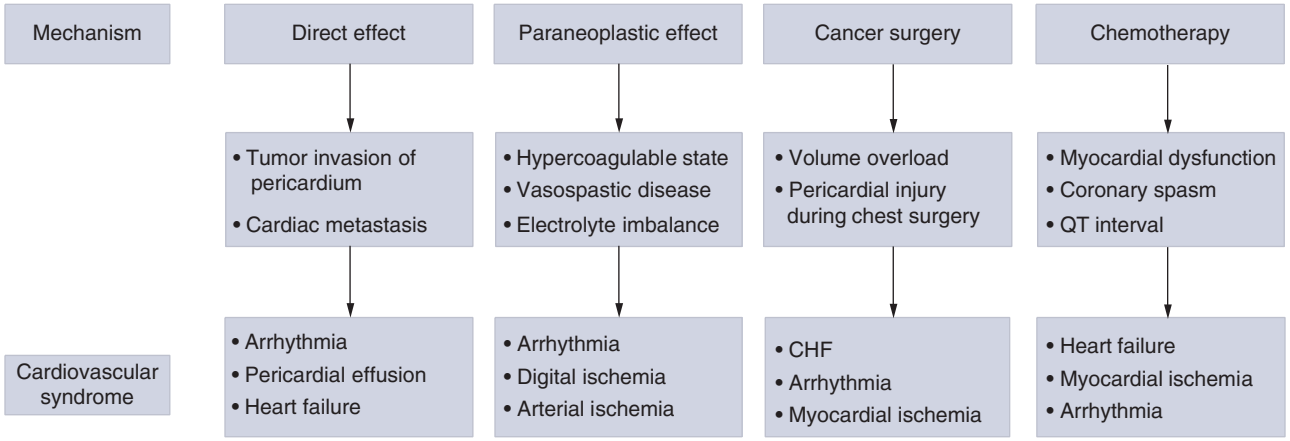


FIGURE 62–3 **Mechanisms and causes of some cardiovascular syndromes observed in patients with cancer. CHF, congestive heart failure.**

Cardiovascular Syndromes Observed in Patients with Cancer

In addition to the direct cardiac toxic effect of certain cancer drugs (Fig. 62–2), many aspects of the CV system can be affected by cancer or cancer therapy, resulting in a variety of CV syndromes (Fig. 62–3).

MYOCARDIAL DYSFUNCTION

Oncocardiologists are often asked to assess patients with cancer with clinical HF symptoms. Although the most feared etiology is the progressive, permanent, and irreversible myocardial damage related to anthracycline toxicity, this in fact constitutes only a small percentage of patients with cancer with clinical HF. The majority of these patients with new-onset HF in the setting of cancer and cancer therapy have symptoms triggered by mechanisms other than anthracycline toxicity. Despite some overlap, a clinically useful approach to evaluating and managing these patients is to divide them into two groups based on their initial clinical presentation as shown in Table 62–1. The first group includes patients presenting with sudden and new-onset acute HF with associated systolic dysfunction. These include cardiomyopathies related to sepsis, stress cardiomyopathy, and myocarditis (toxic or infectious). The second group includes patients presenting with subacute or chronic HF symptoms and includes those with underlying structural heart disease, those with chemotherapy-induced cardiomyopathy, and those with infiltrative myocardial conditions related to their underlying malignancies (ie, amyloidosis) or to cancer therapy (ie, iron overload). Evaluation of these patients typically includes a two-dimensional echocardiogram, cardiac biomarkers (brain natriuretic peptide and troponin), thyroid function tests, iron or ferritin level, ischemia assessment, and occasionally an endomyocardial biopsy.

Acute Cardiomyopathy

The majority of these cases are related to conditions referred to as reversible myocardial dysfunction, or more commonly, stress cardiomyopathy. This phenomenon is typically triggered by sepsis but also occurs in a wide range of acute illnesses (see Table 62–1). Myocardial dysfunction in fact has been documented in up to 40% of patients with sepsis and is a major predictor of mortality in this population.[23,24] During the course of malignancy management, patients with cancer are at risk of going through these acute illnesses, especially during chemotherapy with associated secondary neutropenic sepsis. Physiologically, both left and right ventricular systolic functions are diminished with variable degrees of myocardial depression. This function is typically reversed

TABLE 62–1 Causes of Left Ventricular Systolic and Diastolic Heart Failure in Patients with Cancer

Acute Left Ventricular Systolic Dysfunction (Acute Cardiomyopathy)	Subacute or Chronic Left Ventricular Dysfunction (Cardiomyopathy)
Stress cardiomyopathy	Preexistent cardiomyopathy
Sepsis	Ischemic heart disease
Myocarditis	Nonischemic cardiomyopathy
Viral	Hypertensive heart disease
Chemotherapy	Chemotherapy
Myocardial infarction	Infiltrative cardiomyopathy
Metabolic derangement	Amyloid heart disease
Hypocalcemia	Iron overload

within 7 to 10 days. The exact mechanism for myocardial dysfunction is not well defined, and multiple theories have been suggested including the possibility of altered microcirculatory flow, mitochondrial dysfunction, myofibrillary dysfunction, autonomic dysregulation, altered calcium cellular transportation, and others (Fig. 62–4).[23,25] Clinically, patients with reversible myocardial dysfunction or stress cardiomyopathy are recognized when evidence of new-onset LV dysfunction is documented in the appropriate clinical setting (see Table 62–1). It is frequently associated with repolarization abnormalities on electrocardiography (ECG) and a minimal rise in cardiac troponins. Echocardiographic findings of severe LV dysfunction are typically out of proportion to the ECG changes and the rise in cardiac troponins. The severity of LV dysfunction, however, correlates well with B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP)levels.[23,25] Management is focused on stabilizing blood pressure (BP) using vasopressors if shock is present and transitioning to cardioprotective drugs such as angiotensin-converting enzyme (ACE) inhibitors and β-blockers after the patient is weaned off of pressure support and after BP is stable for 24 to 48 hours.[23] Persistent LV dysfunction beyond 2 weeks should raise suspicion for possible underlying ischemic heart disease or possible viral myocarditis in the setting of immune-compromised patients. These two conditions are typically associated with significant rise in cardiac biomarkers such as troponin and CK-MB (creatine kinase myocardial band). Patients with suspected ischemic heart disease should undergo evaluation and management of coronary artery disease. The diagnosis of viral myocarditis is more challenging because viral cultures and antibody titers have limited diagnostic accuracy. Myocardial biopsy is the gold standard in the general population for diagnosis of viral myocarditis despite its limited diagnostic yield (60% sensitivity and 80% specificity)[26] and can be even more challenging and risky in patients with cancer because they often have coagulopathy with risk of procedural related complications (bleeding, myocardial perforation). The use of empiric therapy with intravenous immunoglobulin (IVIG) for antiviral and immunomodulatory effect in this setting is controversial, especially in view of limited data to supporting benefit of such intervention in the adult population.[27] IVIG is also typically associated with high volume fluid shift, which can exacerbate HF. A suggested algorithm for evaluation of new-onset cardiomyopathy and HF in patients with cancer is summarized in Figure 62–5.

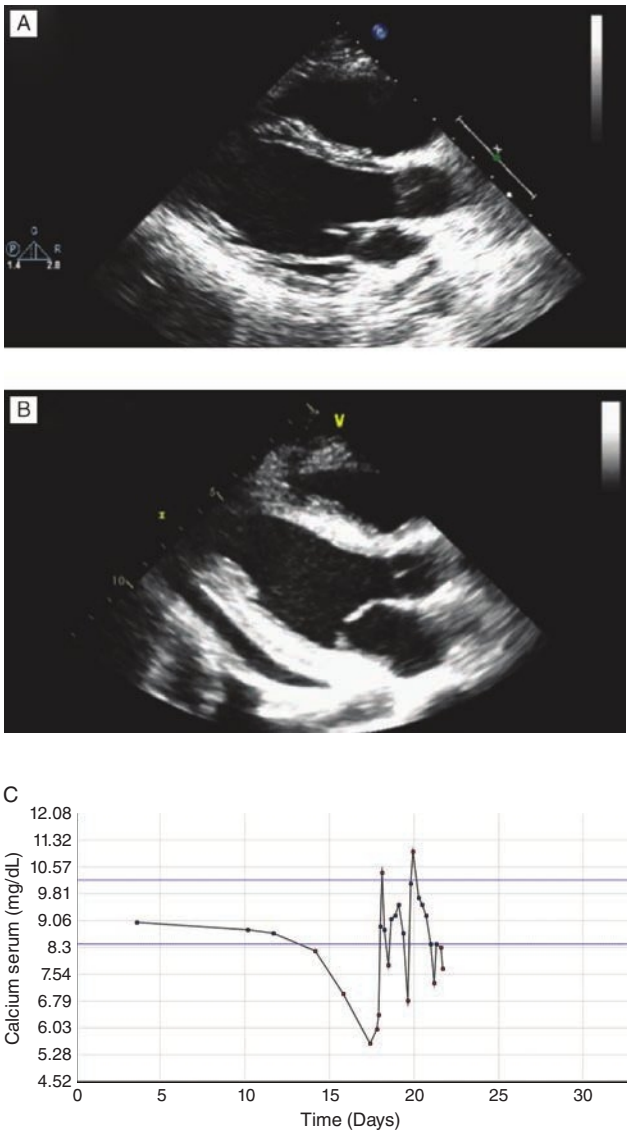


FIGURE62–4 Acute severe cardiomyopathy with shock after chemotherapy for ovarian cancer complicated by severe hypocalcemia. Echocardiographic studies show baseline normal left ventricular systolic function (A), severely depressed systolic function with small pericardial effusion 48 hours after developing severe hypocalcemia (B) after chemotherapy (C).

Cancer Therapy–Induced Cardiomyopathy

Chemotherapy-Induced Cardiomyopathy

Definition

A large number of chemotherapeutic agents have been linked to cytotoxic myocardial injury. Table-62–2 lists several groups of chemotherapeutic agents known to be associated with LV systolic dysfunction or HF. The ones most commonly associated with chemotherapy-induced cardiomyopathy include anthracyclines, alkylating agents, and TKIs. Despite a lack of consensus, cardiotoxicity generally is defined as a drop in left ventricular ejection fraction (LVEF) by 5% or more, to less than 55% in the presence of HF symptoms, or an asymptomatic drop in LVEF by 10% or more to less than 55%.[28] Myocardial toxicity is also classified into type I and type II based on the nature of myocyte injury.

Type I Myocardial Toxicity

Anthracyclines are the prototype drugs that cause type irreversible myocyte damage. Histologic findings include myofibrillar disarray, disruption of cellular organelles, myofibrillar loss, and myocyte death.[29] Myocardial toxicity is dose dependent with a less than 5% chance of cardiomyopathy observed at a cumulative dose of less than 400 mg/m^2 for Adriamycin (150 mg/m^2 for idarubicin and 900 mg/m^2 for epirubicin). This risk jumps to 26% at a cumulative dose of 550 mg/m^2.[30] Anthracycline-related cardiotoxicity has also been classified as acute or chronic. The acute form manifests as nonspecific ECG changes, arrhythmia, myopericarditis, and transient LV dysfunction. The more feared chronic form is marked by LV systolic dysfunction occurring many months to years after exposure and manifests as progressive HF. It is not clear if the acute form of anthracycline-induced cardiotoxicity is in fact the prodrome of the more delayed cardiomyopathy form because it has been shown that myocyte dysfunction can be present even after the first dose of the drug. It is plausible that myocardial reserve allows normal cardiac function despite initial injury until a second insult leads to further myocardial cell loss and subsequent systolic dysfunction. The long-term prognosis for patients with chemotherapy-induced cardiomyopathy is much worse than for those with other causes.[31] For years, the understood mechanism has been based on the free radical and iron hypothesis: the addition of an electron to the quinone moiety of anthracyclines within the cardiomyocytes leads to the generation of excess reactive oxygen species (ROS) and subsequent mitochondrial and intracellular protein damage. This toxicity is further increased when ROS interact with iron, generating a surge of oxidative stress.[32] More recently, the role of topoisomerase IIβ was found to be a key mediator of anthracycline-induced

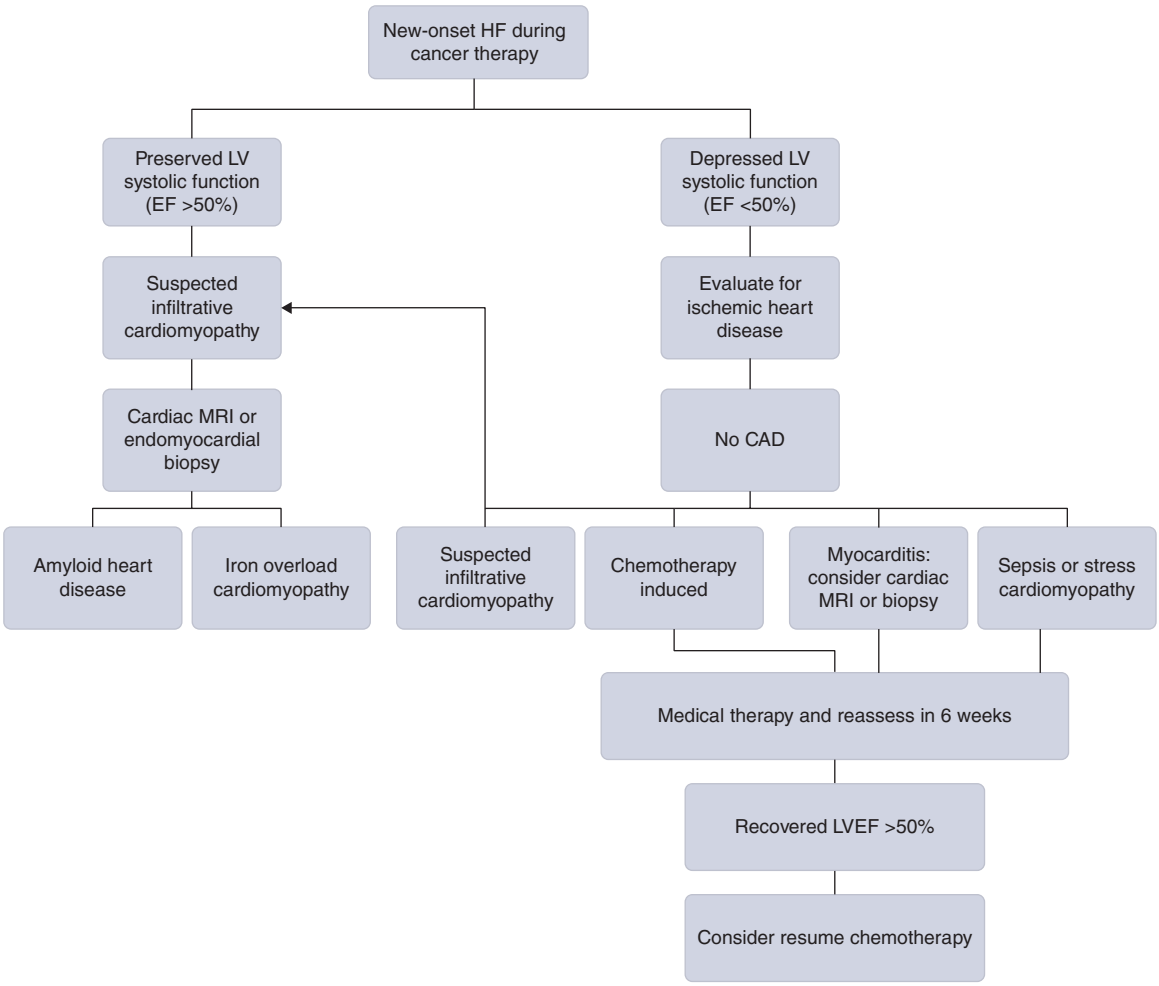


FIGURE 62–5 Algorithm for evaluation of patients with acute cardiomyopathy during cancer therapy. CAD, coronary artery disease; EF, ejection fraction; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging.

TABLE 62–2 The Most Commonly Used Chemotherapeutic Agents Known to Be Associated with Left Ventricular Systolic Dysfunction or Heart Failure

Chemotherapeutic Agent	Mechanism of Toxicity	Cardiomyopathy Incidence	Other Cardiovascular Toxicity
Anthracyclines			
Doxorubicin		5% at 400 mg/m^2 18% at 700 mg/m^2	Arrhythmia
Epirubicin	Oxidative stress		Pericarditis
Idarubicin	Inhibition of topoisomerase IIβ	4% at 900 mg/m^2 15% at 1 g/m^2 5%	Arrhythmia
Anthracycline analogue			
Mitoxantrone		2. 6%	Arrhythmia Hypertension
Monoclonal antibodies			
Rituximab	No direct toxicity		
Cetuximab	Hypomagnesemia related arrhythmia		Arrhythmia
Alemtuzumab	Infusion-related hemodynamic effect	<0.5%	Hypotension
Trastuzumab	ERB/2 receptor–mediated myocyte dysfunction	2%–28%	
Bevacizumab	VEGF inhibition Hypertension-mediated cardiomyopathy	1. 7%–3%	Arterial thrombosis Hypertension
Alkylating agents (at high doses)	Myocarditis	3%–25%	Tamponade
Cyclophosphamide (>1.5 mg/m^2)	Myocardial fibrosis	Rare	Pericardial effusion
Busulfan	Myocarditis	17%	Myocardial infarction, arrhythmia
Ifosfamide (>1 g/m^2)			
Antimetabolites			
Gemcitabine	Noncardiogenic pulmonary edema	7. 1%	
5-FU		2%	Ischemia
Antimicrotubule agents			
Vinca alkaloids (vincristine, vinblastine)	Impairment of myocardial metabolism	3%	Coronary spasm Hypertension
Oral TKIs			
Dasatinib	Mitochondrial toxicity	1%–4%: HF	Hypertension
Lapatinib	Dysregulation of cellular energy		QT prolongation
Pazopanib		Up to 10%–28%: LV systolic dysfunction	Arterial thrombosis
Sorafenib	Mitochondrial toxicity		Arrhythmia
Sunitinib			Fluid retention
Vandetanib			

5-FU, 5-Fluorouracil; FHF, heart failure; LV, left ventricular; tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

cardiomyocyte toxicity. Topoisomerase IIβ is an enzyme present in heart tissue that modulates DNA. Anthracycline-mediated inhibition of topoisomerase IIβ causes double-stranded DNA breaks, which can lead to cardiomyocyte death.[13,33] In a small study by Vejpongsa and Yeh,[33] the level of topoisomerase IIβ was significantly higher in an anthracycline-sensitive group. In the future, use of the topoisomerase IIβ level in peripheral blood leukocytes could be of potential benefit for risk stratification and as a surrogate

biomarker for individual susceptibility to anthracycline- induced cardiotoxicity. Presently, there is not a way to predict which patients will be at higher risk of developing cardiotoxicity from anthracyclines. Close cardiac monitoring with early recognition and treatment of LV dysfunction using β-blockers and ACE inhibitors within the first 6 months of onset has been shown to be associated with a better chance of stabilization and even recovery of cardiac function.[34] These observations are the basis of the current recommendations for routine cardiac monitoring during anthracycline therapy. Different diagnostic tools have been useful in monitoring these patients, including the use of cardiac biomarkers and cardiac imaging studies.[35] However, there is no consensus regarding the best approach and optimal timing for testing. At MD Anderson Cancer Center (MDACC), we typically rely on serial imaging with two- and three-dimensional echocardiography with myocardial strain to monitor these patients as shown in Figure 62–6.

Multiple primary prevention measures have been suggested to lower the risks of anthracycline-induced cardiomyopathy. Continuous infusion instead of repetitive boluses has been shown to be associated with a lower incidence of myocyte damage.[36] The mechanism is believed to be related to the fact that the peak plasma level correlates with the degree of myocyte toxicity, and the area under the curve determines antitumor efficacy. The use of modified preparations of anthracyclines such as liposomal doxorubicin has been associated with lower risk. The use of dexrazoxane is thought to lower risk through iron chelation and through interference with the topoisomerase IIβ complex by preventing it from binding to anthracyclines. In addition, the use of β-blockers and ACE inhibitors or angiotensin receptor blockers has been associated with mixed results in several small prospective studies.[37,38] It is not clear if these medications exert potential cell protection effect or if they only have beneficial hemodynamic effect. At this stage, their role in primary prevention of chemotherapy-induced cardiotoxicity is uncertain.

Type II Myocardial Toxicity

This type of toxicity is associated with reversible disruption of myocyte contractile function; trastuzumab is the prototype drug. Other targeted chemotherapy agents, including several small-molecule oral TKIs, are also suspected to exert type II cardiotoxicity. The mechanism involves disruption of certain signaling pathways responsible for tumor growth and responsible for cardiac cell repair (ErbB2 in the case of trastuzumab), resulting in subsequent myocyte dysfunction but no cell death.[39] Up to one third of patients treated with trastuzumab develop evidence of LV systolic dysfunction or HF symptoms that are often reversible upon discontinuation of this agent.[40] Reinitiation or continuation of trastuzumab after LV systolic function recovers is usually well tolerated. The Food and Drug Administration (FDA) recommends monitoring LV function with imaging every 3 months during therapy. Observational studies, however, have shown that not all patients are at the same risk. Several predisposing factors increase susceptibility for trastuzumab

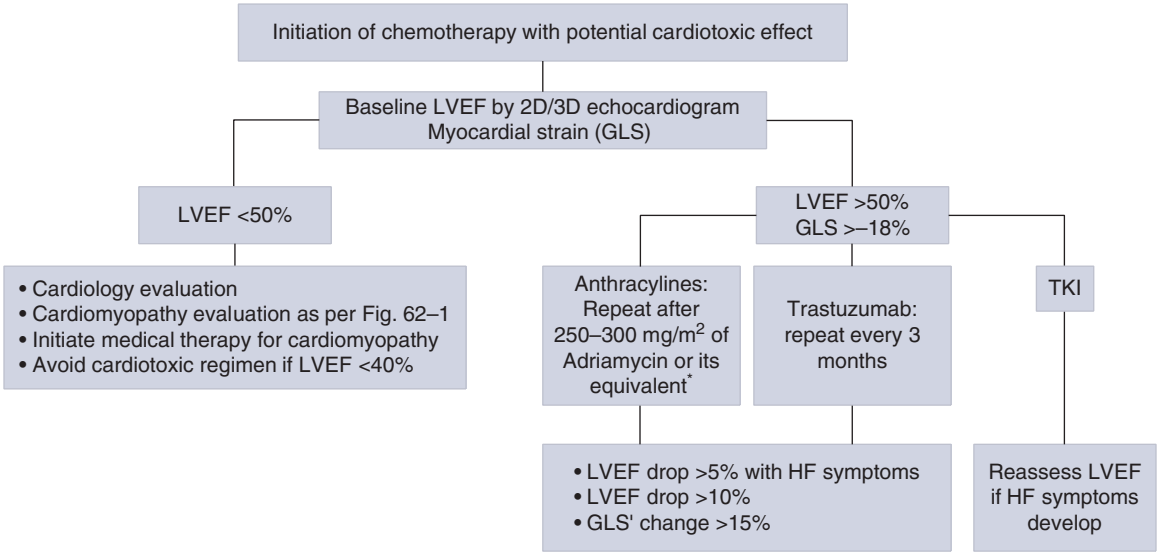


FIGURE 62–6 Algorithm for cardiac monitoring and management of patients receiving potentially cardiotoxic chemotherapy. *Asterisk* **indicates equivalent cardiotoxicity dose to 300 mg/m² of Adriamycin = 150 mg/m² of idarubicin = 900 mg/m² of epirubicin. GLS, global longitudinal strain; HF, heart failure; LVEF, left ventricular ejection fraction; 3D, three-dimensional; TKI, tyrosine kinase inhibitor; 2D, two-dimensional.**

cardiotoxicity. These factors include concomitant use of anthracyclines, advanced age, and hypertension or other underlying structural heart disease. There is an incremental increase in the incidence of LV systolic dysfunction or HF as the number of these risk factors increases. For example, the risk of myocardial dysfunction increases from less than 1% in a young woman with no risk factors to 27% in an older adult patient receiving concomitant anthracylines.[28] A clinical risk stratification model (National Surgical Adjuvant Breast Project (NASBP) cardiac risk score) has been proposed to help risk stratify these patients, but the model needs further studies to be validated.[41]

TKI-related LV dysfunction has been reported since early phase I and phase II clinical oncologic trails. Mechanisms of toxicity are not fully understood; several theories have been proposed, including apoptotic versus nonapoptotic cell death, dysregulation of cellular energy hemostasis through inhibition of 5-adenosine monophosphate-activated protein kinase (AMPK),[42] mitochondrial toxicity, and hypertension-mediated LV dysfunction.[43] The reported incidence of TKI-related cardiomyopathy and HF varies widely between each individual drug (mostly reported with sunitinib, sorafenib, and imatinib) and differs between studies by almost 10=-fold; this is partially related to the fact that cancer trials typically do not have CV events as outcomes, and this likely leads to underestimation of the incidence rate of such events. In addition, the usual clinical HF symptoms of fatigue, dyspnea, and edema of the legs are nonspecific to patients with cancer, leading to limitations in clinical diagnostic accuracy. The incidence of symptomatic HF necessitating medical therapy varies between 1.5% and 15%, and the rate of reported drop in LVEF is between 7% and 28%.[43–47] Time to onset of cardiomyopathy varies between a few weeks to several months after initiation of TKIs. Evidence of reversibility of significant LV dysfunction was seen in only half of the patients after TKIs were discontinued.

Management

When clinical HF or LV systolic dysfunction is confirmed, patients typically are taken off their TKI, and HF drugs are initiated (ACE inhibitors, β-blockers, and diuretics).[48–50] Depending on the patient risk factors and clinical presentation, workup for other possible causes of cardiomyopathy should be performed when appropriate (ie, ischemic heart disease, hypertension). In the absence of strong prospective data, there is not enough information at this stage to support the routine use of cardiac imaging to routinely monitor asymptomatic patients. It is common practice to obtain a baseline two-dimensional echocardiogram study before initiating these drugs with low clinical threshold to obtain repeated echocardiographic studies if dyspnea or fluid retention symptoms develop in patients treated with TKIs.[35,51,52]

Immune Checkpoints Inhibitor–Induced Myocarditis

The incidence of severe adverse events of myocarditis were reported in 0.09% to 2.4% of cancer patients receiving immune check point inhibitors (ICI).[53,54] The combination use of ICIs such as nivolumab and ipilimumab report more frequent and severe myocarditis than single-agent nivolumab (0.27% vs 0.06%; P <.001; five fatal events vs one event).[55] The median latency between receiving the combination of ipilimumab and nivolumab and developing myocarditis was 17 days after the first treatment (range, 13–64 days).[55] However, there have been cases of events developing beyond 32 weeks after starting treatment.[56]

The risk factors might include diabetes mellitus, obstructive sleep apnea, and body mass index greater than 26 in patients receiving combination therapy.[54] Patients with a previous history of cardiac diseases might develop myocarditis. In a small case series of 17 patients, no obvious cardiac- or cancer-specific clinical features predisposed patients to severe myocarditis. However, in a case series of eight patients, five had preexisting CV disease.[57]

Because immune-mediated myocarditis can have a fulminant progression, a close monitoring strategy is recommended, especially when patients with receiving combination therapy.[55] A baseline ECG and weekly testing of troponin levels during weeks 1 to 3 for patients receiving combination immunotherapy is a reported approach.[55] Nonetheless, upon the development of symptoms, a more extensive workup is necessary and should be directed by a consulting cardiologist.[58] Initial workup for those with symptoms includes ECG, troponin, BNP, echocardiography, and chest radiography. High clinical suspicion can require additional testing, including cardiac catheterization with endomyocardial biopsy, cardiac magnetic resonance imaging (MRI), or both.[54,58] The updated Lake Louise Criteria are used in diagnosing myocarditis by cardiac MRI. If one of the main criteria is present, either T2-based marker for myocardial edema (T2mapping or T2-weighted images) or T1-based marker for nonischemic myocardial injury, myocarditis is diagnosed by MRI. Supportive criteria include signs of pericarditis or systolic dysfunction with regional or global wall motion abnormalities (although most cases maintain a preserved LVEF).[57,59] The role of biomarkers is not completely clear, but a troponin T value of equal or greater than 1.5 ng/mL seems to indicate a signal in identifying patients with ICI-related myocarditis and a higher risk of major CV events.[60]

The Society for Immunotherapy of Cancer Toxicity Management Working Group and the American Society of Clinical Oncology have developed clinical practice guidelines that were published in 2017 and 2018, respectively.[58,60] Contrary to the general notion

with the majority of immune-related adverse events (irAEs) in which toxicity can be closely monitored if it is grade 1, the recommendation is to hold ICI for grade 1 cardiac irAEs and permanently discontinue ICI if the cardiac irAE is beyond grade 1. The management of grade 3 and 4 is according to 2019 National Comprehensive Cancer Network guidelines. Initial treatment recommendations include high-dose corticosteroids (1 mg/kg of methylprednisolone for 3–5 days) until cardiac function return to baseline that is then tapered over 4 to 6 weeks. If there is no improvement within 24 hours on steroids, patients with elevated troponin or conduction abnormalities may need immediate transfer to a coronary care unit for further investigation. Addition of antithymocyte globulin and infliximab might be considered.[61] Rechallenging with ICI after myocarditis is controversial given high risk for further cardiac complications.[60] Conduction abnormalities such as high-degree atrioventricular (AV) block maybe seen in fulminant cases.[55] Although the prognosis is poor, our institution reported a case of a patient who presented with third-degree AV block and survived. The patient worsened after treatment with high-dose steroids, but after adding mycophenolate mofetil, he showed clinical improvement. Another treatment to consider for severe, steroid-refractory ICI myocarditis is abatacept, a cytotoxic T-cell lymphocyte antigen-4 (CTLA-4) agonist. Abatacept inhibits CD28–B 7–mediated T-cell co-stimulation at the level of dendritic cells and thus may lead to rapid global T-cell anergy with limited off-target effects of ICI.[62]

Unfortunately, some cardiac toxicities are fulminant and progress to death. However, with prompt recognition and therapy, cardiac contractility and conduction abnormalities can improve.[63] Currently, the relative rarity of these adverse events limits the ability to predict progression or resolution with more certainty. Nevertheless, with more patients receiving immune therapies, the incidence of such events is anticipated to increase, which may provide clarity on treatment algorithms.

Preexisting Cardiac Dysfunction

Patients with underlying diastolic or systolic LV systolic dysfunction, including hypertensive heart disease, ischemic heart disease, or nonischemic cardiomyopathy, are at greater risk of HF in the setting of cancer and cancer therapy. Decompensated HF symptoms in these patients are often triggered by large amounts of intravenous (IV) fluids given during certain chemotherapy infusions (ie, cisplatin). These patients typically respond well to withholding fluids and using diuretics. Standard HF therapies, including β-blockers and ACE inhibitors, are indicated if LV systolic dysfunction is present.[64]

ISCHEMIC ARTERIAL DISEASE IN PATIENTS WITH CANCER

The association between malignancy and ischemic arterial diseases is well established in the literature. The clinical presentation and management of arterial ischemic events in general vary based on the arterial bed and the organ involved; the clinical spectrum includes stroke, myocardial infarction, and visceral and limb ischemia. Looking at two large separate cohorts of patients with cancer, Khorana et al[65,66] reported a 1.5% to 3.1% incidence of arterial ischemic events. The most common events were cardiac, and fewer than 0.5% of events involved limb ischemia. The rate of arterial ischemic events is much higher in specific cancer populations such as those with myeloproliferative disorders (MPDs) and those with hematologic malignancies with secondary amyloidosis. To assess the significance and outcome of these arterial events, Khorana et al[67] prospectively followed 4466 patients with cancer receiving active chemotherapy. Death from thromboembolism was a leading cause of death (9.2%) with a higher rate of death from arterial events compared with venous events.

Etiology and Mechanisms

In addition to the usual causes and the traditional risk factors typically associated with arterial ischemia in the general population, patients with underlying malignancy have added increased risks for arterial ischemic events related to the inherent thrombophilia associated with their cancer and its therapy (Table 62–3). From the clinical perspective, it is useful to divide these cancer-related causes into two broad categories; the first category includes mechanisms, and the second group includes cancer etiologies.

Specific Mechanisms of Arterial Ischemia in Patients with Cancer

Hypercoagulability

Multifactorial mechanisms have been implicated in the pathogenesis of hypercoagulability and thrombosis in the setting of underlying cancer. As shown in (Figure 62–7), circulating and in situ cancer cells can enhance the activity of tissue factor and other cancer procoagulant factors and can activate platelets. These mediators can then trigger coagulation in previously damaged vessels such as the coronary arteries or peripheral arteries or in even previously healthy vessels.[68] The result is cancer enhanced thrombosis, which manifests as (1) low-grade disseminated intravascular coagulation, (2) venous thrombophlebitis, (3) arterial thrombosis, (4) accelerated ischemic

TABLE 62–3 Potential Causes of Arterial Ischemic Events in Patients with and without Malignancy

Patients without Cancer	Patients with Cancer	
Atherosclerosis	Paraneoplastic syndrome	Leukemia
Atrial fibrillation	Tumor invasion	Amyloidosis
Aortic arch plaques	Tumor embolization	Myeloproliferative disorders
Mitral stenosis	Paradoxical embolization	Chemotherapy
Valvular prostheses		Radiation therapy
Infective endocarditis		
Thrombophilia		
Antiphospholipid syndrome		
Antithrombin deficiency		
Protein C and S deficiency		

cardiac and peripheral vascular disease, and (5) nonbacterial thrombotic endocarditis. Another subgroup of patients with cancer with a hypercoagulable condition present with digital ischemia with no evidence of large-vessel involvement (Fig. 62–8). The mechanism is thought to be capillary deposition with antigen-mediated antibody complexes from tumor cells. This paraneoplastic syndrome is usually very difficult to treat; symptoms do not respond to usual vascular therapy until the cancer is fully controlled.[69]

Other Mechanisms

Other reported causes include radiation therapy, tumor embolization, arterial wall invasion by tumor and paradoxical embolization. Often, a specific cause is never identified. In our cohort of 74 patients with acute arterial limb ischemia, 24 confirmed pathology samples were available. The majority of patients (67%) had thrombus, and 21% had associated underlying significant atherosclerotic disease.[70] Tumor invasion of the artery was observed in two patients, and only one patient with leukemia had leukemic cell aggregates (Fig. 62–9).

Thrombotic Events Associated with Specific Malignancies

Myeloproliferative Disorders

MPDs, such as polycythemia vera (PV) and essential thrombocythemia (ET), are associated with vascular events characterized by microcirculatory dysregulation and thrombosis in various central and peripheral terminal arterial beds, leading to ischemic strokes

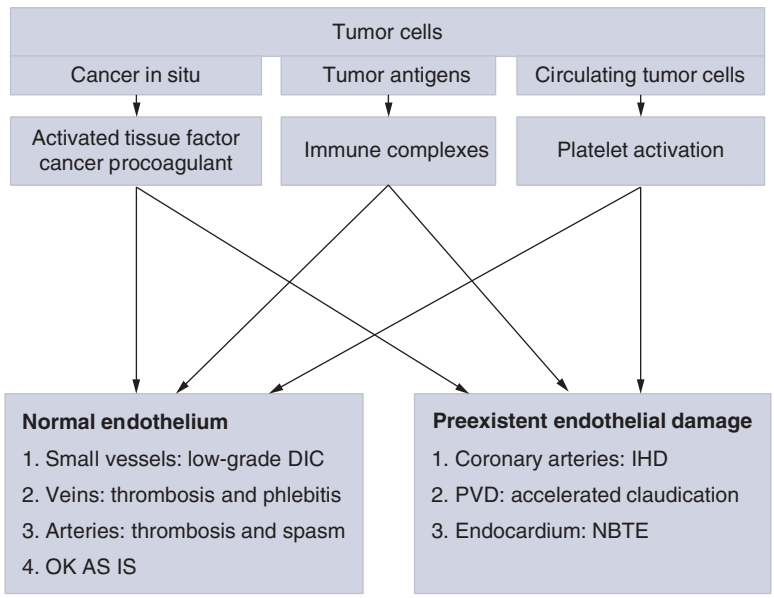


FIGURE 62–7 Suggested mechanisms for the enhanced thrombosis observed in patients with cancer.[47] DIC, disseminated intravascular coagulation; IHD, Ischemic heart disease; PAD, Peripheral Arterial Disease; NBTE, nonbacterial thrombotic endocarditis.



FIGURE 62–8 Digital ischemia in a 72-year-old man with small cell lung cancer.

and acute coronary syndrome.[71,72] The incidence of thrombosis upon diagnosis with PV and ET has been reported between 9.7% and 38.6% in various studies, with 64% to 96.7% of these being arterial events.[73] Primary prevention of thrombosis in MPD involves the use of aspirin.[74]

Acute Leukemia

Although hemorrhage is the typical complication in acute leukemia, arterial ischemic events caused by thrombosis can occur as well. De Stefano et al[75] reported a 1.4% incidence of thrombosis at presentation in acute lymphoblastic leukemia and a 9.6% incidence in acute promyelocytic leukemia. Thromboembolism was reported as the presenting manifestation in more than half of the patients in this study, with 80% venous thromboembolisms (VTEs) and 20% arterial ischemic events.[75] Options for management include leukapheresis, urgent chemotherapy, and sometimes revascularization for large-vessel occlusion.[75]

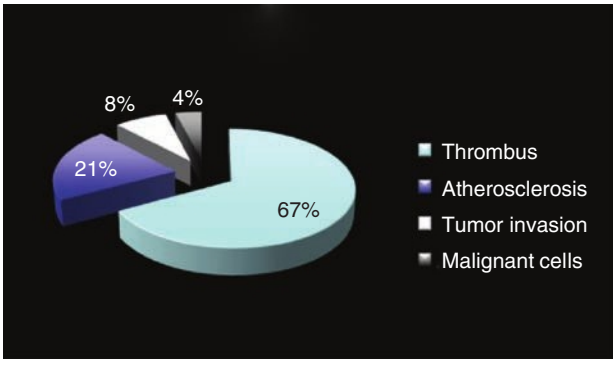


FIGURE 62–9 Cause of acute arterial ischemia at MD Anderson Cancer Center.[37]

Cardiac Amyloidosis

Primary amyloidosis, particularly AL type, has been associated with intracardiac thrombosis and thromboembolic events despite preserved LV ejection fraction and absence of cardiac arrhythmias, with an incidence ranging from 26% to 33%[76,77] and an arterial thromboembolism-related mortality rate of 26% in one study.[77] A variety of mechanisms have been proposed for this phenomenon, including endothelial dysfunction, endomyocardial damage,[78] direct myocardial toxic effect,[79] and hypercoagulability.[80] In managing these patients, the benefit of prophylactic anticoagulation needs to be balanced against the risk of hemorrhage from fragile blood vessels with amyloid deposition.[81]

Arterial Ischemic Events Related to Cancer Management and Therapy

Certain chemotherapeutic agents are known to have a stronger association with arterial ischemic events because of specific pathophysiological mechanisms. These drugs can be divided into two categories (Table 62–4). The first category includes several standard chemotherapeutic agents such as L-asparaginase, cisplatin, 5-FU, capecitabine, and gemcitabine. In a study by De Stefano et al,[75] the incidence of thrombosis in a population with acute lymphoblastic leukemia was shown to increase from 1.4% to 10.6% with L-asparaginase treatment. Cisplatin is known to induce thrombosis by causing endothelial damage and increasing monocyte tissue factor activity and platelet activation with a reported 12% to 17.6%[82] incidence of thrombosis, including strokes, recurrent peripheral arterial events, and aortic thrombosis.[83] 5-FU leads to a decrease in

TABLE 62–4 Chemotherapeutic Agents Associated with Arterial Ischemic Events

Cisplatin
L-Asparaginase
Fluorouracil
Gemcitabine
Capecitabine
Angiogenesis inhibitors: Thalidomide Bevacizumab Sunitinib Sorafenib Ponatinib

protein C and endothelial-independent vasoconstriction via protein kinase C.[84] Gemcitabine has been associated with vascular events ranging from systemic capillary leaks and thrombotic microangiopathy with digital ischemia to VTE.[85]

The second category of cancer drugs associated with arterial ischemia includes the group of angiogenesis inhibitors such as thalidomide and several targeted therapy drugs also known as the vascular signaling pathway inhibitors (VSPIs). These include bevacizumab and several TKIs such as sunitinib, sorafenib, axitinib, pazopanib, and ponatinib. Thalidomide is associated with a risk of vascular thrombosis because of its antiangiogenetic effect and its modulation of adhesion molecules.[86,87] This increased risk was evaluated by Libourel et al.[88] In their prospective cohort study of 195 patients with multiple myeloma, 11 patients developed an arterial ischemic event over a period of 522 patient-years (5.6%).[88] Interestingly, several of these patients developed arterial thrombosis while receiving anticoagulation therapy. Bevacizumab has been linked to serious arterial ischemic events[89,90] through mechanisms such as endothelial damage and overexpression of proinflammatory genes.[91–93] In their population of patients receiving concurrent bevacizumab and chemotherapy, Scappaticci et al[94] reported the absolute rate of arterial events as 5.5 events per 100-person years. Pereg and Lisher[89] reported efficacy of low-dose aspirin in preventing CV complications in patients 65 years of age or older who had a prior history of thromboembolic events and were currently receiving bevacizumab. The mechanism of vascular toxicities associated with TKIs is not well understood and is thought to be partially mediated by nitric oxide (NO) inhibition versus accelerated atherosclerosis and possible interference with platelet function. In a meta-analysis by Choueiri et al,[95] the incidence of arterial ischemia was reported at 4% with a threefold increase in risk in those patients being treated with sunitinib or sorafenib. Arterial ischemia with ponatinib has been reported to be more than 20%, leading to the implementation of major restrictions on indications and monitoring by the FDA.[96]

Management

The management strategy should be tailored to the patient's clinical condition and the cancer type. Primary preventive strategies include lifelong antiplatelet therapy and statins for radiation-induced and known underlying atherosclerotic disease; aspirin and/or hydroxyurea for those with MPDs[97]; and aspirin for patients with a history of prior CV events or who are older than 65 years of age and receiving bevacizumab.[89] Treatment of the acute event varies by type of organ involved (cardiac, central nervous system, limb, or bowel ischemia) and is aimed at reversing ischemia and minimizing organ damage followed by long-term therapy and secondary prevention. The decision to use medical therapy versus a surgical or percutaneous approach for revascularization should be determined by the general condition of the patient and availability of local expertise. Management of these patients is often a challenge based on their bleeding risks, especially in the setting of associated thrombocytopenia. Although acute coronary intervention has been shown to be reasonably safe in these patients,[98] there is a significant concern regarding the need for dual antiplatelet therapy for an extended period of time. Drug-eluting coronary stents pose a special problem in this setting and should be avoided. We typically recommend using bare-metal stents because many of these patients will end up receiving more chemotherapy or surgery for the management of their cancer. The type of long-term anticoagulation recommended for secondary prevention depends on the underlying mechanism and cause. Table 62–5 summarizes some of the therapeutic interventions for arterial ischemic events observed in the setting of malignancy and hematologic disorders.

TABLE 62–5 Therapeutic Interventions of Potential Benefit for Arterial Ischemic Events Observed in the Setting of Malignancy or Hematologic Disorders

Arterial Events Associated with	Treatment Options
Acute leukemia	Chemotherapy and leukapheresis Surgical thromboembolectomy
Radiation therapy	Antiplatelet therapy Statin therapy Percutaneous angioplasty with or without stenting Surgery
Paradoxical embolization	Systemic anticoagulation PFO closure for recurrent events
Myeloproliferative disorders	Aspirin (for primary and secondary prevention) Cell reduction therapy (ie, phlebotomy, hydroxyurea, anagrelide, interferon-α)
Cardiac amyloidosis	Systemic anticoagulation
Bevacizumab	Aspirin (for primary prevention in patients older than 65 years of age or with a history of cardiovascular events)
NBTE	Systemic anticoagulation

NBTE, nonbacterial thrombotic endocarditis; PFO, patient foramen ovale.

CARDIAC ARRHYTHMIA IN PATIENTS WITH CANCER

Patients with cancer have complex comorbidities that predispose them to certain arrhythmias and that limit the therapeutic options when using antiarrhythmia drugs. Patients with underlying malignancy can develop cardiac arrhythmia as a consequence of the malignancy itself or its therapy (Fig. 62–10). When patients with cancer present with cardiac rhythm disturbances, they typically have associated complex comorbidities, and the presence of a rapid heart rate or rhythm irregularity can be simply a sign of a much more complicated and severe acute illness (eg, atrial tachycardia or atrial fibrillation in the setting of acute pulmonary embolism, polymorphic ventricular tachycardia triggered by severe metabolic derangements and electrolyte imbalance while on a QT-prolonging agent). Adequate patient management necessitates accurate diagnosis and identification of the potential causes and mechanisms that trigger these arrhythmias.

Diagnosis and Management

In the absence of clinical data to support a different approach, the management of cardiac arrhythmia in patients with cancer should in general follow the well-established standard-of-care guidelines.[99] Treatment, however, can sometimes differ slightly from those without malignancy. The difference is mainly related to the choice of antiarrhythmic drugs and AV-blocking agents and the timing and safety of anticoagulation. The choice of these drugs should take into consideration the possibility of drug–drug interactions (ie, Cardizem and verapamil are potent CYP inhibitors that can alter the pharmacokinetics of many chemotherapeutic agents; several classes of antiarrhythmic drugs can potentiate QT prolongation observed with many cancer-targeted therapies). In addition, the decision for short- and long-term anticoagulation for atrial fibrillation or flutter should be tailored carefully in each case because many patients face higher risks of bleeding in the setting of thrombocytopenia secondary to the malignancy or its therapy.

Bradyarrhythmias

Bradyarrhythmias can generally be categorized as sick sinus syndrome or heart block. The most common presenting symptoms of bradyarrhythmias include fatigue, lightheadedness, dizziness, or syncope. Many different causes have been linked to bradyarrhythmias in patients with cancer. These include myocardial infiltration, AV nodal blocking drugs such as antiemetics, and certain chemotherapies and immunotherapies. Chemotherapies know to cause bradycardia include paclitaxel and thalidomide. Possible suggested mechanisms include direct effect on the Purkinje system and extracardiac autonomic controls. The incidence of bradycardia with paclitaxel has been reported as high as 31%. A less common but equally important cause of bradycardia is baroreflex failure. This is typically characterized by volatility of heart rate and BP, including profound and severe bradycardia necessitating use of a permanent pacemaker. This is most often seen in patients with cancer who undergo extensive head and neck surgery or receive neck radiation therapy, causing

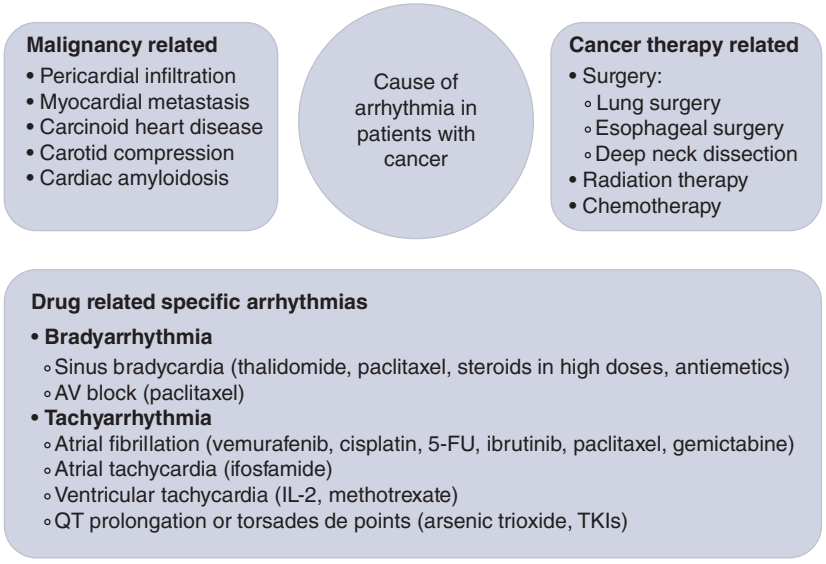


FIGURE 62–10 Causes and mechanisms of cardiac arrhythmia related to cancer and its management. 5-FU, 5-fluorouracil; IL-2, interleukin-2; TKI, tyrosine kinase inhibitor.

dysregulation of the autonomic system at the level of the vascular baroreceptors, the glossopharyngeal or vagal nerves, or the brain stem.[100]

Treatment

Treatment of bradyarrhythmias begins with identifying and removing any potentially offending agents that can exacerbate bradycardia. For severely symptomatic patients, urgent medical therapy with atropine or an IV inotrope, such as dopamine or epinephrine, may be used. In emergency situations, transcutaneous or transvenous pacemaker therapy may be required to maintain hemodynamic support. Long-term support with permanent pacing will depend on the severity of the symptoms related to the bradyarrhythmia and whether or not it is reversible.

Tachyarrhythmias

These are typically classified into four different categories:

1. Irregular tachycardia: atrial fibrillation, atrial flutter, multifocal atrial tachycardia (MAT)
2. Regular narrow QRS-complex tachycardia: sinus tachycardia, atrial tachycardia, supraventricular tachycardia (SVT)
3. Wide QRS-complex tachycardia: ventricular tachycardia, SVT with aberrancy, preexcited tachycardia
4. Polymorphic ventricular tachycardia

Sinus tachycardia is by far the most common cause of rapid heart rate in patients with cancer. It is usually secondary to other concomitant acute illnesses (eg, infection, pneumonia, pulmonary embolism, surgery). Evaluation and treatment of the primary and the precipitating causes are effective.

Atrial fibrillation has been shown in several epidemiologic studies to be more prevalent in patients with cancer compared with the general population.[101] Guzzetti et al[102] reported a threefold increase in the prevalence of atrial fibrillation in patients hospitalized with colon cancer compared with those admitted for non-neoplastic diseases. The highest incidence of malignancy-related atrial fibrillation has been reported in patients undergoing thoracic (6%–32%)[103] and esophageal (9.2%)[104] cancer surgery. Pos-operative atrial fibrillation appears to be associated with higher in-hospital length of stay, intensive care unit admissions, and most important, higher short- and long-term mortality rates.[102]

Acute management of patients with atrial fibrillation follows the general recommendations of urgent cardioversion for hemodynamically unstable patients and initial rate control for stable patients. Ventricular rate control can be achieved using AV-blocking agents such as digoxin, β-blockers, or the nondihydropyridine calcium-channel antagonists (Cardizem or verapamil). Amiodarone can also be considered for rate control in patients with marginal BP or LV dysfunction. For the subgroup of patients with previously known and documented permanent atrial fibrillation, controlling the heart rate and reversing the cause of acute decompensation should suffice.

The clinical decision for short- and long-term anticoagulation for atrial fibrillation is challenging and should be tailored carefully to each patient individually because patients can be at high thromboembolic risk based on the standard risks scores used in cardiology and concomitantly face higher risks of bleeding in the setting of thrombocytopenia secondary to the malignancy or its therapy. On the other hand, a patient with low thromboembolic risks based on these same scores can still be at high risk secondary to an acquired hypercoagulable state related to cancer or its therapy. Figure 62–11 shows a suggested algorithm to help risk stratify patients for anticoagulation in the setting of atrial fibrillation based on their thromboembolic and bleeding risk scores. (This algorithm has not been validated).

Polymorphic Ventricular Tachycardia and QT Prolongation

Patients with cancer require special consideration because of the risk of QT prolongation and torsades de pointes from both chemotherapeutic agents and adjunctive medications. QT intervals as measured by ECG reflect the total duration of the action potential at the cellular level. QT prolongation is associated with increased risk for polymorphic ventricular tachycardia, also known as torsades de pointes, and subsequent sudden cardiac death. The corrected QT interval is considered prolonged when it is greater than 460 ms in women and 440 ms in men. The QT interval varies with the cardiac rate and is typically reported as corrected QT interval (QTc) after correction for the patient's heart rate. Current ECG technology and digital diagnostic algorithms can generate immediate measurement of the QTc interval. It is important to recognize that accurate measurement and interpretation of QTc are essential in minimizing the chances of inappropriate drug discontinuation or overestimation of the true incidence of QT prolongation with these drugs.

In the cancer population, there are several risk factors predisposing patients to QT prolongation and subsequent torsades de pointes. These risks factors include electrolyte imbalance (hypomagnesemia, hypokalemia, hypocalcemia), metabolic derangements (hypothyroidism), and certain cancer therapies including chemotherapeutic agents (Table 62–6). It is of clinical importance to correct any concomitant contributing factors that may predispose to or worsen

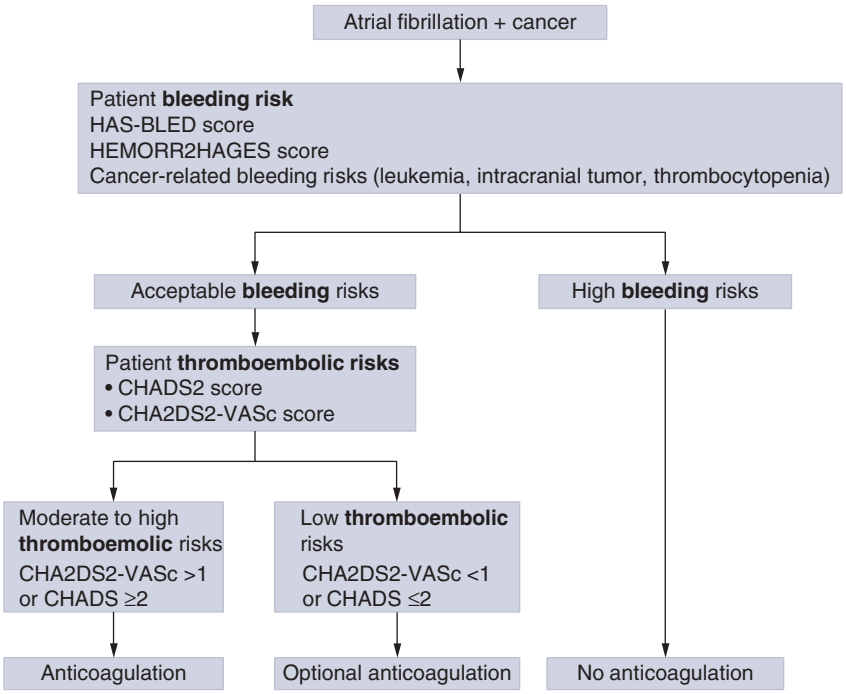


FIGURE 62–11 **Algorithm for decision making regarding antithrombotic therapy in patients with cancer and atrial fibrillation. Thromboembolic risk scores: CHADS2, congestive heart failure, age (if older than 75 years), diabetes, stroke; CHA2DS2VASc, congestive heart failure, age 2 (if older than 75 years), diabetes, stroke, vascular disease, age (65–74 years), sex category; HAS-BLED, hypertension, abnormal renal or liver function, previous stroke, prior major bleeding , labile international normalized ratio, elderly (age older than 65 years), drug or alcohol use; HEMORR2HAGES, hepatic or renal disease, ethanol use, malignancy, older age (older than 75 years), reduced platelets, rebleeding, hypertension (uncontrolled), anemia, genetic factor, elevated risk of fall, stroke.**

QT interval prolongation. Cancer treatment interruption is typically advised when a QT interval is above 500 ms, and permanent treatment discontinuation is recommended if QT prolongation recurs or is associated with ventricular tachycardia or reported syncope. Figure 62–12 shows a useful algorithm to screen and monitor patients being considered for therapy with agents associated with potential QT prolongation and torsades de pointe.

Among the TKIs, a high incidence of QT prolongation has been reported with several of these drugs, leading to an FDA black box warning mandating close ECG monitoring and management recommendations as listed in (Table 62–7).

TABLE 62–6 Drugs Associated with QT Prolongation

Chemotherapy Agent	Nonchemotherapy Agents
BRAF inhibitor	Antiemetics
Vemurafenib	Ondansetron
HDAC inhibitors	Promethazine
Depsipeptide	Antimicrobials
Vorinostat	Voriconazole
Tyrosine kinase inhibitors	Ciprofloxacin
Dasatinib	Moxifloxacin
Lapatinib	Erythromycin
Nilotinib	Clarithromycin
Pazopanib	Analgesic
Sunitinib	Methadone
Vandetanib	
Other	
Arsenic trioxide	

HDAC, histone deacetylase.

PERICARDIAL DISEASES IN PATIENTS WITH CANCER

Pericardial diseases are common in patients with cancer and can manifest as acute pericarditis, pericardial effusion, cardiac tamponade, or constrictive pericarditis. Triggers of pericardial diseases include infectious causes, tumor invasion of the pericardium, or the side effect of cancer therapy, specifically chest radiation or chemotherapy (Table 62–8). The lack of randomized clinical trials makes the management of these syndromes in patients with cancer mainly empirical based on expert opinion and limited data extrapolated from the few trials done in noncancer population.[105,106]

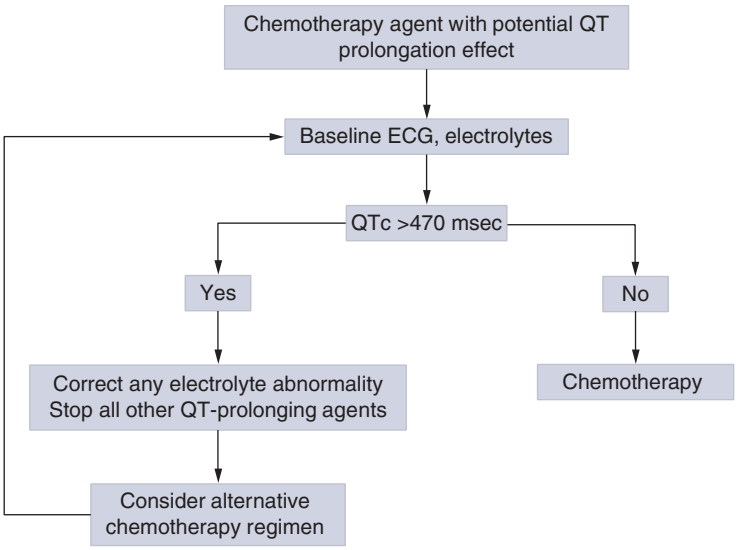


FIGURE 62–12 **Suggested algorithm for the initial assessment and management of patients being considered for potential QT-prolonging chemotherapeutic agents. ECG, electrocardiogram.**

Acute Pericarditis

The diagnosis of pericarditis is based on the findings of pleuritic chest pain, fever, and ST elevation detected by ECG. Patients are typically hospitalized after they present with acute pericarditis if they show evidence of high fever, suspected myopericarditis, or the presence of a large (>20 mm in diameter) pericardial effusion or tamponade physiology detected by echocardiography. Nonsteroidal antiinflammatory drugs (NSAIDs) and aspirin are the mainstays of therapy for acute pericarditis. Intermediate to high doses of NSAIDs are typically used for 10 to 15 days followed by a slow taper over an additional 1 to 2 weeks. Colchicine is often added to the regimen at a dose of 0.6 mg/day for 3 months to help minimize recurrence.[107,108] It is a well-tolerated drug with few side effects reported. Unfortunately, however, the few contraindications to the use of colchicine are common in patients with cancer, particularly in recent stem cell transplant recipients. These contraindications include significant interactions with several drugs, including antifungals, antibiotics, and immunosuppressants such as tacrolimus. These drugs can alter colchicine metabolism such that the level is significantly increased.

The use of corticosteroids is typically discouraged in patients without cancer because of significant side effects and the association with increased incidence of recurrent pericarditis. The situation, however, is often reversed in patients with cancer because of the numerous contraindications to the use of aspirin and NSAIDs in this population. Steroids are typically used in patients with low platelet counts or patients with blood dyscrasias when NSAIDs cannot be used. The evidence comparing the effectiveness of low- versus high-dose steroids is weak. High-dose prednisone of 1.0 to 1.5 mg per kilogram (or its equivalent) over many weeks with a very slow taper is associated with the lowest rate of recurrence but with a high rate of steroid-related side effects. On the other hand, a lower dose of prednisone of 0.2 to 0.5 mg per kilogram is associated with fewer side effects but a higher relapse rate. Because there are no strong data to support one option over the other, we typically use the protocol summarized in (Fig. 62–13).

Pericardial Effusion

Pericardial effusion is a common finding and has been reported in up to 34% of autopsies performed on patients with cancer. Its management is guided by three main factors:

1. Clinical significance of the effusion (presence or absence of associated symptoms)
2. Effusion size
3. Cause of the effusion

ETIOLOGY

In patients with cancer, up to two thirds of pericardial effusions are nonmalignant. The mechanism of effusion in this setting is likely related to a loss of adequate lymphatic drainage of the pericardial sac secondary to lymphangitic spread of the malignancy or mediastinal irradiation. Other causes include infection, radiation, and certain drugs (see Table 62–8). Clarifying the specific cause

TABLE 62–7 Monitoring Recommendations for Small-Molecule Tyrosine Kinase Inhibitors Associated with Prolonged QT Interval

Drug	Monitoring
Pazopanib (Votrient) Bosutinib (Bosulif) Crizotinib (Xalkori) Dasatinib (Sprycel) Lapatinib (Tykerb)	Use caution in patients at risk for QT prolongation, including patients with long QT syndrome, patients taking antiarrhythmic medications or other medications that lead to QT prolongation or potassium-wasting diuretics, and patients with cumulative high-dose anthracycline therapy and conditions that cause hypokalemia or hypomagnesemia Correct hypokalemia and hypomagnesemia before initiation of therapy.
In addition to the general recommendations listed above, the ECG monitoring guidelines listed below must be followed when patients take certain TKIs.	
Vandetanib (Caprelsa)	1. Do not initiate treatment unless the QTcF is <450 msec. 2. Order an ECG at baseline, at 2–4 weeks, at 8–12 weeks, and every 3 months thereafter. 3. During treatment, if QTcF >500 msec, withhold vandetanib and resume at a reduced dose when QTcF is <450 msec.
Nilotinib (Tasigna)	Monitor ECG and QT_c at baseline, at 7 days, with dose change, and periodically. 1. QT_c >480 msec: Withhold treatment, monitor and correct potassium and magnesium levels, and review concurrent medications. 2. If QT_cF returns to <450 msec and to within 20 msec of baseline within 2 weeks, resume at prior dose. 3. If QT_cF returns to 450–480 msec after 2 weeks, reduce dose to 400 mg once daily. 4. If QT_cF >480 msec after dosage reduction to 400 mg once daily, discontinue treatment.
Vemurafenib (Zelboraf)	1. Do not initiate treatment if baseline QT_c >500 msec. 2. Monitor ECG at baseline, at 15 days, then monthly for 3 months, and then every 3 months and with dosage adjustments. 3. During treatment, if QT_c >500 msec, temporarily interrupt treatment; may reinitiate with a dose reduction once QT_c falls to <500 msec. 4. Discontinue (permanently) if, after correction of risk factors, the QT_c continues to increase >500 msec.

[a]ECG, electrocardiogram; TKI, tyrosine kinase inhibitor; QTcF, Fridericia-corrected QT interval.

of an effusion not only helps to define treatment modality but also helps to determine prognosis because malignant effusions are associated with a dismal prognosis of 16% 1-year survival rate compared with a 55% 1-year survival rate in patients with nonmalignant effusions.[109]

Diagnosis

Patients with pericardial effusion may be asymptomatic but may also present with mild symptoms of chest pain, cough, or dyspnea. Extreme cases can present with frank tamponade and shock. Clinicians should be very careful when relying on vital signs to guide management in patients with a pericardial effusion; stroke volume and cardiac output start to drop at an early stage (as the effusion builds up). BP, on the other hand, is maintained by progressive increase in heart rate until it reaches a plateau, after which a threshold is reached and a severe drop in BP follows. Waiting for these clinical findings to manifest (ie, rapid heart rate and a drop in BP) may be too late, and the patient can rapidly progress to shock. Echocardiography is the main diagnostic tool for confirming the diagnosis of a pericardial effusion and detecting tamponade physiology. Pericardial effusion size is classified as small, moderate, or large; large effusions are larger than 2 cm in diameter. Helpful echocardiographic findings to detect early tamponade physiology include the presence of chamber collapse or significant respiratory variation in the mitral or tricuspid valve inflow; these features manifest much earlier than BP drop and heart rate increase.

TABLE 62–8 Causes of Pericardial Diseases in Patients with Cancer

Infection
Tumor invasion
Radiation
Chemotherapy Purine analogues (eg, fludarabine) Antimetabolites (eg, capecitabine) Anthracyclines (eg, doxorubicin) Alkylating agents (eg, cyclophosphamide) Immunotherapy (eg, Immune Checkpoint Inhibitors (ICIS))

Management

There is no evidence that medical therapy plays any role in the management of an effusion, except in the

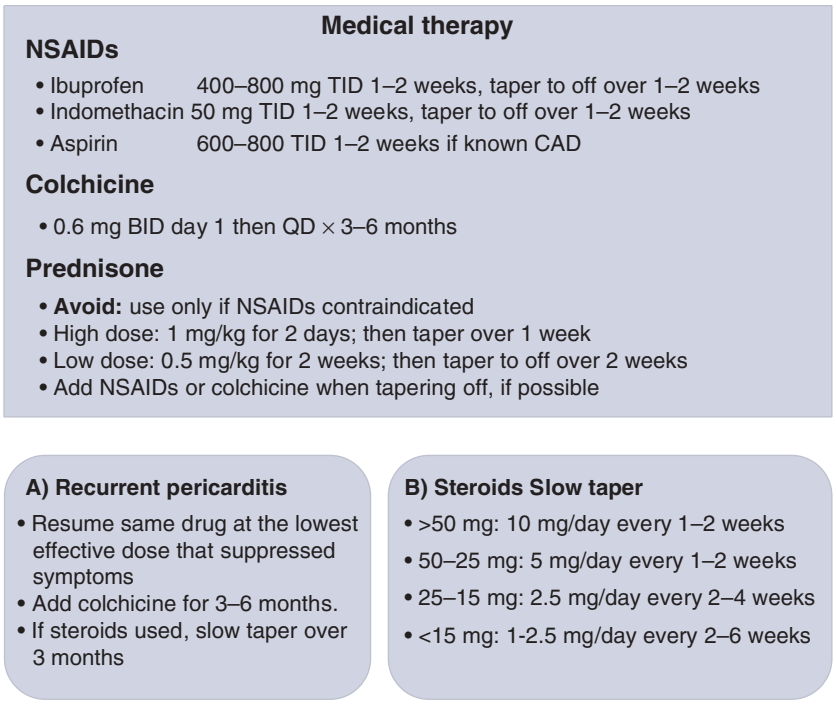


FIGURE 62–13 **Medical management of patients with acute pericarditis. BID, twice a day; CAD, coronary artery disease; NSAID, nonsteroidal antiinflammatory drug; QD, every day; TID, three times a day.**

case of concomitant inflammation (ie, pericarditis). At MDACC, the three main indications for pericardial fluid drainage are: large effusion (>2 cm in diameter), diagnostic purposes, and the presence of clinical or echocardiographic evidence of tamponade physiology. As shown in Figure 62–14, the first step after the detection of a moderate to large pericardial effusion is to assess for clinical or echocardiographic evidence of tamponade. If there is no sign of tamponade, then the effusion size dictates the next step in management: small to moderate effusions (<2 cm in diameter) are monitored clinically and with serial echocardiograms. Larger effusions (those >2 cm in diameter) require drainage because about one third of these patients eventually progress to tamponade.[110]

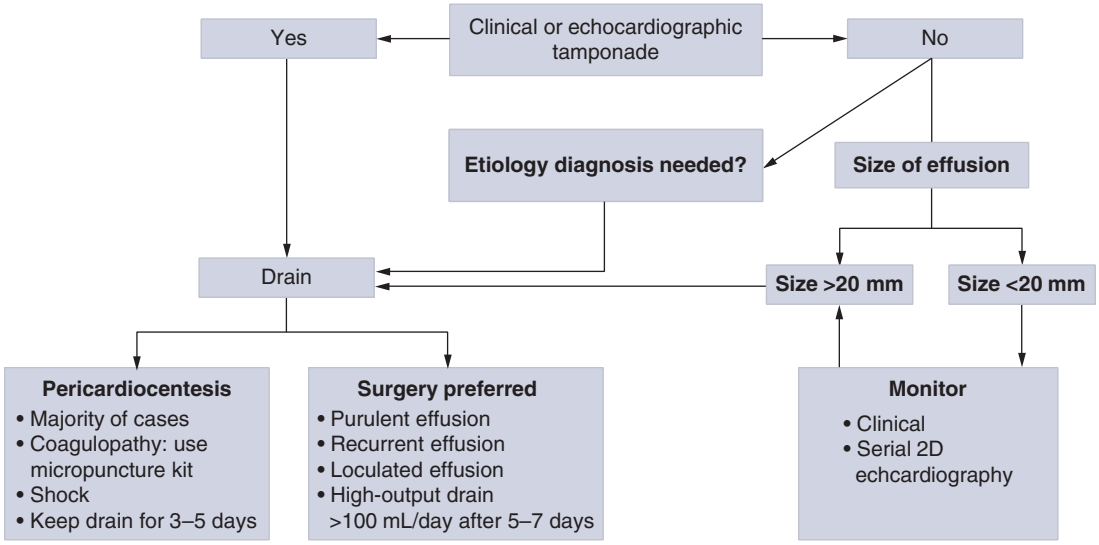


FIGURE 62–14 **Management algorithm for patients with pericardial effusion. 2D, two-dimensional.**

Draining a pericardial effusion can be achieved percutaneously or surgically by creating a pericardial window, and in some clinical centers, by thoracoscopy. Surgery is preferred in the setting of recurrent effusions, purulent effusions, or high-output drainage (>100 mL per day for 5–7 days after percutaneous pericardiocentesis). The percutaneous approach is preferred in the majority of patients at MDACC, especially if the patient has hypotension or a coagulopathy. After pericardiocentesis, pericardial fluid is sent to the laboratory for chemistry, microbiology, cytology, and flow cytometry and sometimes to check for tumor markers.[111] A pericardial draining catheter is typically left in place for 5 days because this approach has shown to lower the effusion recurrence rate by two thirds. Sometimes the catheter is removed early if drainage output is less than 25 mL over 24 hours and if there is no significant residual effusion on an echocardiogram. When performed by experienced teams, pericardiocentesis is a safe procedure with a low complication rate (<5%) and a high success rate (98%).[112] Recently, we were able to demonstrate the feasibility and safety of this approach in a cohort of patients with severe thrombocytopenia related to leukemia or chemotherapy.[113] After initial pericardiocentesis, almost one in four patients will develop recurrent effusions. Chemical pericardiodesis can be considered. However, this approach can be complicated by severe pain, risk of infection, and long-term constrictive physiology in addition to a 10% recurrence rate despite chemical pericardiodesis.[109]

HYPERTENSION AND CANCER MANAGEMENT

Hypertension is known to be the most commonly diagnosed comorbidity in patients with cancer (37%); its prevalence before chemotherapy exposure is similar to that reported in the general population (29%). A much higher rate has been reported in association with certain cancer therapies, including alkylating agents, angiogenesis inhibitors, immunosuppressants, and hormones such as steroids and erythropoietin (EPO) (Table 62–9).[114–116]

Etiology and Pathophysiology

The most common chemotherapeutic agents known to cause hypertension include several of the angiogenesis inhibitors, also referred to as VSPIs. These drugs include anti-VEGF antibody (bevacizumab) and several TKIs (sunitinib, sorafenib, pazopanib, and vandetanib). Hypertension is one of the most common side effects of these drugs. VEGF normally plays an important role in maintaining a balanced vascular tone by regulating NO production in endothelial cells. Hypertension develops when NO bioavailability is reduced, leading to vasoconstriction, increased endothelin production, capillary rarefaction, and increased peripheral resistance.[117,118] New-onset or worsening hypertension with these agents can develop very early (within 24 hours) after initiation but is typically observed within the first few weeks. BP usually returns to baseline shortly after therapy has been discontinued. Several previous limited observations raised the interesting concept of using hypertension as a biomarker of cancer response to VSPIs.[118] More data are needed to further clarify the clinical significance of such observation.

Other classes of chemotherapeutic agents are known to cause hypertension. Incidence and time to hypertensive effect for the VSPIs as well as the other agents used in cancer therapy are provided in Table 62–9. Alkylating agents are commonly used in a large number of oncology protocols to treat patients with various solid tumors and blood cancers. Hypertension is frequent with these agents and is most commonly seen with cisplatin and busulfan and much

TABLE 62–9 Cancer Therapies Associated with New-Onset or Worsening Hypertension

Medications	Overall Incidence of Hypertension (%)
Anti-VEGF antibody	
Bevacizumab	4–35
Tyrosine kinase inhibitors	
Pazopanib	40–47
Sorafenib	17–43
Sunitinib	15–34
Vandetanib	33
Alkylating agents	
Busulfan	36
Cisplatin	39
Calcineurin inhibitors	
Cyclosporine	60–80
Tacrolimus	30
Immunosuppressants	
Mycophenolate mofetil	28–78
mTOR inhibitor: sirolimus	45–49
Other	
Steroids	20
Erythropoietin	13.7–27.7

mTOR, mammalian target of rapamycin; VEGF, vascular endothelial growth factor.

less often with cyclophosphamide. Their effect has been observed both acutely as well as years after therapy has been discontinued; the mechanism is thought to be the result of endothelial dysfunction and arterial vasoconstriction.[114] Calcineurin inhibitors, used for the treatment of graft-versus-host disease, are also associated with a high incidence of hypertension. Cyclosporine and tacrolimus are the major drugs in this class. Their effects are generally seen within the first 6 weeks of therapy and are thought to be the result of the sympathetic system activation and an increase in endothelin-1 synthesis, leading to vasoconstriction.[116] After transplant, many patients also receive immunosuppression with mycophenolate mofetil and the mTOR (mammalian target of rapamycin) inhibitor sirolimus. The mechanism by which these agents cause hypertension is not well understood. Corticosteroids are frequently used in the management of patients with cancer, and they have been associated with variable rates of dose-dependent hypertension. The mechanism by which they cause hypertension is complex but likely involves increased production of angiotensinogen, which induces salt and fluid retention, activation of the sympathetic nervous system, and an increase in patient sensitivity to vasoactive substances. Patients receiving EPO for anemia are also at risk for experiencing severe hypertension. The driving mechanism behind the hypertension is complex and goes beyond just volume expansion. It is also the result of an activation of the renin–angiotensin system and an increase in endothelin-1 with a decrease in NO production caused by changes in the EPO receptor.[116]

Diagnosis and Management

Because hypertension is a risk factor for chemotherapy-induced cardiotoxicity, and poorly controlled hypertension can lead to discontinuation of certain cancer therapies, a prompt and adequate intervention is essential to prevent potential irreversible damage. The Investigational Drug Steering Committee of the National Cancer Institute established a panel of experts to address the concern regarding VSPI-induced hypertension. The recommendations of this panel were published in 2010, and they focused on the evaluation, surveillance, and management of BP problems in patients receiving VSPIs.[119] Treatment of hypertension should begin at the time of diagnosis, without a concern of negatively impacting cancer treatment outcomes.

The choice of a pharmacologic regimen to manage hypertension in patients with cancer should take into consideration several factors. For example, the underlying pathophysiology leading to BP elevation in calcineurin-induced hypertension is caused by excessive vasoconstriction that responds well to dihydropyridine calcium-channel blockers, diuretic agents can help relieve fluid retention associated with steroid-related hypertension, and clonidine has been recommended for the management of severe BP swings in patients with baroreflex failure. Other important factors that need to be considered include the risk of drug–drug interactions. It is also important to consider agents that may have compelling indications in specific types of cancer. Several recent epidemiologic studies reported potential oncologic benefit of β-blockers in melanoma, breast, lung, and colon cancers with mechanism suspected to be mediated by altering β-adrenergic signaling in cancer.[120] It is also important to consider the risks and benefits of medications that target NO or angiotensin II production when determining management strategies for patients taking specific agents such as the VSPIs. Because these anticancer agents cause vasoconstriction in part through a decrease in NO production, medications such as nitrates, phosphodiesterase-5 inhibitors, and nebivolol, a NO-producing β-blocker would in theory seem beneficial. However, there is a theoretical concern that by targeting this pathway, these antihypertension medications might in fact compromise the efficacy of the antitumor therapy.

RADIATION THERAPY–RELATED CARDIOVASCULAR TOXICITY

Radiation therapy to the mediastinum, left breast area, and neck region is a risk factor for premature coronary and carotid atherosclerotic disease (Fig. 62–15). The risk of arterial ischemic events depends on the radiation dose, technique, extent of vasculature exposed, and type of cancer.[121] Radiation therapy is known to accelerate atherosclerosis by triggering oxidative stress, leading to endothelial damage.[122] The acute injury during therapy is sustained for a long period of time via activation of nuclear factor B.[123] Symptoms typically manifest after a long latent period of 5 to 10 years after exposure. Mediastinal exposure is also responsible for a spectrum of CV syndromes, including acute pericarditis, chronic constrictive pericardial disease, valvular heart disease, and myocardial dysfunction with restrictive cardiomyopathy. There does not appear to be a defined threshold level below which radiation therapy is safe to the CV system. Modification of radiation protocols including field planning and breath-holding techniques are currently being used to reduce radiation dose to the CV system. The challenge in managing these patients is the long latency period between exposure and clinical manifestation with many affected patients

being no longer under the care of a treating oncologist. The 2013 expert consensus by the American Society of Echocardiography and the European Association of Cardiovascular Imaging recommend yearly clinical evaluation with a history and physical examination and as needed echocardiogram studies in symptomatic patients. They also recommend a screening echocardiogram at 10 years after chest radiation and every 5 years thereafter. Primary prevention in patients with documented atherosclerosis after radiation therapy includes management of traditional atherosclerotic risk factors.[121] Lifelong antiplatelet therapy and statin therapy are recommended for their antiinflammatory and antithrombotic effects on the irradiated endothelium.[124] Radiation-induced scarring makes surgical intervention difficult; hence, percutaneous angioplasty with or without stenting is becoming the preferred revascularization method with encouraging results for radiation-induced renal, iliac, and femoral arterial disease.[125] Figure 62–16 shows the Department of Cardiology at MDACC recommended algorithm for management and monitoring of these patients.

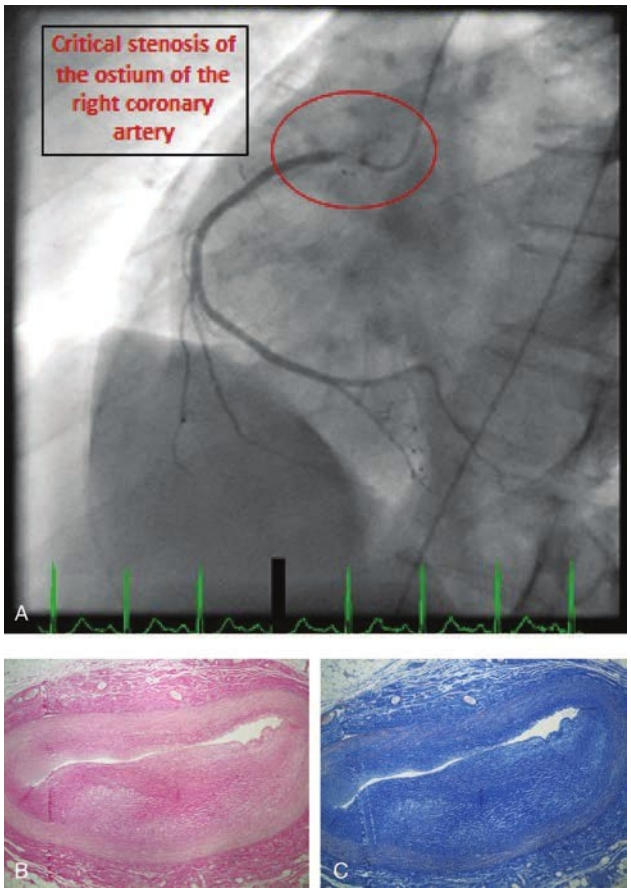


FIGURE 62–15 **A.** Coronary angiogram showing critical, near occlusion of the ostium of the right coronary artery in a 36-year-old patient with prior chest radiation for lymphoma at the age of 5 years. **B.** and **C.** Pathology findings consistent with radiation arteritis.

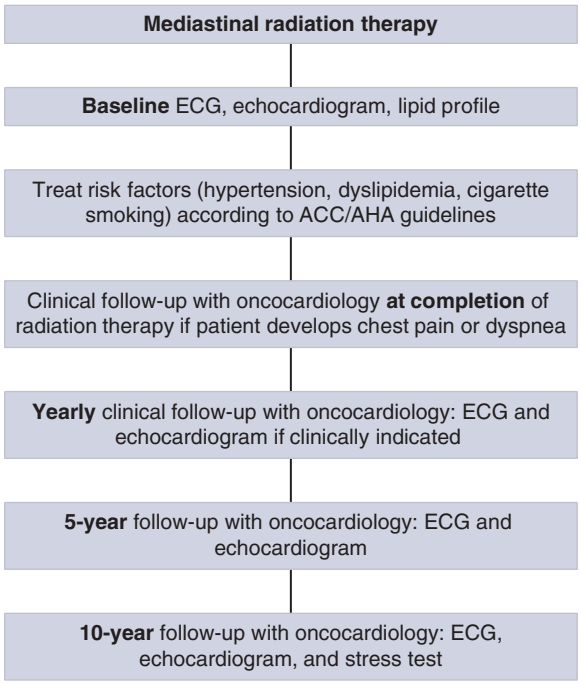


FIGURE 62–16 **MD Anderson Cancer Center Department of Cardiology's recommended algorithm for cardiac monitoring of patients after radiation therapy to the mediastinal area. ACC, American College of Cardiology; AHA, American Heart Association; ECG, electrocardiogram.**

MD ANDERSON PRACTICE TIPS

- Patients with cancer are at higher risk for CV events compared with control, including a 2-fold increase in risk of arterial ischemia and up to a 15-fold increased risk for cardiomyopathy and HF. Cancer survivors are reported to have a 3.6-fold increased risk of CV-specific mortality at 5 years. These increased CV risks are likely the results of normal age-related pathologies in association with secondary effects of cancer therapies and may explain the increased incidence of certain CV syndromes in this population.
- Despite a lack of consensus, *cardiotoxicity* generally is defined as a drop in LVEF by 5% or more, to less than 55% in the presence of HF symptoms, or an asymptomatic drop in LVEF by 10% or more to less than 55%.
- The majority of patients with cancer with HF have symptoms triggered by one of two broad mechanisms: The first include the acute new-onset cardiomyopathies related to sepsis, stress cardiomyopathy, and myocarditis (toxic or infectious). The second include patients presenting with subacute on chronic HF symptoms related to underlying structural heart disease (chronic ischemic or valvular heart disease), chemotherapy-induced cardiomyopathy, or infiltrative myocardial conditions related to their underlying malignancies (ie, amyloidosis) or to cancer therapy (ie, iron overload).
- Patients with underlying malignancy have added increased risks for arterial ischemic events related to the inherent thrombophilia associated with their cancer and its therapy. Chemotherapeutic agents known to have a stronger association with arterial ischemic events include the group of standard chemotherapeutic agents such as L-asparaginase, cisplatin, 5-FU, capecitabine, and gemcitabine. The second category includes the group of angiogenesis inhibitors such as thalidomide and the VSPIs such as bevacizumab, sunitinib, sorafenib, pazopanib, and ponatinib.
- Radiation therapy can accelerate atherosclerosis by triggering oxidative stress, leading to endothelial damage. Mediastinal exposure is also responsible for a spectrum of CV syndromes, including acute pericarditis, chronic constrictive pericardial disease, valvular heart disease, and myocardial dysfunction with restrictive cardiomyopathy. Protocols including field planning and breath-holding techniques are currently being used to reduce radiation dose to the CV system. Primary prevention in patients with documented atherosclerosis after radiation therapy includes management of traditional atherosclerotic risk factors. Radiation-induced scarring makes surgical intervention difficult; hence, percutaneous angioplasty with or without stenting is becoming the preferred revascularization method for coronary and carotid artery revascularization in these patients.
- The three main indications to drain a suspected neoplastic pericardial effusion are large size effusion (>2 cm in diameter), the need for pathology samples for diagnostic or staging purposes, and the presence of clinical or echocardiographic evidence of tamponade physiology. Percutaneous pericardiocentesis is preferred over surgery. It is a safe procedure with a low complication rate (<5%) and a high success rate (98%). After pericardiocentesis, a pericardial draining catheter is typically left in place for 3 to 5 days because this approach has been shown to be associated with a lower rate of effusion recurrence (12%)

REFERENCES

1. Siegel R, DeSantis C, Virgo K, et al. Cancer treatment and survivorship statistics, 2012. *CA Cancer J Clin*. 2012;62(4):220-241.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69(1):7-34.
3. Armenian SH, Xu L, Ky B, et al. Cardiovascular disease among survivors of adult-onset cancer: a community-based retrospective cohort study. *J Clin Oncol*. 2016;34(10):1122-1130.
4. Ning Y, Shen Q, Herrick K, et al. Abstract LB-339: cause of death in cancer survivors. *Cancer Res*. 2012;72:LB-339.
5. Hooning MJ, Botma A, Aleman BM, et al. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. *J Natl Cancer Inst*. 2007;99(5):365-375.
6. Chow EJ, Mueller BA, Baker KS, et al. Cardiovascular hospitalizations and mortality among recipients of hematopoietic stem cell transplantation. *Ann Intern Med*. 2011;155(1):21-32.
7. Baker KS, Ness KK, Steinberger J, et al. Diabetes, hypertension, and cardiovascular events in survivors of hematopoietic cell transplantation: a report from the bone marrow transplantation survivor study. *Blood*. 2007;109(4):1765-1772.
8. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med*. 2006;355(15):1572-1582.
9. Navi BB, Reiner AS, Kamel H, et al. Risk of arterial thromboembolism in patients with cancer. *J Am Coll Cardiol*. 2017;70(8):926.
10. Tukenova M, Guibout C, Oberlin O, et al. Role of cancer treatment in long-term overall and cardiovascular mortality after childhood cancer. *J Clin Oncol*. 2010;28(8):1308-1315.
11. McMullen JR, Boey EJ, Ooi JY, et al. Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling. *Blood*. 2014;124(25):3829-3830.
12. Sawyer DB, Zuppinger C, Miller TA, et al. Modulation of anthracycline-induced myofibrillar disarray in rat ventricular myocytes by neuregulin-1beta and anti-erbB2: potential mechanism for trastuzumab-induced cardiotoxicity. *Circulation*. 2002;105(13):1551-1554.
13. Zhang S, Liu X, Bawa-Khalfe T, et al. Identification of the molecular basis of doxorubicin-induced cardiotoxicity. *Nat Med*. 2012;18(11):1639-1642.
14. Sanguinetti MC, Mitcheson JS. Predicting drug-hERG channel interactions that cause acquired long QT syndrome. *Trends Pharmacol Sci*. 2005;26(3):119-124.
15. Obers S, Staudacher I, Ficker E, et al. Multiple mechanisms of hERG liability: K+ current inhibition, disruption of protein trafficking, and apoptosis induced by amoxapine. *Naunyn Schmiedebergs Arch Pharmacol*. 2010;381(5):385-400.
16. Ghatalia P, Je Y, Kaymakcalan MD, et al. QTc interval prolongation with vascular endothelial growth factor receptor tyrosine kinase inhibitors. *Br J Cancer*. 2015;112(2):296-305.
17. Kim PY, Ewer MS. Chemotherapy and QT prolongation: overview with clinical perspective. *Curr Treat Options Cardiovasc Med*. 2014;16(5):303.
18. Zimmer L, Goldinger SM, Hofmann L, et al. Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. *Eur J Cancer*. 2016;60:210-225.
19. Behling J, Kaes J, Munzel T, et al. New-onset third-degree atrioventricular block because of autoimmune-induced myositis under treatment with anti-programmed cell death-1 (nivolumab) for metastatic melanoma. *Melanoma Res*. 2017;27(2):155-158.
20. Nishimura H, Okazaki T, Tanaka Y, et al. Autoimmune dilated cardiomyopathy in PD-1 receptor-deficient mice. *Science*. 2001;291(5502):319-322.
21. Darby SC, Cutter DJ, Boerma M, et al. Radiation-related heart disease: current knowledge and future prospects. *Int J Radiat Oncol Biol Phys*. 2010;76(3):656-665.
22. Gao R, Zhang J, Cheng L, et al. A phase II, randomized, double-blind, multicenter, based on standard therapy, placebo-controlled study of the efficacy and safety of recombinant human neuregulin-1 in patients with chronic heart failure. *J Am Coll Cardiol*. 2010;55(18):1907-1914.
23. Blanco J, Muriel-Bombin A, Sagredo V, et al. Incidence, organ dysfunction and mortality in severe sepsis: a Spanish multicentre study. *Crit Care*. 2008;12(6):R158.
24. Romero-Bermejo FJ, Ruiz-Bailen M, Gil-Cebrian J, Huertos-Ranchal MJ. Sepsis-induced cardiomyopathy. *Curr Cardiol Rev*. 2011;7(3):163-183.
25. Merx MW, Weber C. Sepsis and the heart. *Circulation*. 2007;116(7):793-802.
26. Hauck AJ, Kearney DL, Edwards WD. Evaluation of postmortem endomyocardial biopsy specimens from 38 patients with lymphocytic myocarditis: implications for role of sampling error. *Mayo Clin Proc*. 1989;64(10):1235-1245.
27. Robinson JL, Hartling L, Crumley E, et al. A systematic review of intravenous gamma globulin for therapy of acute myocarditis. *BMC Cardiovasc Disord*. 2005;5(1):12.
28. Seidman A, Hudis C, Pierri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol*. 2002;20(5):1215-1221.
29. Friedman MA, Bozdech MJ, Billingham ME, Rider AK. Doxorubicin cardiotoxicity. Serial endomyocardial biopsies and systolic time intervals. *JAMA*. 1978;240(15):1603-1606.
30. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. *Cancer*. 2003;97(11):2869-2879.
31. Felker GM, Thompson RE, Hare JM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med*. 2000;342(15):1077-1084.
32. Link G, Tirosh R, Pinson A, Hershko C. Role of iron in the potentiation of anthracycline cardiotoxicity: identification of heart cell mitochondria as a major site of iron-anthracycline interaction. *J Lab Clin Med*. 1996;127(3):272-278.
33. Vejpongsa P, Yeh ETH. Topoisomerase 2[beta]: a promising molecular target for primary prevention of anthracycline-induced cardiotoxicity. *Clin Pharmacol Ther*. 2014;95(1):45-52.
34. Cardinale D, Colombo A, Lamantia G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. *J Am Coll Cardiol*. 2010;55(3):213-220.
35. Plana JC, Galderisi M, Barac A, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2014;27(9):911-939.
36. Valdivieso M, Burgess MA, Ewer MS, et al. Increased therapeutic index of weekly doxorubicin in the therapy of non-small cell lung cancer: a prospective, randomized study. *J Clin Oncol*. 1984;2(3):207-214.
37. Bosch X, Rovira M, Sitges M, et al. Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: the OVERCOME trial (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies). *J Am Coll Cardiol*. 2013;61(23):2355-2362.
38. Kalay N, Basar E, Ozdogru I, et al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. *J Am Coll Cardiol*. 2006;48(11):2258-2262.
39. Ewer MS, Lippman SM. Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. *J Clin Oncol*. 2005;23(13):2900-2902.
40. Ewer MS, Vooletich MT, Durand JB, et al. Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. *J Clin Oncol*. 2005;23(31):7820-7826.
41. Romond EH, Jeong JH, Rastogi P, et al. Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed

by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol*. 2012;30(31):3792-3799.
42. Kerkela R, Woulfe KC, Durand JB, et al. Sunitinib-induced cardiotoxicity is mediated by off-target inhibition of AMP-activated protein kinase. *Clin Transl Sci*. 2009;2(1):15-25.
43. Chu TF, Rupnick MA, Kerkela R, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. *Lancet*. 2007;370(9604):2011-2019.
44. Khakoo AY, Kassiotis CM, Tannir N, et al. Heart failure associated with sunitinib malate: a multitargeted receptor tyrosine kinase inhibitor. *Cancer*. 2008;112(11):2500-2508.
45. Di Lorenzo G, Autorino R, Bruni G, et al. Cardiovascular toxicity following sunitinib therapy in metastatic renal cell carcinoma: a multicenter analysis. *Ann Oncol*. 2009;20(9):1535-1542.
46. Schmidinger M, Zielinski CC, Vogl UM, et al. Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2008;26(32):5204-5212.
47. Telli ML, Witteles RM, Fisher GA, Srinivas S. Cardiotoxicity associated with the cancer therapeutic agent sunitinib malate. *Ann Oncol*. 2008;19(9):1613-1618.
48. Gulati G, Heck SL, Ree AH, et al. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 x 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. *Eur Heart J*. 2016;37(21):1671-1680.
49. Avila MS, Ayub-Ferreira SM, de Barros Wanderley MR Jr, et al. Carvedilol for prevention of chemotherapy-related cardiotoxicity: the CECCY trial. *J Am Coll Cardiol*. 2018;71(20):2281-2290.
50. Cardinale D, Colombo A, Sandri MT, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. *Circulation*. 2006;114(23):2474-2481.
51. Moudgil R, Hassan S, Palaskas N, et al. Evolution of echocardiography in subclinical detection of cancer therapy-related cardiac dysfunction. *Echocardiography*. 2018;35(6):860-868.
52. Zamorano JL, Lancellotti P, Rodriguez Munoz D, et al. 2016 ESC position paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the Task Force for Cancer Treatments and Cardiovascular Toxicity of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37(36):2768-2801.
53. Tajiri K, Ieda M. Cardiac complications in immune checkpoint inhibition therapy. *Front in Cardiovasc Med*. 2019;6:3.
54. Mahmood SS, Fradley MG, Cohen JV, et al. Myocarditis in patients treated with immune checkpoint inhibitors. *J Am Coll Cardiol*. 2018;71(16):1755-1764.
55. Johnson DB, Balko JM, Compton ML, et al. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med*. 2016;375(18):1749-1755.
56. Jain V, Bahia J, Mohebtash M, Barac A. Cardiovascular complications associated with novel cancer immunotherapies. *Curr Treat Options Cardiovasc Med*. 2017;19(5):36.
57. Heinzerling L, Ott PA, Hodi FS, et al. Cardiotoxicity associated with CTLA4 and PD1 blocking immunotherapy. *J Immunother Cancer*. 2016;4:50.
58. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2018;36(17):1714-1768.
59. Ferreira VM, Schulz-Menger J, Holmvang G, et al. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. *J Am Coll Cardiol*. 2018;72(24):3158-3176.
60. Puzanov I, Diab A, Abdallah K, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer*. 2017;5(1):95.
61. John AT, Bryan JS, Julie B, et al. Management of immunotherapy-related toxicities, version 1.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2019;17(3):255-289.
62. Salem JE, Allenbach Y, Vozy A, et al. Abatacept for severe immune checkpoint inhibitor-associated myocarditis. *N Engl J Med*. 2019;380(24):2377-2379.
63. Reddy N, Moudgil R, Lopez-Mattei JC, et al. Progressive and reversible conduction disease with checkpoint inhibitors. *Can J Cardiol*. 2017;33(10):1335.e1313-1335.e1315.
64. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62(16):e147-239.
65. Khorana AA, Francis CW, Culakova E, et al. Thromboembolism in hospitalized neutropenic cancer patients. *J Clin Oncol*. 2006;24(3):484-490.
66. Khorana AA, Francis CW, Blumberg N, et al. Blood transfusions, thrombosis, and mortality in hospitalized patients with cancer. *Arch Intern Med*. 2008;168(21):2377-2381.
67. Khorana AA, Francis CW, Culakova E, et al. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J Thromb Haemost*. 2007;5(3):632-634.
68. Naschitz JE, Yeshurun D, Abrahamson J. Arterial occlusive disease in occult cancer. *Am Heart J*. 1992;124(3):738-745.
69. Chow SF, McKenna CH. Ovarian cancer and gangrene of the digits: case report and review of the literature. *Mayo Clin Proc*. 1996;71(3):253-258.
70. Mouhayar E, Tayar J, Fasulo M, et al. Outcome of acute limb ischemia in cancer patients. *Vasc Med*. 2014;19(2):112-117.
71. Rossi C, Randi ML, Zerbinati P, et al. Acute coronary disease in essential thrombocythemia and polycythemia vera. *J Intern Med*. 1998;244(1):49-53.
72. Marchioli R, Finazzi G, Landolfi R, et al. Vascular and neoplastic risk in a large cohort of patients with polycythemia vera. *J Clin Oncol*. 2005;23(10):2224-2232.
73. Landolfi R, Di Gennaro L, Falanga A. Thrombosis in myeloproliferative disorders: pathogenetic facts and speculation. *Leukemia*. 2008;22(11):2020-2028.
74. Harrison CN, Campbell PJ, Buck G, et al. Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. *N Engl J Med*. 2005;353(1):33-45.
75. De Stefano V, Sora F, Rossi E, et al. The risk of thrombosis in patients with acute leukemia: occurrence of thrombosis at diagnosis and during treatment. *J Thromb Haemost*. 2005;3(9):1985-1992.
76. Roberts WC, Waller BF. Cardiac amyloidosis causing cardiac dysfunction: analysis of 54 necropsy patients. *Am J Cardiol*. 1983;52(1):137-146.
77. Feng D, Edwards WD, Oh JK, et al. Intracardiac thrombosis and embolism in patients with cardiac amyloidosis. *Circulation*. 2007;116(21):2420-2426.
78. Berghoff M, Kathpal M, Khan F, et al. Endothelial dysfunction precedes C-fiber abnormalities in primary (AL) amyloidosis. *Ann Neurol*. 2003;53(6):725-730.
79. Liao R, Jain M, Teller P, et al. Infusion of light chains from patients with cardiac amyloidosis causes diastolic dysfunction in isolated mouse hearts. *Circulation*. 2001;104(14):1594-1597.
80. Browne RS, Schneiderman H, Kayani N, et al. Amyloid heart disease manifested by systemic arterial thromboemboli. *Chest*. 1992;102(1):304-307.
81. Yood RA, Skinner M, Rubinow A, et al. Bleeding manifestations in 100 patients with amyloidosis. *JAMA*. 1983;249(10):1322-1324.
82. Numico G, Garrone O, Dongiovanni V, et al. Prospective evaluation of major vascular events in patients with nonsmall cell lung carcinoma treated with cisplatin and gemcitabine. *Cancer*. 2005;103(5):994-999.

83. Grenader T, Shavit L, Ospovat I, et al. Aortic occlusion in patients treated with Cisplatin-based chemotherapy. *Mt Sinai J Med*. 2006;73(5):810-812.
84. Alter P, Herzum M, Soufi M, et al. Cardiotoxicity of 5-fluorouracil. *Cardiovasc Hematol Agents Med Chem*. 2006;4(1):1-5.
85. Dasanu CA. Gemcitabine: vascular toxicity and prothrombotic potential. *Expert Opin Drug Saf*. 2008;7(6):703-716.
86. Fanelli M, Sarmiento R, Gattuso D, et al. Thalidomide: a new anticancer drug? *Expert Opin Investig Drugs*. 2003;12(7):1211-1225.
87. Baz R, Li L, Kottke-Marchant K, et al. The role of aspirin in the prevention of thrombotic complications of thalidomide and anthracycline-based chemotherapy for multiple myeloma. *Mayo Clin Proc*. 2005;80(12):1568-1574.
88. Libourel EJ, Sonneveld P, van der Holt B, et al. High incidence of arterial thrombosis in young patients treated for multiple myeloma: results of a prospective cohort study. *Blood*. 2010;116(1):22-26.
89. Pereg D, Lishner M. Bevacizumab treatment for cancer patients with cardiovascular disease: a double edged sword? *Eur Heart J*. 2008;29(19):2325-2326.
90. Grivas AA, Trafalis DT, Athanassiou AE. Implication of bevacizumab in fatal arterial thromboembolic incidents. *J BUON*. 2009;14(1):115-117.
91. Yoon S, Schmassmann-Suhijar D, Zuber M, et al. Chemotherapy with bevacizumab, irinotecan, 5-fluorouracil and leucovorin (IFL) associated with a large, embolizing thrombus in the thoracic aorta. *Ann Oncol*. 2006;17(12):1851-1852.
92. Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. *Endocr Rev*. 2004;25(4):581-611.
93. Kilickap S, Abali H, Celik I. Bevacizumab, bleeding, thrombosis, and warfarin. *J Clin Oncol*. 2003;21(18):3542; author reply 3543.
94. Scappaticci FA, Skillings JR, Holden SN, et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. *J Natl Cancer Inst*. 2007;99(16):1232-1239.
95. Choueiri TK, Schutz FA, Je Y, et al. Risk of arterial thromboembolic events with sunitinib and sorafenib: a systematic review and meta-analysis of clinical trials. *J Clin Oncol*. 2010;28(13):2280-2285.
96. Bair SM, Choueiri TK, Moslehi J. Cardiovascular complications associated with novel angiogenesis inhibitors: emerging evidence and evolving perspectives. *Trends Cardiovasc Med*. 2013;23(4):104-113.
97. Landolfi R, Marchioli R, Kutti J, et al. Efficacy and safety of low-dose aspirin in polycythemia vera. *N Engl J Med*. 2004;350(2):114-124.
98. Iliescu C, Durand JB, Kroll M. Cardiovascular interventions in thrombocytopenic cancer patients. *Tex Heart Inst J*. 2011;38(3):259-260.
99. Brugada J, Katritsis DG, Arbelo E, et al. 2019 ESC guidelines for the management of patients with supraventricular tachycardia. The Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC): developed in collaboration with the Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J*. 2019;41(5):655-720.
100. Robertson D, Hollister AS, Biaggioni I, et al. The diagnosis and treatment of baroreflex failure. *N Engl J Med*. 1993;329(20):1449-1455.
101. Farmakis D, Parissis J, Filippatos G. Insights into onco-cardiology: atrial fibrillation in cancer. *J Am Coll Cardiol*. 2014;63(10):945-953.
102. Guzzetti S, Costantino G, Sada S, Fundaro C. Colorectal cancer and atrial fibrillation: a case-control study. *Am J Med*. 2002;112(7):587-588.
103. Imperatori A, Mariscalco G, Riganti G, et al. Atrial fibrillation after pulmonary lobectomy for lung cancer affects long-term survival in a prospective single-center study. *J Cardiothorac Surg*. 2012;7:4.
104. Bhave PD, Goldman LE, Vittinghoff E, et al. Incidence, predictors, and outcomes associated with postoperative atrial fibrillation after major noncardiac surgery. *Am Heart J*. 2012;164(6):918-924.
105. Imazio M, Brucato A, Cemin R, et al. A randomized trial of colchicine for acute pericarditis. *N Engl J Med*. 2013;369(16):1522-1528.
106. Maisch B, Seferovic PM, Ristic AD, et al. Guidelines on the diagnosis and management of pericardial diseases executive summary; the Task Force on the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology. *Eur Heart J*. 2004;25(7):587-610.
107. Imazio M, Brucato A, Cemin R, et al. Colchicine for recurrent pericarditis (CORP): a randomized trial. *Ann Intern Med*. 2011;155(7):409-414.
108. Imazio M, Bobbio M, Cecchi E, et al. Colchicine in addition to conventional therapy for acute pericarditis: results of the COlchicine for acute PEricarditis (COPE) trial. *Circulation*. 2005;112(13):2012-2016.
109. McDonald JM, Meyers BF, Guthrie TJ, et al. Comparison of open subxiphoid pericardial drainage with percutaneous catheter drainage for symptomatic pericardial effusion. *Ann Thorac Surg*. 2003;76(3):811-815; discussion 816.
110. Sagrista-Sauleda J, Angel J, Permanyer-Miralda G, Soler-Soler J. Long-term follow-up of idiopathic chronic pericardial effusion. *N Engl J Med*. 1999;341(27):2054-2059.
111. Karatolios K, Maisch B, Pankuweit S. [Tumor markers in the assessment of malignant and benign pericardial effusion]. *Herz*. 2011;36(4):290-295.
112. Tsang TS, Seward JB, Barnes ME, et al. Outcomes of primary and secondary treatment of pericardial effusion in patients with malignancy. *Mayo Clin Proc*. 2000;75(3):248-253.
113. The Society for Cardiovascular Angiography and Interventions' 36th Annual Scientific Sessions. *Catheter Cardiovasc Interv*. 2013;81(S1):S1-S173.
114. Meinardi MT, Gietema JA, van der Graaf WT, et al. Cardiovascular morbidity in long-term survivors of metastatic testicular cancer. *J Clin Oncol*. 2000;18(8):1725-1732.
115. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med*. 2007;356(2):125-134.
116. Rossi GP, Seccia TM, Maniero C, Pessina AC. Drug-related hypertension and resistance to antihypertensive treatment: a call for action. *J Hypertens*. 2011;29(12):2295-2309.
117. Aparicio-Gallego G, Afonso-Afonso FJ, Leon-Mateos L, et al. Molecular basis of hypertension side effects induced by sunitinib. *Anticancer Drugs*. 2011;22(1):1-8.
118. Rini BI, Cohen DP, Lu DR, et al. Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib. *J Natl Cancer Inst*. 2011;103(9):763-773.
119. Maitland ML, Bakris GL, Black HR, et al. Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors. *J Natl Cancer Inst*. 2010;102(9):596-604.
120. Cole SW, Sood AK. Molecular pathways: beta-adrenergic signaling in cancer. *Clin Cancer Res*. 2012;18(5):1201-1206.
121. Jurado JA, Bashir R, Burket MW. Radiation-induced peripheral artery disease. *Catheter Cardiovasc Interv*. 2008;72(4):563-568.
122. Riley PA. Free radicals in biology: oxidative stress and the effects of ionizing radiation. *Int J Radiat Biol*. 1994;65(1):27-33.
123. Weintraub NL, Jones WK, Manka D. Understanding radiation-induced vascular disease. *J Am Coll Cardiol*. 2010;55(12):1237-1239.
124. Gaugler MH, Vereycken-Holler V, Squiban C, et al. Pravastatin limits endothelial activation after irradiation and decreases the resulting inflammatory and thrombotic responses. *Radiat Res*. 2005;163(5):479-487.
125. Jurado J, Thompson PD. Prevention of coronary artery disease in cancer patients. *Pediatr Blood Cancer*. 2005;44(7):620-624.

63 Pulmonary Complications of Cancer Therapy

Audra J. Schwalk
Saadia A. Faiz
Horiana B. Grosu
Lara Bashora
Vickie R. Shannon

KEY CONCEPTS

- Lung injury caused by cancer therapy results in stereotypical histopathologic disease patterns and syndromes. These lung injury patterns may be triggered by conventional chemotherapy, molecularly targeted agents, and immune modulators. The diagnosis is suggested by a temporal association with the drug and the development of compatible findings, coupled with exclusion of competing diagnoses. Recommendations to guide management of drug-induced lung injury are available, but evidence-based guidelines are limited.
- Albeit rare when compared to other forms of immune-related adverse events (IrAEs), lung involvement, specifically pneumonitis, is recognized as potentially one of the most lethal forms of IrAEs. The Common Terminology Criteria for Adverse Events stratifies pneumonitis based on the presence and severity of clinical symptoms, and treatment recommendations are based on these categories.
- Various cancer-related conditions may cause pulmonary hypertension (PH), and each condition is represented in the five categories of the revised 2019 World Health Organization classification scheme for PH. Each PH category is managed in a specific manner, and treatment of the underlying malignancy may lead to resolution or improvement of PH in some instances.
- Symptoms of malignant central airway obstruction (CAO) may mimic other more common diseases and may not develop until greater than 50% narrowing of the main airways has occurred. A high degree of suspicion must be maintained in patients at increased risk for CAO presenting with symptoms of cough, hemoptysis, stridor, focal wheezing, dyspnea, atelectasis, or recurrent or persistent postobstructive pneumonia.
- Pleural effusion is common in patients with cancer and can arise from malignant involvement of the pleura or secondary to a variety other causes such as bronchial obstruction, infiltration of mediastinal lymph nodes, superior vena cava syndrome, trapped lung, pulmonary embolism, or atelectasis. Chest radiography, chest computed tomography (CT), and thoracic ultrasonography are the imaging modalities most commonly used in evaluating potential causes and contributors to pleural effusion.
- Sleep disturbances are quite common in patients with cancer and can include insomnia, poor sleep efficiency, early awakening, excessive daytime sleepiness, and restless legs. These sleep disorders may occur during all phases of cancer care and can persist for months to years after completion of cancer therapy. Cognitive behavioral therapy is the treatment of choice for patients with many of these sleep disturbances.

Chest medicine is inextricably intertwined with cancer medicine as a result of the propensity for cancer therapy or the disease itself to affect the lungs. Pulmonary complications in patients with cancer may manifest as injury to the pulmonary interstitium, alveolar–capillary membrane, pleura, pulmonary circulation, or airways or may involve multiple intrathoracic structures. This chapter reviews cancer-related pulmonary complications, including lung toxicities associated with aggressive chemotherapy and radiotherapy regimens; noninfectious lung disorders arising in the post–stem cell transplant setting; and cancer-related pleural diseases, sleep disorders, and vascular disease. A focus of this review is to identify, discuss, and provide practical algorithms for the diagnosis and treatment of these complications with emphasis on issues in which early diagnosis may have a significant impact on patient management and outcome.

CHEMOTHERAPY-INDUCED LUNG INJURY

Injury to the lung caused by cancer therapy results in stereotyped histopathologic disease patterns and syndromes (Tables 63–1 and 63–2). Lung toxicity has been described after exposure to conventional chemotherapy as well as molecularly targeted agents and immune modulators. Interstitial lung disease and alveolar lung injury patterns are the most frequent. Pleural effusions, pulmonary vascular disease, and, less frequently, drug-induced granulomatous disease, and lymphadenopathy have also been described. In addition to direct lung injury, chemotherapy-induced immune suppression may predispose patients to life-threatening pneumonias.

The diagnosis of drug-induced lung injury (DILI) is hampered by the frequent use of multi-agent and multimodality therapies. In addition, overlapping clinical, radiographic, and pathologic manifestations of lung injury caused by infections, aspiration, cancer relapse, radiation and cancer-induced cardiac disease confound clinical distinctions between these entities and render precise estimates of DILI difficult. Other conditions that may mimic DILI include aspiration pneumonitis, diffuse alveolar hemorrhage (DAH), and cardiogenic pulmonary edema.[1,2] Predisposing factors, such as older age, cumulative dose, concomitant or sequential radiotherapy, oxygen administration, prior lung injury, and the use of multidrug regimens not only increase the risk of DILI but may also shorten the latency period between drug exposure and the development of clinical symptoms.

The diagnosis of DILI is suggested by a temporal association between drug exposure and the development of compatible clinical, radiographic, and laboratory evidence of lung injury, coupled with the exclusion of competing diagnoses. Interstitial and mixed alveolar–interstitial opacities, manifested as ground-glass opacities, reticular lines, septal thickening, and mosaic attenuation, typically localize to the peripheral and lower lung zones on chest imaging studies. Upper lobe–predominant disease may be seen with hypersensitivity reactions and accompanied by skin rash and wheezing. Bronchoscopy with performance of bronchoalveolar lavage (BAL), transbronchial biopsies, or both may be helpful in excluding infection or background disease. For example, findings of BAL eosinophilia of greater than 25% are supportive of drug-induced eosinophilic pneumonia (EP). Increased numbers of hemosiderin-laden macrophages on BAL fluid or progressively bloody saline aliquots on sequential BAL samples is supportive of DAH. A BAL lymphocytosis of greater than 50% with decreased CD4/CD8 ratios on BAL fluid are suggestive of interstitial lung disease; however, these findings are not sufficient to distinguish interstitial lung disease caused by drug toxicity from other causes. None of these histopathologic findings are pathognomonic of DILI.

Clinical manifestations of drug-induced interstitial lung disease include low-grade fever, dry cough, and dyspnea, which typically develop insidiously, usually within weeks to a few months after initiation of the first or subsequent cycles of therapy.[3,4] Pulmonary fibrosis may immediately ensue or occur as a late manifestation of DILI months to years after exposure to some agents, such as bleomycin, busulfan, cyclophosphamide, gemcitabine, and BCNU (carmustine). Bronchospasm and allergic reactions are common manifestations of infusion reactions that typically occur within minutes to hours of therapy.

Evidence-based guidelines in the management of patients with DILI are limited. In most cases, drug withdrawal is recommended after sufficient evidence to implicate the culprit agent with pneumotoxicity is established. Systemic corticosteroids have proven efficacy in the treatment of patients with DILI patterns such as hypersensitivity pneumonitis (HP), EP, and bronchiolitis obliterans organizing pneumonia (BOOP) . In other entities, (pulmonary fibrosis, bronchiolitis obliterans), no beneficial role has been established. Corticosteroid therapy should be considered in patients with progressive, steroid-responsive, or advanced-stage lung injury patterns. No guidelines for corticosteroid management in patients with DILI are currently available. General recommendations include starting doses of prednisone at 40 to 60 mg or weight-based dosing at 0.75 to 1 mg/kg daily with tapers over a 1- to 3-month time period, pending response to therapy. With few exceptions (see later), drug rechallenge is not recommended.

SPECIFIC HISTOPATHOLOGIC CORRELATES OF DRUG-INDUCED LUNG INJURY

Organizing Pneumonia

Organizing pneumonia (OP) represents an inflammatory process resulting from lung injury in which intraluminal polyploid plugs of proliferating fibroblasts and myofibroblasts form buds within alveolar ducts within the distal alveolar spaces. OP is a well-known histopathologic response to DILI. This pathological pattern is not specific for DILI and may develop as a result of injury caused by other lung insults, including infection or trauma. Low-grade fever, cough, dyspnea, and pulmonary infiltrates on chest imaging are prominent clinical findings. Migratory patchy, alveolar opacities predominating in the lung periphery are the most common findings on computed

TABLE 63–1 Lung toxicity Caused by Conventional Chemotherapeutic Agents: Histologic Patterns of Lung Injury

Disorder	Alkylating Agents	Antimetabolites and Purine Analogs	Cytotoxic Antibiotics	Nitrosoureas	Podophyllotoxins	Taxanes	TKIs and Immunomodulators	Other
NCPE, ARDS, PF	Busulfan Cyclophosphamide	Methotrexate Azathioprine Ara-C Fludarabine Gemcitabine Pentostatin	Bleomycin Mitomycin C	BCNU CCNU	Irinotecan Topotecan	Paclitaxel Docetaxel	G-CSF GM-CSF IL-2 TNF IFN-γ	
Bland pulmonary hemorrhage		Azathioprine						ATRA
NSIP	Busulfan Cyclophosphamide Temozolomide Melphalan Chlorambucil	Methotrexate Azathioprine Fludarabine Gemcitabine	Bleomycin	BCNU CCNU	Irinotecan Etoposide	Paclitaxel Docetaxel	G-CSF GM-CSF IFN-γ Thalidomide	Procarbazine
Airway disease	Cyclophosphamide Oxaliplatin Iphosphamide	Gemcitabine Nelarabine	Bleomycin Mitomycin C		Irinotecan Etoposide	Paclitaxel Docetaxel	IFN-α	Anthracyclines L-asparaginase
Hypersensitivity pneumonitis	Cyclophosphamide Oxaliplatin Busulfan	Methotrexate Ara-C Gemcitabine 6-Mercaptopurine	Bleomycin	BCNU	Etoposide Teniposide	Docetaxel		Procarbazine BCG
Organizing pneumonia	Busulfan Cyclophosphamide Oxaliplatin	Methotrexate	Bleomycin	BCNU CCNU	Topotecan		IFN-γ Thalidomide GM-CSF	
Eosinophilic pneumonia	Oxaliplatin	Methotrexate Fludarabine Cladribine	Bleomycin				IL-2 IFN-γ	
Granulomas		Fludarabine					IFN-α	Procarbazine
Pleural disease	Cyclophosphamide	Methotrexate Azathioprine Gemcitabine	Mitomycin C	BCNU	Docetaxel	Docetaxel	IL-2 IFN-α G-CSF/GM-CSF	ATRA Procarbazine
Mediastinal or hilar lymphadenopathy		Methotrexate	Bleomycin				IFN-γ	
PH: PAH, PVOD, PE		Gemcitabine (PVOD) Zinostatin (PAH)	Bleomycin (PVOD) Mitomycin C (PAH, PVOD)	BCNU (PVOD) CCNU (PVOD)	Etoposide (PVOD)		IL-2 (PAH) IFN-α, -γ, -β Thalidomide (PE) Lenalidomide (PE) Pomalidomide (PE)	Tamoxifen L-asparaginase Thalidomide Revlimid

Ara-C, cytarabine; ARDS, acute respiratory distress syndrome; ATRA, all-*trans*-retinoic-acid; BCNU, carmustine; CCNU, lomustine; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL-2, interleukin-2; mAbs, monoclonal antibodies; NCPE, noncardiogenic pulmonary edema; NSIP, nonspecific interstitial pneumonitis; PAH, pulmonary arterial hypertension; PE, pulmonary embolism; PF, pulmonary fibrosis; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; TNF, tumor necrosis factor; TKI, tyrosine kinase inhibitor.

TABLE 63–2 Lung Toxicity Caused by Targeted Therapies and Immune Checkpoint Inhibitors: Histologic Patterns of Lung Injury

Disorder	Monoclonal Antibodies	Tyrosine Kinase Inhibitors	Rapamycin Inhibitors	Proteosome Inhibitors	Immune Checkpoint Inhibitors
Pneumonitis or ILD dyspnea not otherwise specified		EGFR: imatinib, gefitinib, erlotinib, afatinib, osimertinib ALK: crizotinib, ceritinib, alectinib, brigatinib MEK: trametinib, cobimetinib, binimetinib Bcr-Abl: imatinib, nilotinib, dasatinib PIK3: idelalisib, copanlisib, duvelisib MET: capmatinib Bcr-Abl: imatinib, nilotinib, dasatinib PIK3: idelalisib, copanlisib, duvelisib, apelisib FLT3: midostaurin, gilteritinib BRAF: encorafenib, binimetinib, vemurafenib			
NCPE, ARDS, and PF	EGFR: panitumumab CD20: rituximab CD22: Moxetumomab Her2: trastuzumab, Ado-trastuzumab-emestane, fam-trastuzumab deruxtecan	EGFR: imatinib, gefitinib, erlotinib ALK: crizotinib, ceritinib, alectinib, brigatinib MEK: trametinib, cobimetinib, binimetinib	Everolimus Temsirolimus	Bortezomib Carfilzomib Ixazomib	CTLA-4–ipilimumab PD-1: nivolumab, pembrolizumab, cemiplimab PD-L1: atezolizumab, avelumab, durvalumab
Pulmonary hemorrhage	VEGF: bevacizumab CD20: rituximab CD33: gemtuzumab				PD-1: nivolumab, pembrolizumab
NSIP	Rituximab Trastuzumab	Gefitinib Dasatinib	Temsirolimus Everolimus	Bortezomib Carfilzomib	CTLA-4–ipilimumab PD-1: nivolumab, pembrolizumab, cemiplimab PD-L1: atezolizumab, avelumab, durvalumab
Bronchospasm	All mAbs: drugs formulated using fully mouse and chimeric (mouse, human) proteins confer highest rates			Bortezomib	
Granulomatous inflammation (sarcoid-like reactions)		BRAF: dabrafenib, vemurafenib			All immune checkpoint inhibitors

(*Continued*)

TABLE 63–2 Lung Toxicity Caused by Targeted Therapies and Immune Checkpoint Inhibitors: Histologic Patterns of Lung Injury (*Cont.*)

Disorder	Monoclonal Antibodies	Tyrosine Kinase Inhibitors	Rapamycin Inhibitors	Proteosome Inhibitors	Immune Checkpoint Inhibitors
Organizing pneumonia	CD20: rituximab Her2: trastuzumab				
Cytokine release syndrome		Jakafi: ruxolitinib FLT3: gilteritinib			CAR T TILs
Pleural disease		EGFR: gefitinib Bcr-Abl: dasatinib > imatinib, bosutinib, nilotinib			
Infections	CD52: alemtuzumab				
Pulmonary vascular disease: PAH, PVOD, DVT	VEGF: bevacizumab	Dasatinib		Bortezomib	

ALK, anaplastic lymphoma kinase; ARDS, acute respiratory distress syndrome; Bcr-Abl, breakpoint cluster region-Abelson; CAR T, chimeric antigen receptor T-cells; CD, cluster of differentiation; CTLA-4, cytotoxic T-cell lymphocyte antigen-4 ; DVT, deep vein thrombosis; EGFR, epidermal growth factor receptor; FLT3, fms-like tyrosine kinase 3; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; MEK, mitogen-activated extracellular signal-regulated kinase; NCPE, noncardiogenic pulmonary edema; NSIP, nonspecific interstitial pneumonitis; PAH, pulmonary arterial hypertension; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PF, pulmonary fibrosis, PIK3, phosphoinositide 3 kinase; PVOD, pulmonary veno-occlusive disease; TIL, tumor infiltrating lymphocyte; VEGF, vascular endothelial growth factor.

tomography (CT) imaging of the chest (Fig. 63–1). Other imaging patterns, including solitary inflammatory infiltrates and diffuse bilateral infiltrates in association with interstitial opacities and small superimposed alveolar opacities, are less common. OP is established by excluding alternative diagnoses such as infection or malignancy. Lung biopsy is often necessary for definitive diagnosis. OP has been associated with an extensive list of cytotoxic agents, including anthracyclines, cladribine, oxaliplatin, interferon-α (INF-α), rituximab, and thalidomide. Molecular targeted agents, including (epidermal growth factor receptor [EGFR]) inhibitors,[5–13] Bcr-Abl (breakpoint cluster region-Abelson) tyrosine kinase inhibitors (TKIs),[14–17] anaplastic lymphoma kinase (ALK) inhibitors,[13,18] mitogen-activated protein kinase enzymes MEK1 and MEK2,[19] phosphoinositol kinase 3,[20,21] CD20 inhibitors,[22] Her2 receptor antagonists,[23–25] rapamycin analogs,[26,27] and immune checkpoint inhibitors (ICIs),[28–32] have also been implicated in the development of OP. Cessation of the culprit agent and initiation of systemic corticosteroids results in rapid resolution of respiratory signs and symptoms in most cases.

Nonspecific Interstitial Lung Disease

Nonspecific interstitial pneumonitis (NSIP) is one of the most common morphologic patterns of interstitial lung disease. Dry cough and progressive dyspnea develop insidiously, over weeks to months, after drug exposure. Radiographic findings may include pleural-based, lower lobe ground-glass attenuations, reticular lines, mosaic patterns, and nodules. Injury to epithelial and endothelial cells leads to alveolar edema and diffuse alveolar damage early on, which may progress



FIGURE 63–1 A 66-year-old man with advanced-stage adenocarcinoma of the lung presented 2 days after cycle 2 of nivolumab, carboplatin, and pemetrexed with a dry cough and dyspnea. Bilateral patchy areas of ground-glass opacities and consolidation seen on chest computed tomography (CT) imaging (B) were new when compared with baseline studies (A). Notice the prominent air bronchogram (*arrow* in B). Bronchoscopy with bronchoalveolar lavage and biopsies were positive for organizing pneumonia. Microbiologic studies were negative for infection. Symptoms resolved and CT abnormalities were markedly improved after 4 weeks of high-dose steroid treatment (C).

to end stage fibrotic lung disease despite drug withdrawal and corticosteroid therapy. Cytotoxic agents that have been most frequently associated with NSIP include bleomycin, mitomycin, the nitrosoureas, busulfan, gemcitabine, paclitaxel, cyclophosphamide, ifosfamide, methotrexate, irinotecan, and oxaliplatin. Among the molecular targeted therapies, the mammalian target of rapamycin (mTOR) inhibitors (everolimus, temsirolimus), EGFR inhibitors (gefitinib, erlotinib, cetuximab, panitumumab), and proteasome inhibitors (bortezomib, carfilzomib) are frequently cited (Fig. 63–2).[26,33–35]

Noncardiogenic Pulmonary Edema, Diffuse Alveolar Damage, and Acute Respiratory Distress Syndrome

Drug-induced injury to the alveolar–capillary membranes may result in capillary leak and a permeability (noncardiogenic) pulmonary edema. Acute respiratory distress syndrome (ARDS) and its histologic hallmark, diffuse alveolar damage (DAD), may ensue as the disease progresses. These reactions may be unrelated to drug dosage or duration of therapy. Busulfan, bleomycin, cyclophosphamide, gemcitabine, oxaliplatin, etoposide, cytarabine, and vinblastine; the molecularly targeted agents (gefitinib, erlotinib, cetuximab, moxetumomab); the antilymphocyte monoclonal antibodies (mAbs; rituximab, alemtuzumab, ofatumumab); and the rapamycin inhibitors (everolimus, temsirolimus) are most often implicated in the development of drug-induced noncardiogenic pulmonary edema (NCPE). NCPE leading to ARDS has been described after use of ruxolitinib, a novel JAC1/2 inhibitor, as a result of a cytokine rebound reaction. This reaction is mitigated with the preemptive use of corticosteroids and supportive therapy.[36,37] Cytokine storm has also been described after all-*trans*-retinoic acid (ATRA) and arsenic trioxide therapies in the treatment of patients with acute promyelocytic leukemia (APL). The so-called differentiation syndrome occurs in up to 25% of patients with APL undergoing induction therapy, which is characterized by potentially fatal NCPE and ARDS. Unlike many of the lung injury processes, in patients with ATRA and arsenic-related differentiation syndrome, de-escalation of drug dose, rather than drug withdrawal, along with systemic steroid therapy has been associated with successful resolution of toxicity in patients with mild to moderate forms of this syndrome.[38,39] DAH is typically seen as sequelae of alveolar–capillary membrane injury and thus in the setting of ARDS and DAD. Occasionally, bland alveolar hemorrhage have been described in the absence of DAD after rituximab and alemtuzumab therapy.[36,40] Massive, and sometimes fatal, bleeding has been reported during bevacizumab therapy for treatment of central airway tumors.[41] ARDS with and NCPE has been implicated in granulocyte and granulocyte-macrophage colony-stimulating factors administration, particularly in association with non-Hodgkin's lymphoma.

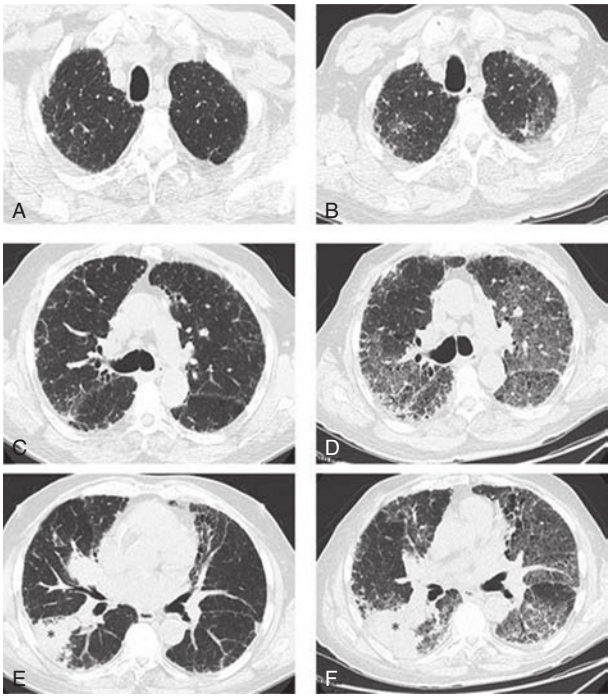


FIGURE 63–2 **A 68-year-old man presented with progressive dyspnea and dry cough 4 months after initiation of panitumumab for colorectal cancer. At baseline, emphysematous changes and subpleural reticulations are seen (A, C, and E), consistent with the patient's known history of idiopathic pulmonary fibrosis. Repeat chest computed tomography (CT) imaging demonstrated a significant interval increase in mid- and lower lobe–predominant bilateral patchy ground-glass attenuation with increased underlying septal thickening and focal sparing along the pleural surfaces (B, D, and F). CT findings were consistent with nonspecific interstitial pneumonitis, which was confirmed on lung biopsy. Metastatic lesions are noted in both lungs, the largest of which overlies the right lower lobe (E and F, *asterisks*)**

Diffuse Alveolar Hemorrhage

AH is characterized by diffuse pulmonary infiltrates, increased hemosiderin-laden macrophages in the BAL fluid and progressively hemorrhagic BAL return. Drug-induced DAH is rare but has been reported in association with azathioprine, ATRA, gemtuzumab, and rituximab. Fatal DAH has been reported.[42–44] Acute dyspnea, hypoxia, and occasionally fever and hemoptysis are presenting symptoms. Treatment strategies include drug withdrawal and high-dose steroids, although evidence-based support for the later has not been validated in any large, randomized trials.

Eosinophilic Pneumonia

EP is characterized by marked eosinophil accumulation within the lung interstitium and alveolar spaces and may be caused by variety of infectious agents, inhaled toxins, and pharmacologic agents. Methotrexate, bleomycin, cladribine, fludarabine, and INF-α are the most frequently implicated agents in the development of EP. Patients typically present with an acute febrile illness, dry cough, and dyspnea accompanied by bilateral parenchymal infiltrates on CT imaging. A compatible history coupled with imaging findings, exclusion of competing diagnoses, and greater than 25% eosinophils on BAL fluid establishes the diagnosis. Peripheral eosinophilia may be absent initially but increases with progressive disease. Late disease is marked by hypoxemic respiratory failure. Drug-induced EP is typically steroid responsive with a favorable prognosis when diagnosed early. Withdrawal of the culprit agent may be sufficient in early stages of disease. Steroids are indicated for advanced cases associated with respiratory failure.[45–47]

Granulomatous Pneumonitis

Several drugs, including fludarabine, rituximab, procarbazine, INF-α, and the class of drugs known as ICIs, are capable of inducing granulomatous reactions in the lungs, similar to HP and sarcoidosis. Granulomatous inflammation caused by drugs is typically non-necrotizing, as opposed to necrotizing granulomas seen with infections. However, infectious causes, such as mycobacteria and fungal pathogens, must be excluded.

Hypersensitivity Pneumonitis

HP-like reactions typically occur after repeated drug exposure to an offending agent and are characterized clinically by fever, dyspnea, dry cough, and rash. Symptoms typically occur over the first 3 to 4 weeks after drug exposure and may wax and wane without adjustments in therapy. Poorly formed noncaseating granulomas and BAL lymphocytosis are common histopathologic findings. Upper lobe–predominant disease is characteristic, particularly in chronic forms of the disease. Methotrexate is the prototype agent associated with HP, which may develop after oral, intravenous, intrathecal, and intramuscular routes of methotrexate administration. HP has also been reported after bleomycin, gemcitabine, oxaliplatin, procarbazine, the nitrosoureas, 6-mercaptopurine, busulfan, and Bacillus Calmette-Guerin (BCG) therapy. Drug withdrawal and steroid therapy typically produce favorable outcomes, with complete resolution of clinical signs and symptoms in most cases.

Sarcoid-Like Reactions

Sarcoid-like reactions are uncommon sequelae of anti–tumor necrosis factor (TNF) agents (etanercept, adalimumab), INF therapy, methotrexate, the *BRAF* inhibitors (vemurafenib and dabrafenib), and the ICIs.[48–55] These agents may elicit a systemic granulomatous reaction that is indistinguishable from sarcoidosis. Asymptomatic infiltrates and micronodules distributed along bronchovascular bundles and hilar and mediastinal lymphadenopathy signal the onset of disease, which typically develops early, after the first few cycles of therapy (Fig. 63–3). Mild dyspnea and dry cough are infrequent complaints. Extrathoracic sarcoid-like reactions involving the skin, liver, and brain occurring concomitantly or sequentially have also been described (Fig. 63–4). Whether drug-related sarcoid-like reactions exacerbate subclinical sarcoidosis, render the immune system more susceptible to sarcoidosis, or is a distinct entity from true sarcoid is unclear. Sarcoid-like reactions are characterized by lymphangitic distribution of non-necrotizing granulomas, mediastinal lymphadenopathy, and pulmonary infiltrates. BAL fluid analysis frequently demonstrates a CD4-predominant lymphocytosis, giving rise to an increased CD4/CD8 ratio (CD4/CD8 ratio >1). Spontaneous resolution often occurs with discontinuation of the offending agent. Systemic corticosteroid therapy is typically not required but has been used in patients in which the culprit drug is continued because of its therapeutic efficacy in treating the underlying disease and lack of other treatment options.[56]

Pleural Effusions

Drug-induced pleural effusions may occur as an isolated toxicity to the pleura or as a manifestation of a generalized pleuroparenchymal abnormality. Drugs that have been associated with the development of pleural effusions include docetaxel, ATRA, methotrexate, INF-α, and the TKIs (dasatinib, imatinib, and bosutinib).[57–61] These small- to moderate-sized effusions are typically exudative and lymphocyte predominant and may be unilateral or bilateral. Withdrawal of the offending agent may result in spontaneous resolution in some cases.

Pulmonary Vascular Disorders

The development of thromboembolic disease, pulmonary hypertension (PH), and pulmonary veno-occlusive disease have all been described after use of conventional chemotherapeutic, molecularly targeted, and immune modulating agents. Increased rates of venous thromboembolism (VTE; pulmonary embolism [PE] and deep vein thrombosis [DVT]) have been reported

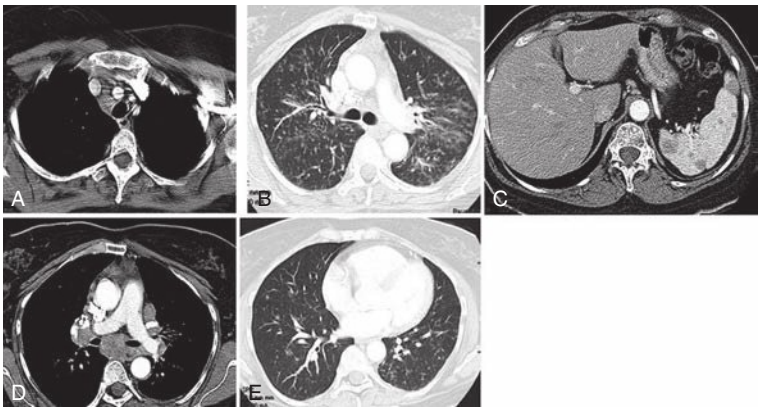


FIGURE 63–3 **A to E. Ipilimumab-related sarcoidosis. A 66-year-old man developed dry cough and dyspnea after the third cycle of ipilimumab therapy for refractory malignant melanoma. Bronchoscopy with bronchoalveolar lavage and transbronchial biopsies revealed T-lymphocyte alveolitis with increased CD4 and noncaseating granulomas without associated evidence of infection or malignancy.**

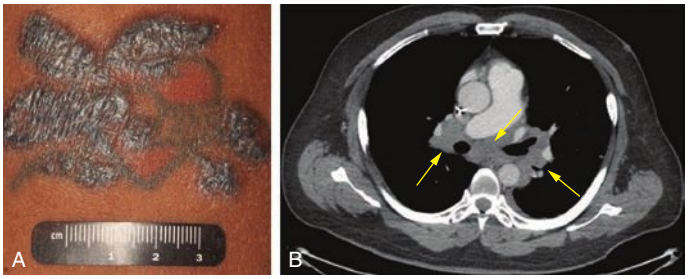


FIGURE 63–4 **A 52-year-old man presented with nodular skin lesions, including lesions growing over the area of an old tattoo (A), and bilateral hilar lymphadenopathy (B, *arrows*) after cycle 3 of ipilimumab and nivolumab for urothelial carcinoma. Biopsy of the skin lesions and endobronchial ultrasound biopsies of the hilar lymph nodes showed noncaseating granulomas, consistent with sarcoidosis. Skin lesions and lymphadenopathy resolved after 3 months of systemic steroid therapy.**

with ALK-inhibitor (crizotinib), Bcr-Abl inhibitor (ponatinib), and the vascular endothelial growth factor (VEGF) inhibitors (bevacizumab, sunitinib, sorafenib, pazopanib).[41,62–64] In addition, the immunomodulating, angiogenesis inhibitors (thalidomide, Revlimid) in combination with steroids, doxorubicin, or BCNU are associated with 14% to 43% increased risk of thromboembolic events (Fig. 63–5). The risk of thrombosis is reduced to 3% with DVT prophylaxis, which is now the standard of care for patients undergoing thalidomide- or lenalidomide-based therapies. Other agents, including hormonal therapies, growth factors, and erythropoietic agents, contribute to cancer-associated VTE.

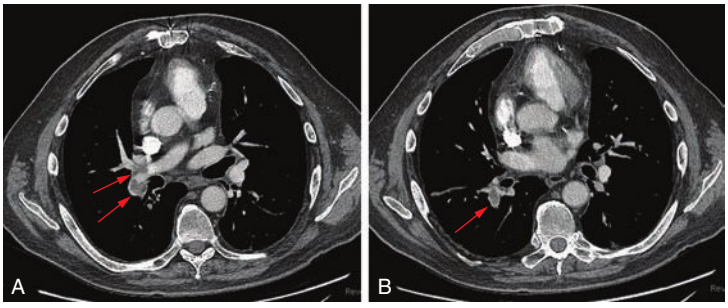


FIGURE 63–5 **Computed tomography angiogram showing multiple filling defects within the right-sided pulmonary artery (A, *arrows*) extending to the segmental and subsegmental branches (B, *arrows*), consistent with large pulmonary emboli. The patient was being treated with thalidomide-based therapy for melanoma.**

Pulmonary Hypertension

PH has been associated with several drugs, including bleomycin, busulfan, BCNU, and INF. Pulmonary arterial hypertension (PAH) has been definitively associated with dasatinib (a multi-kinase Bcr-Abl TKI) and possibly with bosutinib, and INF-α and INF-β. After dasatinib-associated PAH develops, drug withdrawal without rechallenge is recommended. Pulmonary vasodilator therapy may be needed until pulmonary arterial pressures improve. No reports of PAH after exposure to imatinib or the more selective Bcr-Abl–targeted TKIs (nilotinib, ponatinib) have been reported, but bosutinib has been implicated as well.[65–68] Bleomycin and BCNU have also been implicated in the development of pulmonary veno-occlusive disease (PVOD), an irreversible and often fatal form of PH that is characterized by fibrous obliteration of pulmonary venules.

Drug-Induced Airway Disease

Intravenous (IV) administration of virtually all chemotherapeutic and targeted agents may trigger an infusion reaction. Symptoms of dry cough, dyspnea, wheezing, chest pain, and hypoxia typically develop within minutes to several hours after drug infusion and may be life threatening. Infusion reactions may manifest as IgE-mediated, type 1 hypersensitivity reactions (carboplatin, oxaliplatin, and L-asparaginase) or as anaphylactoid reactions, mediated by cytokine release. Although vinca alkaloids are rarely associated with lung toxicity, severe bronchospasm has been described when these agents are given with concurrent or sequential administration of mitomycin therapy.[69,70] Other agents that commonly cause bronchospasm during or shortly after infusion include alemtuzumab, L-asparaginase, and the anthracyclines.[60,71–76] mAb infusion is a notorious source of infusion reactions, with the highest rates are seen among agents that contain the higher amounts of mouse protein. Infusion reactions may be triggered by the drug itself or in response to the vehicle in which the drug is formulated. The latter reaction is often seen following the administration of many of the mAbs. This is particularly true of the taxane class of drugs. For example, paclitaxel is formulated in Cremophor EL, a highly allergenic polyoxyethylated castor oil solvent. Docetaxel is formulated in polysorbate 80. Both vehicles may induce mast cell or basophil activation and subsequent hypersensitivity reaction. Other drugs that are formulated in Cremophor EL (cyclosporine, teniposide, ixabepilone) or polysorbate 80 (etoposide) may trigger similar reactions and should be avoided in patients with a history of infusion reactions after taxane administration.[77,78] Histamine receptor antagonists and steroids are recommended as standard prophylaxis before taxane administration, which has reduced the incidence of taxane-induced bronchospasm from 30% to 2%.[78] Close monitoring during and immediately after drug infusion is critical because breakthrough infusion reactions may occur despite prophylaxis.

Pneumonitis Associated with Immunotherapy: Immune Checkpoint Inhibitors

ICIs with their primary targets, programmed cell death receptor 1 (PD-1), programmed cell death-ligand 1 (PD-L1), and cytotoxic T-cell lymphocyte antigen-4 (CTLA-4), represent a significant addition in the therapeutic landscape for patients with advanced cancers. Initially approved for the treatment of patients with malignant melanoma, these agents are now approved for a broad array of hematologic malignances and solid tumors, including Hodgkin lymphoma and advanced-stage carcinomas involving the kidneys, lung, head and neck, bladder, and skin. ICIs act by releasing the negative regulatory controls involved in T-cell activation, thereby increasing T-cell–mediated immune response. This mechanism of action is thought to be responsible for both the therapeutic efficacy of ICI therapy and the driver behind a peculiar spectrum of toxicities, known as immune-related adverse events (IrAEs). IrAEs are common sequelae of ICI therapy, with a variable incidence of 20% to 90% across ICI regimens and cancer types.[79,80] These off-target, T-cell–driven inflammatory responses may affect virtually every organ system. Lung involvement is less common than other forms of IrAEs, occurring in 3% to 10% of patients.[31,81–83] However, pneumonitis, the most common form of lung IrAE, is recognized as one of the most potentially lethal forms of ICI-related toxicity and is therefore clinically relevant.

The incidence and clinical presentation of ICI-related lung injury are conditioned by the tumor type being treated, preexisting comorbidities, and the specific drug category and ICI treatment combinations. For instance, pneumonitis rates are highest among patients with non–small cell lung cancer (NSCLC; 7.2%–19%, all grades) compared with patients with other tumor types, including melanoma, head and neck squamous cell carcinoma, and urothelial carcinoma.

Patients with preexisting fibrotic lung disease and prior radiotherapy also appear to have an augmented risk of ICI-related pneumonitis, although these associations have not been fully elucidated.[84–89] The relationship between ICI drug class and pneumonitis risk is well established, with excess rates of pneumonitis among patients given PD-1–PD-L1 axis blockade as monotherapy compared with those given CTLA-4 blocking agents (Fig. 63–6). Anti–PD-1–CTLA-4 dual therapies and ICIs plus chemotherapy or chemoradiation combinations that confer their own toxicity risk

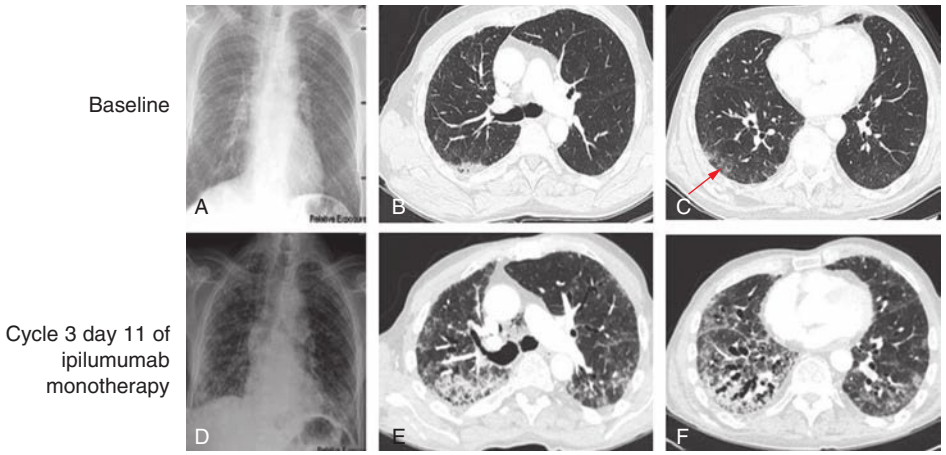


FIGURE 63–6 **Posteroanterior chest radiograph at baseline (A) and after three cycles of ipilimumab monotherapy (D) for prostate cancer. At baseline, subpleural reticular changes are noted and appear most prominent at the lung bases, consistent with a known history of idiopathic pulmonary fibrosis (B and C, *arrow*). After cycle 3 of ipilimumab, increased septal thickening with marked worsening of subpleural fibrotic changes and ground-glass opacities are seen (E and F). The acute worsening in pulmonary fibrosis may have been potentiated by ipilimumab therapy.**

are associated with a two- to threefold increase in pneumonitis incidence compared with ICI monotherapy.[86,90,91] In addition, ICI-related pneumonitis after dual and multimodality therapies is often more severe with slower recovery times.[91]

The Common Terminology Criteria for Adverse Events (CTCAE) stratifies pneumonitis based on the presence and severity of clinical symptoms (Table 63–3). In this scoring system, asymptomatic radiographic abnormalities (grade 1) and radiographic changes accompanied by mild dyspnea or cough (grade 2) are specified as low-grade pneumonitis, severe or medically significant symptoms that are not immediately life threatening (grade 3) or life-threatening symptoms that require urgent medical attention (grade 4) designate high grade pneumonitis, and all respiratory-related deaths are assigned to grade 5 pneumonitis. The spectrum of ICI-related pneumonitis patterns is similar to histopathologic correlates caused by other drugs. OP and NSIP are the most frequently observed patterns HP, DAD with ARDS, PF, DAH, bronchiolitis, and sarcoid-like reactions have also been reported.[29,31,86,87,92] Lung injury may manifest as a single histopathologic pattern, as more than one pattern simultaneously, or as different patterns with relapsed disease.

The concomitant or sequential appearance of other IrAEs involving the gut, liver, endocrine glands, and skin occurs in 60% of patients and should heighten the suspicion for lung-related IrAE. At presentation, nearly two thirds of patients have low-grade pneumonitis associated with asymptomatic pulmonary infiltrates (CTCAE grade 1) or nonspecific symptoms of dyspnea, cough, and rarely chest pain (CTCAE grade ≤2). Patients with higher grade disease commonly present with life-threatening signs and symptoms of hypoxemia and acute respiratory distress.[89] No pathognomonic signs are noted on physical examination. Auscultation of rales at the lung bases is a nonspecific finding and more often observed in patients with higher grade disease. Unlike toxicity associated with other systemic antineoplastic therapies, signs and symptoms of pneumonitis commonly occur months to years after the last dose of ICI therapy, with a median time to onset between 5.2 and 12 weeks. Shorter intervals have been reported among patients with primary lung cancer (2.9–7.7 weeks) and patients treated with combination therapy regimens (median onset, 2.7 months; range, 9 days–6.9 months).[31,86]

TABLE 63–3 National Cancer Institute Common Terminology of Criteria for Adverse Events

Pneumonitis Grade	Characteristics
1 (mild)	Asymptomatic; radiographic findings
2 (moderate)	Symptomatic; not interfering with ADLs
3 (severe)	Symptomatic; interfering with ADLs or oxygen indicated
4 (life threatening, disabling)	Life threatening or ventilator support required
5 (Death)	

ADLs, activities of daily living.

The diagnosis of ICI pneumonitis is based on a compatible history and CT findings coupled with the exclusion of competing diagnoses, including infection, tumor progression, pulmonary edema, and alveolar hemorrhage. Bronchoscopic examination is an important early tool in the diagnostic evaluation and should be used to interrogate alternative diagnoses. BAL fluid cultures are helpful when results are positive, although negative culture results may not definitively exclude infection. BAL fluid analysis typically reveals a predominant CD8-positive lymphocytosis. Elevated eosinophils on BAL fluid have also been reported. Examination of tissue obtained from transbronchial or surgically obtained lung biopsies may be helpful in identifying a specific histologic subtype of pneumonitis, which may have prognostic significance. Impairment of forced expiratory volume in 1 second (FEV_1) and diffusing capacity of the lung for carbon monoxide on pulmonary function tests (PFTs) may precede clinical and radiographic findings and represent two of the earliest signals of lung injury.[86] However, the role of pulmonary testing as a reliable predictor of pneumonitis and the threshold change that signals clinically significant disease have not been clarified.

TREATMENT AND OUTCOME

Several investigations suggest that early development of IrAEs within 4 to 6 weeks of ICI initiation predicts improved overall survival and progression-free survival.[93] However, the incidence of pneumonitis was low in these studies. In studies in which the incidence of ICI-related pneumonitis is higher, pneumonitis is a clear poor prognosticator, particularly among patients with NSCLC and in patients with higher grade disease.[93–95]

Treatment strategies for ICI pneumonitis have not been validated in any prospective trials and are guided by CTCAE pneumonitis grades (Table 63–4). Asymptomatic patients (grade 1) may be monitored as outpatients for the development of symptoms. If the patient remains asymptomatic and there is no evidence of disease progression on a CT chest or deterioration in lung function before the subsequent scheduled dose of ICI (within 3–4 weeks), ICI therapy may be cautiously continued. If any symptoms develop, ICI therapy should be interrupted and treatment strategies escalated to grade 2 or higher, depending on the severity of symptoms. Systemic corticosteroid therapy is recommended for patients with pneumonitis that is grade 2 or higher after infection and other competing diagnoses have been excluded. No randomized controlled trials are available to guide optimal steroid dose or duration in this setting; therefore, treatment duration is largely dictated by response to steroid therapy. Steroids are usually dosed at 1 to 2 mg/kg/day and continued over 4 to 6 weeks. Patients with grade 2 pneumonitis are typically managed as outpatients and may be considered for drug rechallenge with close follow-up after resolution of signs and symptoms.

Permanent withdrawal of ICI therapy and inpatient initiation of corticosteroids at 1 to 2 mg/kg/day is recommended for patients with pneumonitis grades 3 and 4. We typically continue the higher dose steroids until symptoms have returned to grade 1 (usually 7 days), at which time steroids may be slowly tapered. Pneumonitis flares have been reported after rapid steroid tapers in 25% of patients.[86] The steroid taper should be tailored to the severity of the pneumonitis event and response to initial therapy, typically 6 weeks. If no clinical improvement is demonstrated after 48 to 72 hours of corticosteroid therapy, intensification of immunosuppressive therapy with the addition of other immunosuppressive agents is generally recommended. Infliximab, azathioprine, mycophenolate mofetil, cyclophosphamide, and tocilizumab have been used but not rigorously studied in this setting. Thus, the optimal timing, dose, duration, and favored secondary immunosuppressive agent in this setting has not been determined. Andecdotal support for the TNF-α inhibitor, infliximab, in recalcitrant ICI pneumonitis is largely based on extrapolated reports of successful treatment of ICI-related colitis.[96,97] Support for other agents, such as intravenous immunoglobulin) and the interleukin-6 inhibitor tocilizumab is derived from small case reports and case series.[98] Infectious prophylaxis against *Pneumocystis jirovecii pneumonia* (PJP) for patients requiring prolonged, high-dose steroid therapy is generally advocated, although the dose of steroids defines "high dose" and the duration of steroids that defines "prolonged" have not been clearly established. In general, PJP prophylaxis is recommended for steroid doses of 20 mg or higher for a duration of 30 days or longer.[99,100] Pharmacologic prophylaxis against steroid-induced gastrointestinal (GI) stress ulcers should also be considered. Baseline screening for tuberculosis is suggested for all patients before initiating anti–TNF-α agents, given the known propensity for these agents to increase the susceptibility to serious infections, including reactivation of latent tuberculosis.[101–104]

Approximately 25% to 33% of patients may experience recurrent IrAEs after initial resolution of signs and symptoms. Recrudescence of signs and symptoms may occur after drug rechallenge or emerge as an unprovoked pneumonitis, months after drug discontinuation. Life-threatening toxicities involving the lungs, heart, or central nervous system are considered absolute contraindications to drug rechallenge. If clinically significant pneumonitis recurs following reinstitution of the drug, permanent discontinuation of the ICI agent is recommended.

TABLE 63–4 Treatment Guidelines for Immune Checkpoint Inhibitor Pneumonitis

Grade of Pneumonitis	Grade 1	Grade 2	Grade 3	Grade 4
Definition	Asymptomatic chest imaging findings	Mild symptoms that limit ADLs	Severe debilitating symptoms that limit self-care	Life-threatening symptoms
Intervention indicated?	No	Yes	Yes	Yes
FOB, BAL, PFTs	Yes	Yes	Yes, if stable	Yes, when stable
Treatment	• Consider holding drug.	• Hold drug. • Consider hospitalization. • Start steroids (prednisone 1–2 mg/kg/day PO or methylprednisolone 1 mg/kg/day IV). • Consider antibiotics.	• Discontinue drug. • Hospitalize. • Start high-dose IV methylprednisolone. • Add antibiotics.	• Discontinue drug. • Admit to ICU and intubate. • Start high-dose IV methylprednisolone. • Add antibiotics.
Follow-up	• Reassess after 3 weeks. • If completely resolved or non-drug-related: continue treatment. • If worsening. treat as grade 2 or ¾.	• Reassess every 1–3 days. • Symptoms improving: slowly taper steroids. • Symptoms worsening: treat as grade ¾.	• Reassess daily. • No symptom improvement or symptoms worsening after 48 hours: add additional immunosuppressive therapy (infliximab, cyclophosphamide, mycophenolate, tocilizumab).	• Reassess daily. • No symptom improvement or symptoms worsening after 48 hours: add additional immunosuppressive therapy (infliximab, cyclophosphamide, mycophenolate, tocilizumab).
Duration of treatment	N/A	4–6 weeks	4–6 weeks	4–6 weeks
ICI rechallenge?	Yes	May be considered if symptoms resolve to grade 1	No	No

ADL, activity of daily living; BAL, bronchoalveolar lavage; FOB, fiberoptic bronchoscopy; ICI, immune checkpoint inhibitor; ICU, intensive care unit; IV, intravenous; NA, not applicable; PFT, pulmonary function test; PO, by mouth.

RADIATION-INDUCED LUNG INJURY

Clinically significant radiation-induced lung injury is the most common dose-limiting complication of thoracic radiation therapy (RT), occurring in 5% to 20% of patients.[105] Recent advances in radiation techniques and delivery systems, such as proton therapy, three-dimensional conformal RT, intensity-modulated RT, and stereotactic body RT, purport lower lung injury rates while delivering higher target doses of radiation to the lung. Factors associated with radiation delivery (total radiation dose, dose per fraction, volume of irradiated lung, and beam characteristics and arrangements) as well as clinical factors (preexisting lung disease, underlying poor pulmonary reserve, prior radiotherapy, multimodality regiments, rapid steroid withdrawal) all potentiate the appearance and severity of radiation pneumotoxicity. Radiographically apparent lung injury is common with total doses of radiation that exceed 40 Gy and is rare at doses below 20 Gy.[106,107] Hyperfractionated radiation doses delivered to the smallest lung volume is recommended.

Acute clinical radiation pneumonitis, heralded by dyspnea, low-grade fever, and dry cough, develops insidiously over 1 to 3 months after completion of radiation. Radiographic changes typically precede clinical symptoms, appearing 3 to 4 weeks after RT. Discrete ground-glass opacities, ill-defined patchy nodules, or consolidation with air bronchograms and volume loss within the irradiated field are common early findings that evolve over the ensuing 6 to 23 months, leaving a linear scar. Regional fibrosis is seen in nearly all patients, including those without clinical symptoms, and is characterized by the appearance of

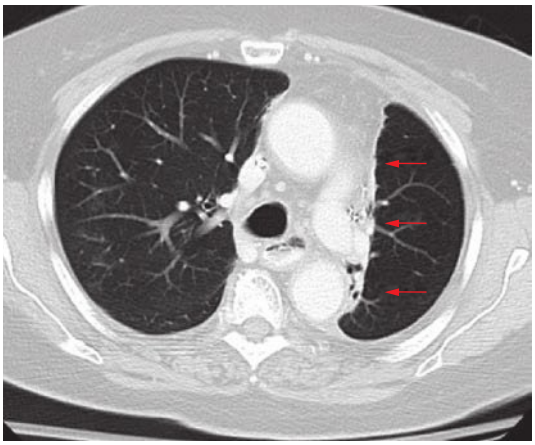


FIGURE 63–7 Radiation fibrosis 1 year after completion of radiation therapy for adenocarcinoma of the lung. Fibrotic changes are demarcated by a linear scar (*arrows*). There is associated significant volume loss of the left lung.

a well-demarcated area of volume loss, linear densities, bronchiectasis, retraction of the lung parenchyma, tenting and elevation of the hemidiaphragm, and ipsilateral pleural thickening within the irradiated field (Fig. 63–7). Postradiation volume loss, bronchiectasis, and consolidation may occur after the newer modes of RT delivery but typically are less extensive than injury patterns after conventional radiation.[108,109]

Radiation recall pneumonitis (RRP) is a rare inflammatory reaction that develops within a previously irradiated field after certain chemotherapy and molecularly targeted therapies. This reaction has been most often observed after taxane- and anthracycline-based therapies. Gemcitabine, etoposide, vinorelbine, trastuzumab, and erlotinib may also trigger this disease.[110–112] The small molecule kinase inhibitors involving the EGFR (erlotinib), VEGF (sunitinib), and mTOR pathways (everolimus) have also been implicated in triggering RRP. ICIs associated with PD-1/PD-L1 axis and CTLA-4 blockade have also been added to the list of triggers.[110,113–122] Clinically, RRP is signaled by dry cough, fever, and dyspnea, and accompanied by ground-glass opacities and areas of consolidation that conform to the prior radiation treatment portal. RRP may develop during the first or subsequent course of therapy with the inciting agent, which may be weeks to years after completion of RT. Drug withdrawal and corticosteroid therapy may mitigate symptoms of radiation pneumonitis but have not been shown to be of benefit in the treatment of patients with radiation fibrosis. Drug reintroduction without reemergence of RRP has been successful in some cases.[112,117]

Pleural effusions may develop as early (within 6 months) and late (1–5 years) sequelae of RT. Effusions are typically small and ipsilateral or bilateral. Reactive mesothelial cells with negative pleural fluid cytology are common. Most RT-induced pleural effusions are asymptomatic, although pleuritic chest pain and dyspnea are occasionally presenting symptoms. Radiation-related OP and EP have been described in patients with breast cancer and may involve nonirradiated areas of the lung.[109,110,123] These lung injury patterns are characterized by migratory pulmonary opacities that develop 1 to 3 months after completing RT. A prior history of asthma or atopy, coupled with blood or tissue eosinophilia, supports the diagnosis of radiation-induced EP. Both lung injury patterns are typically steroid responsive.

NONINFECTIOUS PULMONARY COMPLICATIONS OF HEMATOPOIETIC STEM CELL TRANSPLANTATION

Pulmonary complications remain a formidable threat to the success of hematopoietic stem cell transplantation (HSCT). Posttransplant lung injury occurs in up to 60% of patients as a consequence of direct toxicities from conditioning regimens, delayed bone marrow recovery, prolonged immunosuppressive therapy, and graft-versus-host disease (GVHD). Recipients of allogeneic HSCT are at increased risk of infectious complications, owing to the increased rates of GVHD and the protracted need for immunosuppressive therapy in this group of patients. Antimicrobial prophylaxis has emerged as standard protocol after HSCT, effectively reducing the rates of transplant-related infections. Noninfectious pulmonary complications, however, remain a major cause of post-HSCT morbidity and mortality.[117] Infectious and noninfectious pulmonary complications after HSCT are temporally related to immune recovery and the development of GVHD (Table 63–5).

Early-onset pulmonary complications occur within the first 100 days after transplant and include diffuse pulmonary edema, DAH, peri-engraftment respiratory distress syndrome (PERDS), idiopathic pneumonia syndrome (IPS), delayed pulmonary toxicity syndrome, and PVOD (Table 63–6). Bronchiolitis obliterans syndrome (BOS), cryptogenic organizing pneumonitis (COP), posttransplant lymphoproliferative disorder (PTLD) comprise the late-onset pulmonary complications, which typically occur more than 100 days after HSCT (Table 63–7). Each of these entities is briefly discussed next.

Early-Onset Noninfectious Pulmonary Complications

Early-onset pulmonary complications are characterized by nonspecific symptoms of acute dyspnea,

TABLE 63–5 Infectious and Noninfectious Complications of Hematopoietic Stem Cell Transplantation

Timing After HSCT	Risk Factors	Infectious	Noninfectious
Pre-engraftment (days 0–30)	Conditioning or preparative regimen Neutropenia	Bacterial infections (gram-negative and gram-positive species) Fungal infections (aspergillosis, *Candida*) Respiratory viruses (eg, RSV, parainfluenza, influenza, metapneumovirus, rhinovirus) HSV ARDS caused by sepsis	Pulmonary edema Pleural effusion Engraftment syndrome Diffuse alveolar hemorrhage Transfusion-related lung injury Idiopathic pneumonia syndrome Chemotherapy-induced lung injury Radiation-induced lung injury
Early postengraftment (days 31–100)	Impaired cellular and humoral immunity Delayed lung injury from the conditioning or preparative regimen	Gram-positive bacterial infections Respiratory viruses (eg, RSV, parainfluenza, influenza, metapneumovirus, rhinovirus) Other viral infections (CMV, adenovirus, HSV) Fungal infections (aspergillosis, PJP) Parasitic infections (*Toxoplasma gondii*)	Diffuse alveolar hemorrhage Idiopathic pneumonia syndrome Radiation-induced lung injury Chemotherapy-induced lung injury
Late postengraftment (>100 days)	Delayed immune recovery Immunosuppression Chronic GVHD	Viral infections (CMV, adenovirus, varicella zoster reactivation Fungal infections (aspergillosis, PJP Respiratory viruses (eg, RSV, parainfluenza, influenza, metapneumovirus, rhinovirus) Encapsulated bacteria (chronic GVHD) ARDS caused by infection EBV	Bronchiolitis obliterans syndrome due to chronic GVHD Bronchiolitis obliterans organizing pneumonia Chemotherapy-induced chronic lung injury Radiation-induced chronic lung injury

ARDS, acute respiratory distress syndrome; CMV, cytomegalovirus; EBV, Epstein-Barr virus; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; HSV, herpes simplex virus; PJP, *Pneumocystis jiroveci* pneumonia; PTLD, posttransplantation lymphoproliferative disorder; RSV, respiratory syncytial virus.

cough, and fever with associated diffuse pulmonary infiltrates. The exclusion of competing diagnosis such as infection, cardiac disease, and renal failure, along with documentation of diffuse infiltrates, are supportive findings. Diffuse pulmonary edema may develop as a result of increased hydrostatic capillary pressure or permeability pulmonary edema and is one of the most common early complications of HSCT. Hydrostatic and permeability causes of HSCT may coexist and overlap with other early-onset pulmonary complications, which confounds diagnosis. The diagnosis is supported by diffuse bilateral pulmonary infiltrates, with or without bilateral pleural effusions, and coupled with the absence of competing diagnoses, such as infection on diagnostic evaluation. DAH may occur as a result of widespread alveolar injury in association with PERDS, DAD, or IPS or as a separate syndrome. Bronchoscopic findings of DAH include sequential aliquots of progressively bloody BAL fluid. Cytologic evidence of greater than 20% hemosiderin-laden macrophages on BAL fluid is also supportive. Hemoptysis only occurs in approximately 20% to 25% of patients with DAH. DAH may develop independent of thrombocytopenia or coagulopathy. Supportive therapy is standard. The benefits of steroid therapy have not been definitively proven. PERDS may develop after both allo- and autologous transplants and is characterized by fever, hypoxemia, noncardiogenic pulmonary edema, erythematous skin rash, and weight gain arising during the peri-engraftment period. DAH complicates

TABLE 63–6 Early-Onset (<100 Days) Pulmonary Complications After Hematopoietic Stem Cell Transplantation

Parameter	Diffuse Alveolar Hemorrhage	Peri-engraftment Respiratory Distress Syndrome	Idiopathic Pneumonia Syndrome	Pulmonary Veno-occlusive Disease
ncidence	1%–21%	12%–60%	1%–5%	Rare case reports
Transplant type	Autologous = allogeneic	Autologous > allogenic	Allogeneic > autologous	Allogeneic > autologous
Onset	Acute, 1–3 month after HSCT	Acute, within 5–7 days of neutrophil engraftment	1–3 months after HSCT	2–6 months after HSCT
Risk factors				
Clinical symptoms and signs	Cough, progressive dyspnea Hemoptysis: rare (<25%) Progressively bloody lavage fluid on BAL	Fever, dyspnea, dry cough, skin rash, weight gain, edema	Fever, cough dyspnea, hypoxemia	Progressive dyspnea
Histopathologic pattern	≥20% hemosiderin-laden macrophages in BAL fluid	Neutrophilic inflammation on BAL fluid Diffuse alveolar damage (biopsy contraindicated caused by low platelets)	Diffuse alveolar damage	Fibrous intimal proliferation of pulmonary venules; may also involve arterioles
Radiographic findings	Diffuse infiltrates; may be central early on	Bilateral infiltrates; pleural effusions; findings range from mild NCPE to ARDS	Bilateral interstitial infiltrates	Cardiomegaly, enlarged pulmonary arteries on chest radiography or CT
Treatment	Supportive; response to steroids variable	Excellent response to steroids	Supportive; poor response to steroids	Supportive; no benefit from steroids
Prognosis	Less favorable prognosis when advanced; may progress to multiorgan system failure, sepsis, and death	Favorable	Poor	Poor

ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; CT, computed tomography; HSCT, hematopoietic stem cell transplant; IPS, idiopathic pneumonia syndrome; NCPE, noncardiogenic pulmonary edema.

PERDS in approximately one third of patients.[124—126] Growth factor administration, infusion of increased numbers of CD34-positive cells, prolonged neutropenia, and peripheral blood source of stem cells all confer an increased risk of PERDS. Reductions in morbidity and mortality have been noted after steroid therapy in several small studies.[127,128]

Another early-onset diffuse lung disease, IPS, typically develops 14 to 90 days after transplant. The presence of GVHD, CMV seropositivity, older age, total-body radiation, transplant type, human leukocyte antigen (HLA) disparity, and transplantation for malignancy other than leukemia, are possible risk factors.[129,130] High-dose steroids, broad-spectrum antibiotics, and supportive care are the mainstays of treatment. Mortality rates may exceed 50% at 5 years despite aggressive therapy.

PVOD is a rare complication of HSCT that results in intractable dyspnea associated with severe PH. Symptoms of dyspnea and fatigue develop insidiously several weeks to months after HSCT. Treatment options are limited, with the 2-year mortality rate approaching 100%. DPTS occurs in 29% to 64% of autologous transplant recipients who received BCNU-, cyclophosphamide-, or cisplatin-based pretransplant conditioning regimens.

TABLE 63–7 Late-Onset (>100 Days) Pulmonary Complications After Hematopoietic Stem Cell Transplantation

Parameter	Bronchiolitis Obliterans Syndrome	Cryptogenic Organizing Pneumonia
Incidence (%)	2–30	2
Transplant type	Allogeneic	Allogeneic and autologous
Onset	Late, 4–24 months after HSCT; usually around 1 year	2– 2 months post-HSCT; usually within first 100 days
Risk factors	GVHD	
Clinical symptoms and signs	Cough, progressive dyspnea, wheezing Obstructive findings on PFTs; DLCO may be normal Diagnosis based on clinical, physiological, and radiographic criteria	Fever, dyspnea, dry cough, skin rash, weight gain, edema Restrictive findings on PFTs; DLCO reduced Usually requires surgical lung biopsy for diagnosis
Histopathologic pattern	BO; cellular and constrictive bronchiolitis Neutrophil-predominant BAL fluid	OP; intraluminal organizing fibrosis in distal airspaces; mild interstitial inflammation Lymphocyte-predominant BAL fluid
Radiographic findings	Hyperinflation on chest radiography; otherwise routinely normal; CT findings include mosaic attenuation (early) and air trapping, bronchiectasis (late)	Bilateral, patchy airspace disease with ground-glass appearance; may be nodular
Treatment	Supportive; immunosuppressive therapy; variable response to steroids; poor response to therapy and progressive disease with respiratory failure may occur	Steroid-responsive disease
Prognosis	Less favorable with advanced disease	Favorable; potentially reversible disease

BO, bronchiolitis obliterans; BOS, bronchiolitis obliterans syndrome; BAL, bronchoalveolar lavage; COP, cryptogenic organizing pneumonia; CT, computed tomography; DLCO, diffusing capacity of the lungs for carbon monoxide; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplant; OP, organizing pneumonia; PFT, pulmonary function test.

This syndrome is heralded by dry cough, dyspnea, and bilateral pulmonary infiltrates, which typically occur 45 days after HSCT. Corticosteroid therapy leads to complete resolution of symptoms in 92% of patients.[131]

Late-Onset Noninfectious Complications

Chronic GVHD, an immunologic posttransplant disorder in which donor cells attack healthy host tissue, is the most common late complication of allogeneic HSCT.[132—134] Involvement of GVHD in the lung results in BOS, a nonspecific lung injury causing inflammation, smooth muscle hypertrophy, and concentric intraluminal fibrosis of the small airways. The clinical hallmark of BOS is airflow limitation (Table 63–8).[132—134] Patients are often asymptomatic during the early stages of BOS, leading to delays in diagnosis. At presentation during late stages of the disease, wheezing, dry cough, and dyspnea on exertion predominate as airflow obstruction progresses. Recurrent sinusitis and antecedent "cold" symptoms are common before diagnosis. Hyperinflation may be seen on plain chest radiographs, which are otherwise normal.[130,135] The lack of a precise definition and uniform diagnostic criteria along with a paucity of knowledge regarding the pathogenesis of BOS and delays in diagnosis represent distinct challenges in management. The National Institutes of Health recently provided consensus guidelines in the diagnosis of BOS, which require (1) evidence of airflow obstruction (FEV_1/FVC [forced vital capacity] <0.7 and FEV_1 <75% of predicted), with evidence of air trapping on PFT; (2) increased residual volume (>120% predicted); (3) air trapping, small airway thickening, or bronchiectasis on expiratory CT or lung biopsy or pathological confirmation of constrictive bronchiolitis; and (4) absence of any infectious process on radiographic, laboratory, or clinical testing.[136] The prognosis of BOS poor, with 5-year survival estimates of only 13%. Immunosuppressive therapy with corticosteroids and calcineurin inhibitors comprises the mainstay of treatment (Table 63–9). Recent studies have demonstrated stabilization of FEV_1 with high-dose inhaled corticosteroids. Small clinical trials and observational studies have suggested a beneficial impact of other agents, including azithromycin, montelukast, azathioprine, sirolimus, and antithymocyte globulin, on lung function.[15,137,138] Early disease recognition is crucial to improvements in therapy and survival.

COP, also known as idiopathic BOOP, is seen almost exclusively among allogeneic HSCT recipients with GVHD. Presenting symptoms include dry cough, dyspnea, and fever, accompanied by a restrictive defect on PFTs and bilateral patchy infiltrates on chest imaging studies. COP is typically steroid responsive, although

TABLE 63–8 Suggested Diagnostic Criteria of Bronchiolitis Obliterans After Hematopoietic Stem Cell Transplantation

1	Allogeneic HSCT
2	Chronic GVHD
3	Insidious onset of dyspnea, cough, and wheezing, usually 100 days after transplantation
4	Normal chest radiograph
5	HRCT of the chest (with inspiratory and expiratory views) showing areas of air trapping on expiratory views (mosaic pattern), hyperinflation, micronodular changes or bronchial dilatation, with no parenchymal involvement
6	PFT showing new onset of airflow obstruction ($FEV_1/FVC < 0.7$ and FEV_1 < 75% of predicted), not responsive to bronchodilators
7	Exclusion of an infectious process by appropriate radiologic, serologic, and microbiologic studies (obtained by sinus aspirate, upper respiratory tract viral screen, sputum culture, or BAL)

BO, bronchiolitis obliterans; BAL, bronchoalveolar lavage; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GVHD, graft-versus-host disease; HRCT, high resolution computed tomography; HSCT, hematopoietic stem cell transplant; PFT, pulmonary function test.

TABLE 63–9 Suggested Approach to the Management of Bronchiolitis Obliterans After Hematopoietic Stem Cell Transplantation

1	Confirm the diagnosis of bronchiolitis obliterans (see Table 63–8)
2	Systemic corticosteroids (prednisone 1–1.5 mg/kg/day); taper gradually over 6–12 months
3	Immunosuppressive therapy (eg, cyclosporine A or tacrolimus)
4	Maintenance macrolide treatment
5	Inhaled bronchodilators
6	Prophylactic therapy against PJP, fungi, and CMV
7	Antireflux measures
8	Consider inhaled corticosteroids
9	Consider extracorporeal photodynamic therapy
10	Consider IVIGs
11	In advanced cases: • Long-term oxygen therapy • Outpatient pulmonary rehabilitation • Consider lung transplantation

BO, bronchiolitis obliterans; CMV, cytomegalovirus; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplant; IVIG, intravenous immunoglobulin; PJP, *Pneumocystis jirovecii pneumonia.*

no evidence-based guidelines regarding dosage and duration of corticosteroid therapy are currently available. Normalization of chest radiographs and PFTs may be seen within 1 to 3 months of therapy.[134,139—142]

PTLD is a well-recognized complication of both solid organ transplantation and allogeneic HSCT. The disease is characterized by uncontrolled B-cell proliferation of donor-derived, Epstein-Barr virus–infected lymphocytes. Major risk factors include the use of T-cell–depleted donor stem cells, unrelated or HLA-mismatched related donor cells, and antithymocyte globulin predisposes to the development of PTLD. PTLD complicates approximately 1% of allogeneic HSCTs but may increase to 22% in patients with two or more risk factors. The lymph nodes, liver, spleen, and lungs are the primary targets of PTLD. Dyspnea and fever typically develop 4 to 12 months after transplant, accompanied by interstitial and intraalveolar infiltrates and ill-defined nodules. Reduction of immunosuppressive agents and administration of anti-CD20 (rituximab) therapy represent primary therapy.[133,143] The prognosis is generally poor.

VASCULAR DISEASE

VTE is a well-recognized complication of cancer and its therapy. The manifestations of VTE, PE, and DVT are seen in 20% of patients with cancer. Cancer is associated with a four- to sevenfold increased risk of VTE compared with patients without cancer.[144,145] Evidence suggests that tumor type and stage as well as specific cancer therapies influence the absolute risk of thromboembolism. Hematologic malignancies, followed by lung and GI cancer, have the highest absolute risk, especially in the first few months of diagnosis. Furthermore, surgery, immobility, hormonal therapy, growth factors, angiogenesis inhibitors, erythropoietic agents, corticosteroids, and central venous catheters all impact the overall likelihood of thrombotic complications.[146—148] Rates of VTE as high as 28% to 43% have been reported in patients treated with combination antiangiogenic therapies, such as thalidomide and steroids or certain cancer chemotherapies (doxorubicin or BCNU). Many patients, especially those with hematologic malignancies, may have thrombocytopenia in the setting of VTE. In a study evaluating risk factors for VTE in acute leukemia, thrombocytopenia and a cancer diagnosis within 12 months, central venous catheters, hematopoietic growth factors, high-dose corticosteroids, L-asparaginase, and the new immunomodulatory agents were all associated with increased risk of VTE.[149] Unprovoked VTE may herald an impending diagnosis of cancer in patients without known malignancy, primarily in the subsequent 2 years. D-dimer assays and scoring systems developed to estimate the

pretest probability of VTE are neither sufficiently specific nor sensitive enough to rule out VTE in patients with cancer.[148,150] CT pulmonary angiography is the standard imaging technique for diagnosing PE and permits evaluation of competing diagnoses.

Treatment options for PE are based on risk stratification, and the tiers include low-risk PE, intermediate-risk or submassive PE, and high-risk or massive PE.[151] Low-risk PE or those found incidentally on staging scans are treated with anticoagulation. In patients that are hemodynamically unstable, echocardiogram and cardiac biomarkers (B-type natriuretic peptide [BNP], N-terminal pro-BNP [NT-proBNP], troponin I or T) are used to classify massive PE. Significant echocardiographic findings may include right ventricular dilatation, right ventricular hypokinesis, tricuspid regurgitation, septal flattening, paradoxical septal wall motion, PH, and lack of inspiratory collapse of the inferior vena cava.[152] Full-dose thrombolysis may be indicated in massive PE, and other interventions, including surgical embolectomy, inotropic and vasopressor support, pulmonary vasodilator therapy, or mechanical circulatory support devices, may be indicated. For submassive PE, several large evidence-based trials, including Pulmonary Embolism International Thrombolysis Study (PEITHO), no longer support thrombolysis. Catheter-directed thrombolysis and half-dose thrombolysis are still under investigation.[153,154] In all cases, contraindications to anticoagulant therapy should be weighed against the potential benefits of treatment.

Abundant studies have demonstrated superior efficacy and safety of low-molecular-weight heparin (LMWH) over conventional vitamin K antagonists in the management of cancer-related VTE. These studies suggest a lower risk of recurrent VTE without an associated increased risk of major bleeding complications compared with vitamin K antagonists and support LMWH as first-line treatment of patients with cancer-associated thrombosis. Recent trials in patients with cancer have established noninferiority of direct oral anticoagulant therapy (edoxaban, rivaroxaban, apixaban) in patients with cancer with LMWH, but increased bleeding risk was reported with edoxaban and rivaroxaban.[155—158] In those with thrombocytopenia, current guidelines recommend a reduction in LMWH by 50% with a platelet count of 25,000 to 50,000/μL and discontinuation for a platelet count less than 25,000/μL.[152,159—163]

Guidelines for VTE prophylaxis and treatment in the cancer setting have been established. LMWH is the preferred agent based on superior efficacy and safety data. In patients with impaired renal function, unfractionated heparin or fondaparinux should be considered. Recommendations include a 7- to 10-day course of LMWH for patients with cancer undergoing surgery, which should be started preoperatively. Among patients at high risk for VTE, 4 weeks of LWMH is recommended. Thromboprophylaxis is not warranted in the routine management of ambulatory cancer patients. This recommendation is based on analysis of the known risk of bleeding among patients with cancer and potential benefits of anticoagulant therapy in this setting. However, when patients are hospitalized, VTE prophylaxis should be considered. Conversely, prophylactic LMWH is recommended for ambulatory patients with multiple myeloma who are receiving thalidomide- or lenalidomide-based combination therapy. Prophylactic anticoagulation to prevent catheter-associated thrombosis is not recommended. After being established, full anticoagulant therapy should be initiated.

A variety of conditions in the cancer setting may be associated with PH, defined as an elevated mean pulmonary artery pressure of 25 mm Hg or greater at rest. These conditions are represented in all five categories of the revised 2019 World Health Organization (WHO) classification scheme for PH (Table 63–10). For example, chemotherapeutic agents, such as dasatinib and PVOD caused by chemotoxins, thoracic radiation, and stem cell transplantation are known causes of PAH (group 1). Cancer treatment–related left heart disease is a common cause of PH (group 2). Hypoxemic pleuroparenchymal diseases caused by tumor infiltration, infection, and chemotoxicity are well known sources of group 3 PH. Increased rates of acute and chronic PE as well as splenectomy in the cancer setting are associated with chronic thromboembolic PH (group 4). Finally, myeloproliferative disorders and entrapment or compression of large pulmonary vessels by infection and treatment-related mediastinal fibrosis, adenopathy, or neoplasms are recognized risk factors of group 5 PH.[164—171] PH is known to be associated with advanced myelofibrosis, albeit rarely. The cause of PH in this clinical scenario is unknown but is thought to be secondary to the inefficient extramedullary hematopoiesis that occurs as a result of bone marrow fibrosis. Other proposed contributors include porto-PH secondary to organomegaly, pulmonary vascular congestion and obstruction, tumor microemboli, parenchymal lung disease, acute or chronic thromboemboli, and chemotherapeutic agents. In addition, many patients with myelofibrosis-related PH have been found to have elevated filling pressures on echocardiogram, suggesting that in addition to PAH (WHO group 1) and PH related to multiple mechanisms (WHO group 5), left-sided heart disease (WHO group 2) may be the culprit in many of these patients.[172,173] Regardless of the cause, the development of significant PH in cancer portends

a worse prognosis. Dyspnea, nonproductive cough, and hypoxemia develop insidiously in cancer-related PH and may progress to respiratory failure and death. There have been rare case reports of resolution of myelofibrosis-associated PH after HSCT; therefore, this treatment may provide benefits for select patients outside of its anticipated hematologic effects.[172] In most cases, supportive care and treatment of the underlying disease are the mainstays of therapy. The utility of pulmonary vasodilator agents, including treatment strategies that target nitric oxide, endothelin, and prostaglandin pathways, in the management of cancer-related PH has not been definitively studied. Vasodilator therapy in the setting of cancer-related PVOD should be used with extreme caution because fatal pulmonary edema precipitated by vasodilator therapy in this setting has been reported.[164–167]

TABLE 63–10 2019 World Health Organization Classification Scheme for Pulmonary Hypertension

Class	Subclass
1. PAH	1.1 Idiopathic PAH 1. 2 Heritable PAH 1. 3 Drug and toxin induced 1. 4 Associated with 1.4.1 Connective tissue disease 1. 4.2 HIV infection 1. 4.3 Portal hypertension 1. 4.4 Congenital heart diseases 1. 4.5 Schistosomiasis 1′ PVOD and/or pulmonary capillary hemangiomatosis 1″ Persistent pulmonary hypertension of the newborn
2. PH caused by left heart disease	2.1 LV systolic dysfunction 2. 2 LV diastolic dysfunction 2. 3 Valvular heart disease 2. 4 Congenital or acquired left heart inflow or outflow tract obstruction and congenital cardiomyopathies
3. PH caused by lung disease or hypoxia	3.1 COPD 3. 2 Interstitial lung disease 3. 3 Other pulmonary disease with mixed restrictive and obstructive pattern 3. 4. Sleep-disordered breathing 3. 5 Alveolar hypoventilation disorders 3. 6 Chronic exposure to high altitude 3. 7 Developmental lung diseases
4. CTEPH	
5. PH with unclear or multifactorial etiologies	5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy 5. 2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangiomyomatosis 5. 3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders 5. 4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure

COPD, chronic obstructive pulmonary disease; CTEPH, chronic thromboembolic pulmonary hypertension; HIV, human immunodeficiency virus; LV, left ventricular; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease.

MALIGNANT CENTRAL AIRFLOW OBSTRUCTION

Malignant central airway obstruction (MCAO) refers to obstruction at the level of the trachea, mainstem bronchi, or bronchus intermedius. Cough, stridor, wheezing, dyspnea, atelectasis, and recurrent or persistent postobstructive pneumonia are common presenting symptoms. Hemoptysis, which can be massive and life threatening, may also occur. Stridor signals a proximal obstruction at the level of the trachea or larynx, whereas focal wheezing is typically secondary to obstruction distal to the main carina. Tracheal stenosis resulting in airway narrowing of 50% or greater is associated with a 16-fold increase in airflow resistance. Thus, obstructive symptoms typically develop with airway occlusions of 50% or more.[174] Tracheal diameters of 8 mm are associated with dyspnea on exertion, whereas resting dyspnea typically does not develop until tracheal diameters are 5 mm or less. Confounding factors such as chronic obstructive pulmonary disease, mucosal edema, and increased airway secretions may precipitate inexorable dyspnea even in patients with only moderate tumor-related airflow limitation. Patient presentation is influenced by underlying conditions as well as obstruction-related factors such as location and degree of obstruction and rate of development. Compromised airway caliber may be secondary to endoluminal tumor, extrinsic compression, or direct extension of tumor through the airway wall (mixed obstruction). Optimization of therapy is predicated on the location and extent of airway disease and quantification of airflow limitation. Except for rare findings of tracheal deviation on plain films, chest radiographs are of very limited value in defining the anatomic extent of airway tumors. Blunting of the flow–volume loop on PFT is an insensitive signal of upper airway obstruction and typically only occurs once the tracheal caliber is reduced to less than 10 mm (Fig. 63–8).[175] The use of spirometry in patients with severe airway obstruction is not recommended because it may precipitate frank respiratory failure.

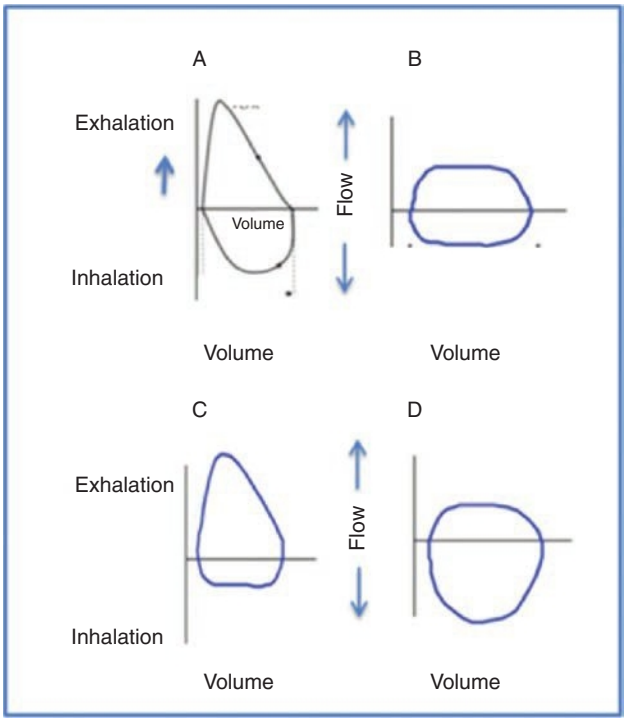


FIGURE 63–8 **Flow–volume loops characteristic of various patterns of upper airway obstruction. A. Normal flow–volume loop. B. Flattening of both the inspiratory and expiratory limbs of the flow–volume loop, consistent with fixed upper airway obstruction. C. Flattening of the inspiratory limb, consistent with dynamic extrathoracic obstruction. D. Flattening of the expiratory limb, consistent with dynamic intrathoracic obstruction.**

Bronchoscopic examination is central to the diagnosis and treatment of MCAO. Characterization and histologic confirmation of the tumor as well as determination of the extent of obstruction attributable to endoluminal or extraluminal disease are important findings that help to guide treatment decisions. Therapeutic strategies for predominantly endoluminal disease include surgical resection and mechanical debulking using the rigid bronchoscope and associated instruments. Endobronchial argon plasma coagulation, laser therapy, electrocautery, microdebrider, and cryotherapy are therapeutic options for predominantly endobronchial disease and provide rapid relief of obstruction when performed during rigid bronchoscopy. Brachytherapy and photodynamic therapy are additional options for treatment of endobronchial disease but typically have a delayed effect. Balloon bronchoplasty, endobronchial stent placement, and RT are reasonable treatment options for patients with predominantly extraluminal disease. A multimodality approach that includes endobronchial tumor debulking and stent placement is common because many patients present with mixed endo- and extraluminal disease (Fig. 63–9). Treatment options are based on the type of obstruction (Figure 63–10).

PLEURAL DISEASES IN THE CANCER SETTING

Nearly 50% of all patients with cancer develop pleural effusions. These may be malignant (MPE), which occur in up to 15% of all patients with cancer, or paramalignant.[176] The later results from direct or indirect effects of tumor on the pleural space and includes causes such as bronchial obstruction, infiltration of mediastinal lymph nodes, superior vena cava syndrome, trapped lung, PE, and atelectasis. Paramalignant effusions occur on the involved hemithorax and are typically small to moderate in size with negative pleural fluid cytology results. MPEs rank second as the leading cause of exudative effusions after parapneumonic effusions. MPEs may be quite large, and in contrast to parapneumonic effusions, pleural fluid cytology results are positive in more than 60% of patients.[177] Malignant pleural involvement may also occur in the absence of pleural fluid in patients with either primary pleural tumors or metastatic disease to the pleura.[178,179]

Fifty percent of all cancer-related pleural effusions are caused by lung cancer. Breast carcinoma and effusions caused by hematologic malignancies, including lymphoma and leukemias, are also common causes. Progressive dyspnea and dry cough are presenting symptoms in most patients and may be accompanied by constitutional symptoms of malaise, anorexia, and weight loss with advanced disease. Preprocedure imaging is an important component of the diagnostic workup and treatment planning. Standard chest radiographs and bilateral decubitus films provide critical information regarding effusion size, position of the mediastinum and diaphragms, presence of fluid loculations, and characteristics of the underlying lung parenchyma. Patients with large pleural effusions and associated contralateral shift of the mediastinum should undergo prompt therapeutic thoracentesis. A centered or ipsilateral shift of the mediastinum with associated pleural effusion may signify frozen mediastinum, tumor encasement of the ipsilateral mainstem bronchus, or extensive parenchymal involvement due to lymphangitic spread of tumor, infection, or other infiltrative lung diseases. Any of these diagnoses may cause ipsilateral opacification of the lung and mimic a large pleural effusion (Fig. 63–11). Pleural effusions in this setting should therefore be approached with caution.[180]

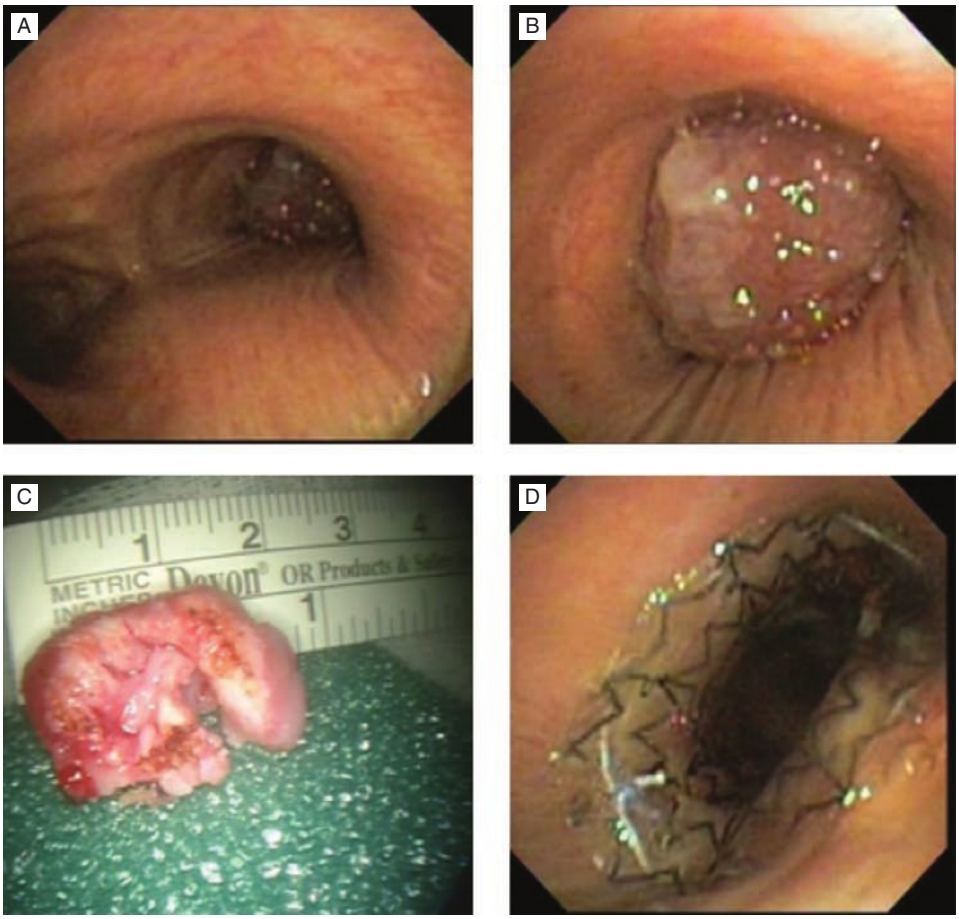


FIGURE 63–9 **A to D. Bronchoscopic images showing complete obstruction of the right mainstem bronchus secondary to an endobronchial tumor (A, B). The large endobronchial tumor was excised tumor using electrocautery (C). This obstruction was managed with a multimodality approach using electrocautery snare followed by endobronchial stent placement (D).**

Ultrasonography is easy to learn and interpret and provides guidance in locating the optimal site for pleural procedures. Pleural ultrasonography also provides valuable information regarding pleural fluid characteristics, including the presence of loculations, fibrin strands, and pleural metastases. CT provides valuable anatomic information of the visceral and parietal pleura, chest wall, lung parenchyma, and mediastinal structures and is particularly useful in characterizing the pleural fluid

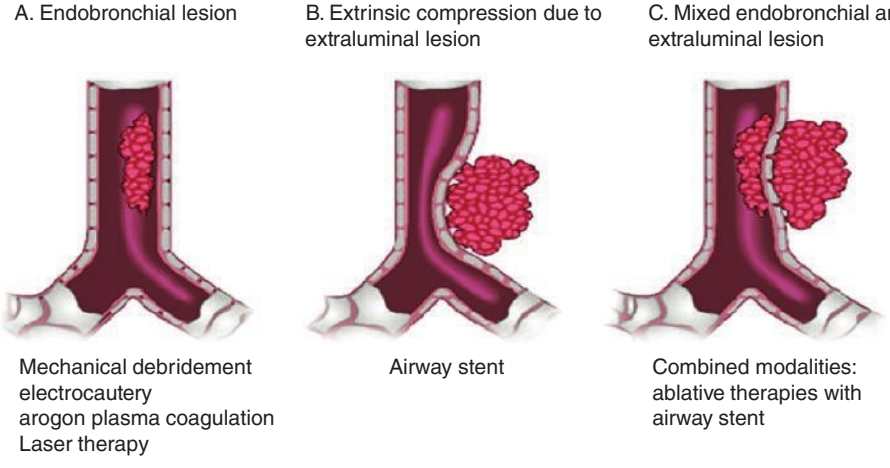


FIGURE 63–10 **Characterization of malignant central airflow obstruction and potential bronchoscopic treatment modalities**

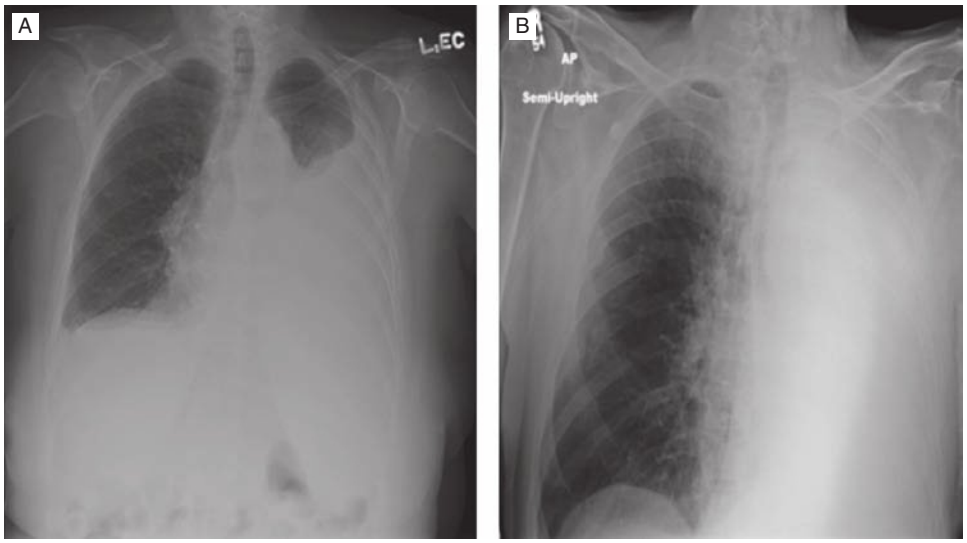


FIGURE 63–11 **A. Chest radiograph with a large left pleural effusion causing compression of the left lung and contralateral shift of the mediastinum. B. Chest radiograph with a large left pleural effusion with ipsilateral shift of the mediastinum in a patient with a central airway obstruction and a nonexpandable lung.**

and identifying competing diagnoses.[181] Findings on positron emission tomography (PET)–CT and conventional CT imaging, such as irregular, thickened, or nodular pleural surfaces, suggest malignancy (Fig. 63–12). Pleural enhancement with IV contrast material is also suggestive of malignancy, although pleural inflammation may be associated with similar findings. Recent studies have shown PET imaging with 18-fluorodeoxyglucose to be useful in delineating pleural tumors and extrapleural extension of disease in patients with malignant pleural mesothelioma (MPM). Magnetic resonance imaging of the pleural space is also valuable in displaying pleural tumors. This imaging strategy provides excellent soft tissue contrast and delineation of extrapleural invasion of the chest wall, spine, nerves, and mediastinal vascular structures.[181] This information is complementary to chest CT imaging and markedly enhances surgical planning for patients with MPM.

Nearly all MPEs are categorized as exudates using Light's criteria.[182] The cytologic or histologic confirmation of malignant cells on pleural fluid or biopsy is key to diagnosis, although pleural cytology results are only positive in 62% of patients.[177] The sensitivity of pleural fluid cytology varies considerably depending on the underlying malignancy with mesothelioma and hematologic malignancies having significantly lower diagnostic yield than adenocarcinomas.[183] Regarding solid tumors, whereas sarcomas, head and neck cancers, and renal cell carcinomas have the lowest sensitivity, the diagnostic yield of pleural fluid cytology from breast, pancreatic, ovarian, and lung cancers is much higher.[183,184] Flow cytometry with identification of tumor markers may improve the diagnostic yield of cytologically negative effusions by 33%. This diagnostic strategy has proved particularly useful when pleural effusions associated with lymphoma, leukemia, or multiple myeloma are suspected.[185,186] A definitive diagnosis is yielded after closed pleural biopsy in only 44% of patients but increases to 77% with the addition of pleural fluid cytology.[177] More recent advances in pleuroscopic and image-guided biopsy techniques have improved the diagnostic yield compared with traditional closed need biopsy in the diagnosis of pleural malignancy. For example, pleuroscopy and CT-guided pleural biopsies exhibit a 95% and 87% sensitivity in the diagnosis of pleural malignancies, respectively. The addition of pleural fluid cytology to pleuroscopy offers only a marginal increase in the diagnostic yield.[185,186]

With few exceptions, the presence of MPE portends a poor prognosis with mean survival measured in months. Treatment is therefore focused on palliation. Factors such as associated symptoms, performance status, volume of fluid evacuated, whether symptom palliation and lung reexpansion were achieved with prior thoracenteses, time course for recurrence, and expected tumor response to systemic therapy should be considered in management options (Fig. 63–13). Among patients with newly diagnosed chemo- or radiosensitive tumors (lymphoma, breast cancer, small cell lung cancer, prostate cancer, thyroid cancer, germ cell cancer), simple thoracentesis while awaiting response to definitive therapy is reasonable. Most MPEs recur within 30 days of the

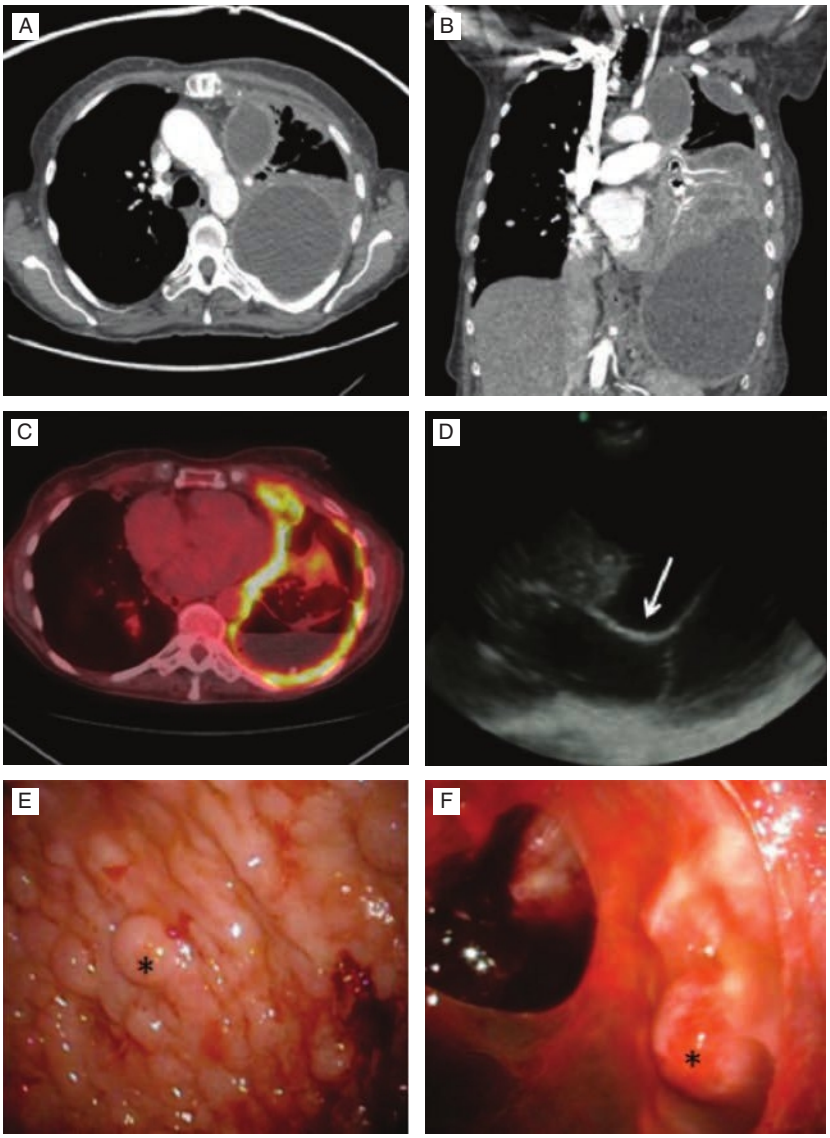


FIGURE 63–12 **Multiloculated pleural effusion on axial (A) and coronal (B) computed tomography (CT) views. C. Classic positron emission tomography–CT appearance in a patient with pleural mesothelioma. D. Corresponding ultrasound image showing loculated pleural fluid. Mesothelioma pleural deposits (E) and significant pleural adhesions (F) visualized during pleuroscopy in a patient with mesothelioma.**

prior thoracentesis. Repeated thoracentesis is also recommended in patients with slowly reaccumulating pleural effusions and a short life expectancy (1–3 months). Poor performance status is predictive of limited survival among patients with recurrent MPEs.[187] Evacuation of pleural fluid is ideally ultrasound guided, which is associated with lower rates of pneumothorax.[188] In recently published guidelines for the management of MPEs, the British Thoracic Society endorses symptom-limited pleural fluid evacuation not to exceed 1.5 L of fluid in one sitting.[189] In our experience, symptom-limited evacuation of up to 2.0 to 2.5 L of pleural fluid in one sitting is safe among patients with contralateral mediastinal shift secondary to a large pleural effusion. Chest pain, cough, and dyspnea are limiting symptoms that should prompt discontinuation of the procedure. Cautious evacuation of large volumes of pleural fluid is recommended in patients with centered or ipsilateral shift of the mediastinum. Pleural pressure measurements during thoracentesis have not been shown to be superior to symptom-limited pleural drainage in reducing the risk of procedure-related complications.[190]

Indwelling pleural catheter (IPC) placement is an increasingly viable palliative option for patients with recurrent MPEs. Patients whose life expectancy exceeds 30 days and those in whom symptomatic

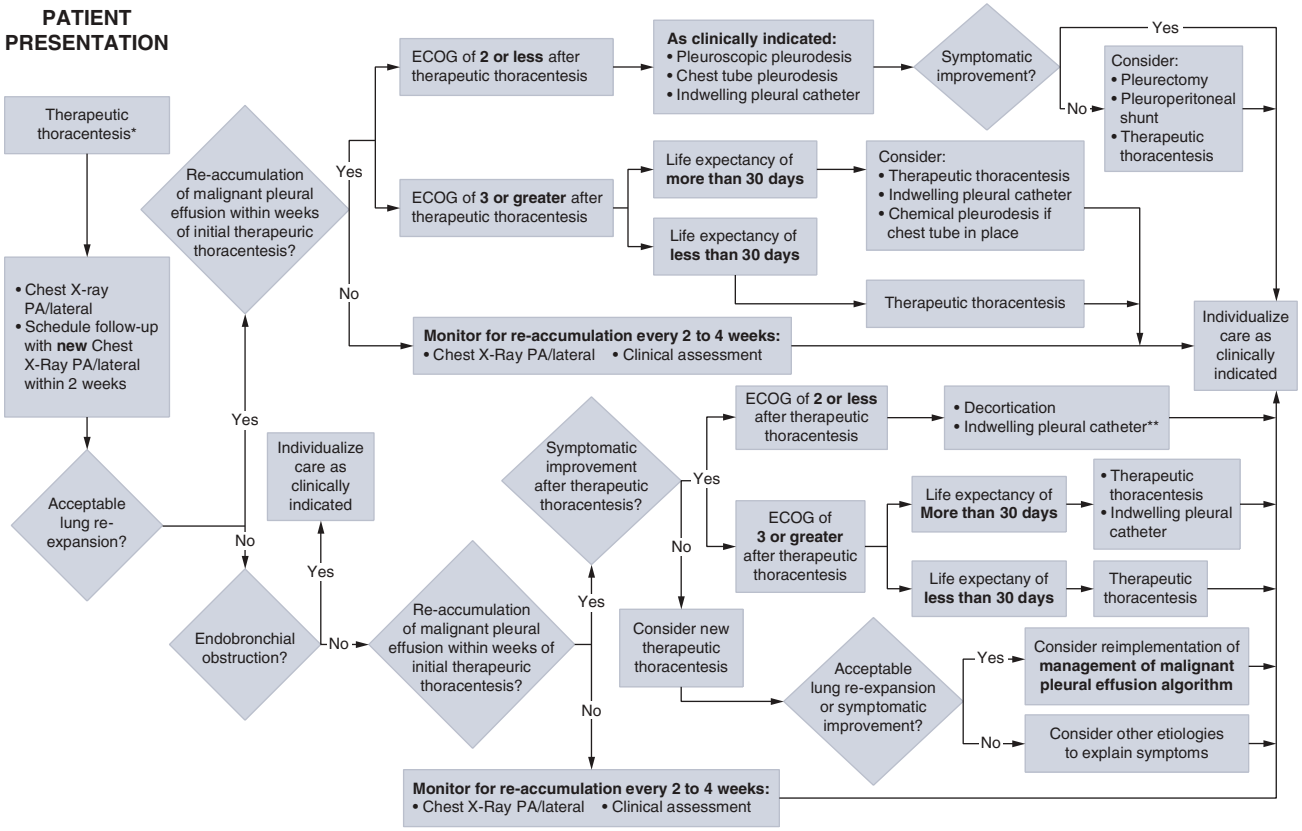


FIGURE 63–13 **Algorithm for the management of malignant pleural effusions. ECOG, Eastern Cooperative Oncology Group; PS, performance status.**

improvement was achieved on prior thoracenteses are ideal candidates for IPC placement. Lung reexpansion after thoracentesis is not a requirement for IPC use because they are also a feasible treatment option for patients with symptomatic trapped lung.[191] Most catheters are placed in the outpatient setting. Designated family members and caretakers are then trained on the proper use of the catheter. Daily home drainage is recommended initially followed by drainage every other day as pleural fluid volume decreases. In our experience, 94% of patients reported symptom relief, and in 52%, effective pleurodesis with subsequent removal of the catheter was achieved. The average time from catheter insertion to removal was 32 days (Fig. 63–14). Empyema and persistent pain at the insertion site were rare complications of IPC placement in our review. Recurrent effusion has also been rarely described in a small group of patients after catheter removal.[192]

Chemical pleurodesis using asbestos-free talc is a widely used strategy in the management of patients with MPE. Several studies have shown talc to be superior to other sclerosants (bleomycin, tetracycline) in achieving pleurodesis.[193] Eligible patients for this procedure should have a good performance status (Eastern Cooperative Oncology Group score, 0–2) and report symptomatic relief and lung reexpansion after prior thoracentesis. Pleuroscopic talc poudrage and talc slurry instillation via small-bore chest tube are both viable methods of chemical pleurodesis with no significant difference in pleurodesis failure rates.[194] The use of an IPC plus talc slurry administration has been evaluated and is also a safe and effective option for the treatment of MPE in outpatients.[195]

The management of recurrent chylous effusions is a particular challenge because of the potential for severe lymphopenia, nutritional depletion, and water and electrolyte loss from prolonged loss of chyle. These effusions, when cancer related, require treatment of the underlying malignancy. Parenteral alimentation, talc pleurodesis, and IPC placement represent reasonable alternatives in the management of recalcitrant effusions.[196] Pleuroperitoneal shunt placement is an attractive treatment option that permits reabsorption of chyle in the peritoneum and mitigates the risk of malnourishment and immune suppression. However, the small-volume shunt removal and increased potential for pump obstruction limits the utility of this treatment

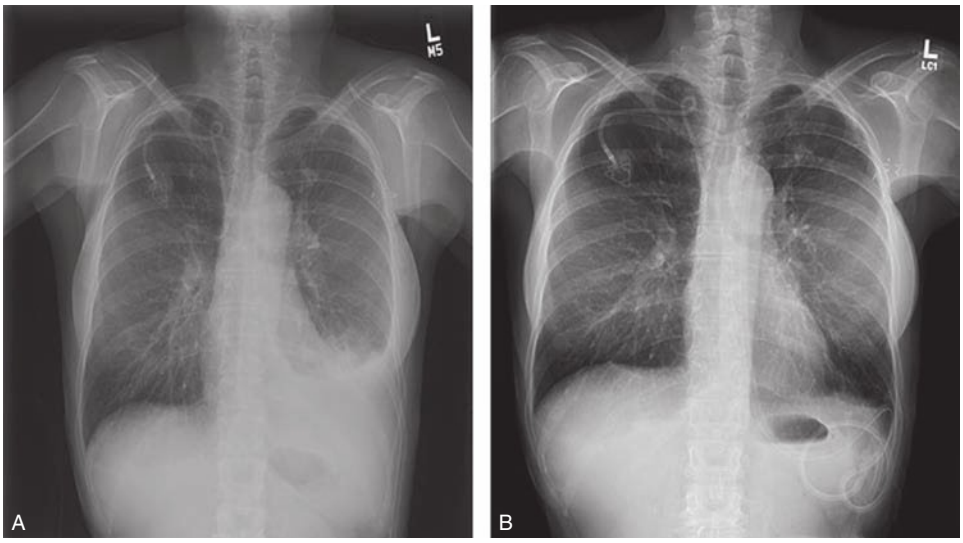


FIGURE 63–14 **A. Chest radiograph before indwelling pleural catheter (IPC) placement showing a left-sided pleural effusion. B. Chest radiograph after IPC placement with resolution of the pleural effusion.**

modality. Embolization of the thoracic duct has not been definitively studied but appears well tolerated.

SLEEP DISTURBANCES IN CANCER THERAPY

Nearly half of all patients with cancer develop sleep disturbances. Insomnia, poor sleep efficiency, early awakening, excessive daytime sleepiness, and restless legs may occur during all phases of cancer care and persist for many months to years after completion of cancer therapy. The biochemical changes inherent to cancer growth, anticancer therapies, and cancer-related symptoms of fatigue, pain, and depression may all adversely impact sleep quality.[197] Sleep disturbances, on the other hand, may have important implications in cancer incidence, treatment, prevention, and survivorship. For example, sleep duration appears to influence cancer risk. Excess cancer prevalence has been demonstrated among insomniacs with sleep times of less than 5 hours per night and patients undergoing 9 or more hours of sleep nightly.[198] In the American Nurses' Health Study, a relative increased risk of breast cancer was demonstrated among nurses working rotating shifts for many years.[199–201] In another study, cancer mortality increased by fivefold among patients with a protracted history of severe sleep apnea.[202] Elevations in inflammatory mediators, such as VEGF, induces disturbed sleep.[203] Sleep loss and, in particular REM (rapid eye movement) sleep deprivation, is hyperanalgesic. Thus, insomnia, which is common in the cancer setting, may confer an increased sensitivity to pain.[204] Sleep-disordered breathing may be increased in the cancer setting because of use of pain medications (eg, opioids) or with certain malignancies.[205] Higher rates of obstructive sleep apnea is seen among patients with head and neck cancers.[206]

Finally, sleep disruption, insomnia, and fatigue may persist after cancer therapy is completed. Cancer-related fatigue and sleep disorders appear to be closely linked, and their prevalence and association may vary greatly during the course of cancer care.[203,207—209] Cognitive behavioral therapy is the treatment of choice for insomnia and suboptimal sleep hygiene, which may improve quality of life and decrease sedative-hypnotic medication use.

SUMMARY

Lung injury associated with cancer therapy may manifest as a diverse spectrum of disorders affecting all components of the respiratory system, including the pulmonary parenchyma, vasculature, airways, and pleura. In addition, cancer and its treatment may profoundly impact sleep hygiene. These disorders contribute substantially to the morbidity and mortality of cancer therapy and may limit cancer care. Early recognition of key clinical, radiologic, and histopathologic features of lung injury and prompt initiation of therapy are key in the successful management of patients with these disorders.

MD ANDERSON PRACTICE TIPS

- Guidelines for the management of DILI caused by conventional chemotherapies and molecular targeted agents are limited and primarily based on expert opinion. Permanent drug withdrawal with or without the addition of systemic glucocorticoids is a frequent management strategy. Optimal dose, timing, and duration of glucocorticoids in the management of patients with DILI have not been elucidated in any prospective controlled trials. In general, 40 to 60 mg of prednisone or its equivalent or weight-based dosing at 0.75 to 1 mg/kg daily is recommended with a taper over a 1- to 3-month time period, depending on response to therapy. With only a few exceptions, drug rechallenge is not recommended.
- Treatment strategies for patients with ICI pneumonitis are guided by CTCAE pneumonitis grades but have yet to be validated in any prospective trials. Treatment ranges from cautious continuation of immunotherapy and monitoring of imaging and symptoms in asymptomatic patients with early (grade I or II) pneumonitis to permanent drug withdrawal, steroid administration, and other immunosuppressive therapies in patients with advanced (grade 3 and 4) disease.
- The use of antimicrobial prophylaxis has resulted in a significant decline in post-HSCT infectious pulmonary complications; however, noninfectious complications remain a major cause of post-HSCT morbidity and mortality. These heterogeneous lung complications are categorized as early (occurring within the first 100 days of HSCT) and late (occurring at day 100 after HSCT or later) events and are influenced by the rate of immune reconstitution and the development of posttransplant GVHD. Prognosis varies depending on the underlying condition.
- Chest radiography has a low sensitivity for diagnosing central airway obstruction (CAO). Therefore, chest CT should be obtained when CAO is suspected. Early referral to a pulmonary specialist is recommended in stable patients with suspected CAO. In unstable or symptomatic patients with advanced disease, emergent referral for further evaluation and airway management is imperative.
- Evaluation and management of pleural effusions is indicated in most patients with treatments tailored by associated symptoms, performance status, size of the effusion, and volume of fluid evacuated during initial drainage. Whether symptom palliation and lung reexpansion were achieved with prior thoracenteses, time course for recurrence, and expected tumor response to systemic therapy are other factors that influence treatment strategies. Optimal management typically involves detailed discussions with the patient by a multidisciplinary team.
- Screening for sleep disturbances in patients with cancer is important given the prevalence of sleep disorders in this patient population. Sleep disturbances may confer increased sensitivity to pain and are closely associated with cancer-related fatigue. As such, sleep hygiene may have important implications in cancer incidence, treatment, prevention, and survivorship.

REFERENCES

1. Camus P, Fanton A, Bonniaud P, et al. Interstitial lung disease induced by drugs and radiation. *Respiration*. 2004;71(4):301-326.
2. Camus P, Kudoh S, Ebina M. Interstitial lung disease associated with drug therapy. *Br J Cancer*. 2004;91(suppl 2):S18-S23.
3. Vahid B, PE. M. Infiltrative lung diseases: complications of novel antineoplastic agents in patients with hematological malignancies. *Can Respir J*. 2008 15(4):211-216.
4. Vahid B, Marik PE. Pulmonary complications of novel antineoplastic agents for solid tumors. *Chest*. 2008;133(2):528-538.
5. Takano T, Ohe Y, Kusumoto M, et al. Risk factors for interstitial lung disease and predictive factors for tumor response in patients with advanced non-small cell lung cancer treated with gefitinib. *Lung Cancer*. 2004;45(1):93-104.
6. Kudoh S, Kato H, Nishiwaki Y, et al. Interstitial lung disease in Japanese patients with lung cancer: a cohort and nested case-control study. *Am J Respir Crit Care Med*. 2008;177(12):1348-1357.
7. Spigel DR, Lin M, O'Neill V, Hainsworth JD. Final survival and safety results from a multicenter, open-label, phase 3b trial of erlotinib in patients with advanced nonsmall cell lung cancer. *Cancer*. 2008;112(12):2749-2755.
8. Jänne PA, Yang JC, Kim DW, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med*. 2015;372(18):1689-1699.
9. Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol*. 2014;15(2):213-222.
10. Wu YL, Cheng Y, Zhou X, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017;18(11):1454-1466.
11. Chua W, Peters M, Loneragan R, Clarke S. Cetuximab-associated pulmonary toxicity. *Clin Colorectal Cancer*. 2009;8(2):118-120.
12. Satoh T, Gemma A, Kudoh S, et al. Incidence and clinical features of drug-induced lung injury in patients with advanced colorectal cancer receiving cetuximab: results of a prospective multicenter registry. *Jpn J Clin Oncol*. 2014;44(11):1032-1039.
13. Reck M, van Zandwijk N, Gridelli C, et al. Erlotinib in advanced non-small cell lung cancer: efficacy and safety findings of the global phase IV Tarceva Lung Cancer Survival Treatment study. *J Thorac Oncol*. 2010;5(10):1616-1622.
14. Rosado MF, Donna E, Ahn YS. Challenging problems in advanced malignancy: case 3. imatinib mesylate-induced interstitial pneumonitis. *J Clin Oncol*. 2003;21(16):3171-3173.
15. Bergeron A, Rea D, Levy V, et al. Lung abnormalities after dasatinib treatment for chronic myeloid leukemia: a case series. *Am J Respir Crit Care Med*. 2007;176(8):814-818.
16. Ohyanagi F, Ando Y, Nagashima F, et al. Acute gefitinib-induced pneumonitis. *Int J Clin Oncol*. 2004;9(5):406-409.
17. Rajda J, Phatak PD. Reversible drug-induced interstitial pneumonitis following imatinib mesylate therapy. *Am J Hematol*. 2005;79(1):80-81.
18. Hwang HJ, Kim MY, Choi CM, Lee JC. Anaplastic lymphoma kinase inhibitor related pneumonitis in patients with non-small cell lung cancer: clinical and radiologic characteristics and risk factors. *Medicine (Baltimore)*. 2019;98(48):e18131.
19. Ascierto PA, Ferrucci PF, Fisher R, et al. Dabrafenib, trametinib and pembrolizumab or placebo in BRAF-mutant melanoma. *Nat Med*. 2019;25(6):941-946.
20. Gopal AK, Kahl BS, de Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med*. 2014;370(11):1008-1018.
21. Flinn IW, Kahl BS, Leonard JP, et al. Idelalisib, a selective inhibitor of phosphatidylinositol 3-kinase-δ, as therapy for previously treated indolent non-Hodgkin lymphoma. *Blood*. 2014;123(22):3406-3413.
22. Liu X, Hong XN, Gu YJ, et al. Interstitial pneumonitis during rituximab-containing chemotherapy for non-Hodgkin lymphoma. *Leuk Lymphoma*. 2008;49(9):1778-1783.
23. Vahid B, Mehrotra A. Trastuzumab (Herceptin)-associated lung injury. *Respirology*. 2006;11(5):655-658.
24. Radzikowska E, Szczepulska E, Chabowski M, Bestry I. Organising pneumonia caused by trastuzumab (Herceptin) therapy for breast cancer. *Eur Respir J*. 2003;21(3):552-555.
25. Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med*. 2020;382(7):610-621.
26. Duran I, Siu LL, Oza AM, et al. Characterisation of the lung toxicity of the cell cycle inhibitor temsirolimus. *Eur J Cancer*. 2006;42(12):1875-1880.
27. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet*. 2008;372(9637):449-456.
28. Michot JM, Bigenwald C, Champiat S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. *Eur J Cancer*. 2016;54:139-148.
29. Naidoo J, Page DB, Li BT, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Ann Oncol*. 2015;26(12):2375-2391.
30. Su Q, Zhu EC, Wu JB, et al. Risk of pneumonitis and pneumonia associated with immune checkpoint inhibitors for solid tumors: a systematic review and meta-analysis. *Front Immunol*. 2019;10:108.
31. Suresh K, Naidoo J, Lin CT, Danoff S. Immune checkpoint immunotherapy for non-small cell lung cancer: benefits and pulmonary toxicities. *Chest*. 2018;154(6):1416-1423.
32. Xia B, Herbst RS. Immune checkpoint therapy for non-small-cell lung cancer: an update. *Immunotherapy*. 2016;8(3):279-298.
33. Dabydeen DA, Jagannathan JP, Ramaiya N, et al. Pneumonitis associated with mTOR inhibitors therapy in patients with metastatic renal cell carcinoma: incidence, radiographic findings and correlation with clinical outcome. *Eur J Cancer*. 2012;48(10):1519-1524.
34. Gartrell BA, Ying J, Sivendran S, et al. Pulmonary complications with the use of mTOR inhibitors in targeted cancer therapy: a systematic review and meta-analysis. *Target Oncol*. 2014;9(3):195-204.
35. Maroto JP, Hudes G, Dutcher JP, et al. Drug-related pneumonitis in patients with advanced renal cell carcinoma treated with temsirolimus. *J Clin Oncol*. 2011;29(13):1750-1756.
36. Tefferi A, Litzow MR, Pardanani A. Long-term outcome of treatment with ruxolitinib in myelofibrosis. *N Engl J Med*. 2011;365(15):1455-1457.
37. Beauverd Y, Samii K. Acute respiratory distress syndrome in a patient with primary myelofibrosis after ruxolitinib treatment discontinuation. *Int J Hematol*. 2014;100(5):498-501.
38. Rogers JE, Yang D. Differentiation syndrome in patients with acute promyelocytic leukemia. *J Oncol Pharm Pract*. 2012;18(1):109-114.
39. Luesink M, Jansen JH. Advances in understanding the pulmonary infiltration in acute promyelocytic leukaemia. *Br J Haematol*. 2010 151(3):209-220.
40. Sachdeva A, Matuschak GM. Diffuse alveolar hemorrhage following alemtuzumab. *Chest*. 2008;133(6):1476-1478.
41. Sandler A. Bevacizumab in non small cell lung cancer. *Clin Cancer Res*. 2007;13((15 Pt 2)):s4613-s4616.
42. Lin TS, Penza SL, Avalos BR, et al. Diffuse alveolar hemorrhage following gemtuzumab ozogamicin. *Bone Marrow Transplant*. 2005;35(8):823-824.

43. Alexandrescu DT, Dutcher JP, O'Boyle K, et al. Fatal intra-alveolar hemorrhage after rituximab in a patient with non-Hodgkin lymphoma. *Leuk Lymphoma*. 2004;45(11):2321-2325.
44. Nicolls MR, Terada LS, Tuder RM, et al. Diffuse alveolar hemorrhage with underlying pulmonary capillaritis in the retinoic acid syndrome. *Am J Respir Crit Care Med*. 1998;158(4):1302-1305.
45. Robak T, Błasińska-Morawiec M, Krykowski E, et al. 2-Chlorodeoxyadenosine (cladribine)-related eosinophilia in patients with lymphoproliferative diseases. *Eur J Haematol*. 1997;59(4):216-220.
46. Sezer O, Schmid P, Hallek M, et al. Eosinophilia during fludarabine treatment of chronic lymphocytic leukemia. *Ann Hematol*. 1999;78(10):475-477.
47. Trojan A, Meier R, Licht A, Taverna C. Eosinophilic pneumonia after administration of fludarabine for the treatment of non-Hodgkin's lymphoma. *Ann Hematol*. 2002 81(9):535-537.
48. Kikawada M, Ichinose Y, Kunisawa A, et al. Sarcoidosis induced by interferon therapy for chronic myelogenous leukaemia. *Respirology*. 1998;3(1):41-44.
49. Kim C, Gao J, Shannon VR, Siefker-Radtke A. Systemic sarcoidosis first manifesting in a tattoo in the setting of immune checkpoint inhibition. *BMJ Case Rep*. 2016;2016.
50. Sybert A, Butler TP. Sarcoidosis following adjuvant high-dose methotrexate therapy for osteosarcoma. *Arch Intern Med*. 1978;138(3):488-489.
51. Pietropaoli A, Modrak J, Utell M. Interferon-alpha therapy associated with the development of sarcoidosis. *Chest*. 1999;116(2):569-572.
52. Ramstein J, Broos CE, Simpson LJ, et al. IFN-gamma-producing T-helper 17.1 cells are increased in sarcoidosis and are more prevalent than T-helper type 1 cells. *Am J Respir Crit Care Med*. 2016;193(11):1281-1291.
53. Lomax AJ, McGuire HM, McNeil C, et al. Immunotherapy-induced sarcoidosis in patients with melanoma treated with PD-1 checkpoint inhibitors: case series and immunophenotypic analysis. *Int J Rheum Dis*. 2017;20(9):1277-1285.
54. Firwana B, Ravilla R, Raval M, et al. Sarcoidosis-like syndrome and lymphadenopathy due to checkpoint inhibitors. *J Oncol Pharm Pract*. 2017;23(8):620-624.
55. Souza GH, Thien CI, Castro VB, Gripp AC. Sarcoidosis secondary to lymphocyte active immunotherapy treated with infliximab. *An Bras Dermatol*. 2018;93(5):764-765.
56. Chopra A, Nautiyal A, Kalkanis A, Judson MA. Drug-induced sarcoidosis-like reactions. *Chest*. 2018;154(3):664-677.
57. Huggins JT, Sahn SA. Drug-induced pleural disease. *Clin Chest Med*. 2004;25(1):141-153.
58. Wohlrab J, Liu M, Anderson E, Kia Noury D. Docetaxel induced pleural effusions [abstract]. *Chest*. 2002;122(94S-95S).
59. Busmanis IA, Beaty AE, Basser RL. Isolated pleural effusion with hematopoietic cells of mixed lineage in a patient receiving granulocyte-colony-stimulating factor after high-dose chemotherapy. *Diagn Cytopathol*. 1998;18(3):204-207.
60. Anderson P, Höglund M, Rödjer S. Pulmonary side effects of interferon-alpha therapy in patients with hematological malignancies. *Am J Hematol*. 2003;73(1):54-58.
61. Goldsby R, Pulsipher M, Adams R, et al. Unexpected pleural effusions in 3 pediatric patients treated with STI-571. *J Pediatr Hematol Oncol*. 2002;24(8):694-695.
62. Socinski MA, Langer CJ, Huang JE, et al. Safety of bevacizumab in patients with non-small-cell lung cancer and brain metastases. *J Clin Oncol*. 2009;27(31):5255-5261.
63. Procopio G, Verzoni E, Gevorgyan A, et al. Safety and activity of sorafenib in different histotypes of advanced renal cell carcinoma. *Oncology*. 2007;73(3-4):204-209.
64. Nalluri SR, Chu D, Keresztes R, et al. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis. *JAMA*. 2008;300(19):2277-2285.
65. Godinas L1, Guignabert C, Seferian A, et al. Tyrosine kinase inhibitors in pulmonary arterial hypertension: a double-edge sword? *Semin Respir Crit Care Med*. 2013 34(5):714-724.
66. Montani D, Bergot E, Gunther S, et al. Pulmonary arterial hypertension in patients treated by dasatinib. *Circulation*. 2012;125(17):2128-2137.
67. Abratt RP, Morgan GW. Lung toxicity following chest irradiation in patients with lung cancer. *Lung Cancer*. 2002;35(2):103-109.
68. Divisi D, Di Francesco C, Di Leonardo G, Crisci R. Preoperative pulmonary rehabilitation in patients with lung cancer and chronic obstructive pulmonary disease. *Eur J Cardiothorac Surg*. 2013;43(2):293-296.
69. Dyke RW. Acute bronchospasm after a vinca alkaloid in patients previously treated with mitomycin. *N Engl J Med*. 1984;310(6):389.
70. Rivera MP, Kris MG, Gralla RJ, White DA. Syndrome of acute dyspnea related to combined mitomycin plus vinca alkaloid chemotherapy. *Am J Clin Oncol*. 1995;18(3):245-250.
71. Skubitz KM, Skubitz AP. Mechanism of transient dyspnea induced by pegylated-liposomal doxorubicin (Doxil). *Anticancer Drugs*. 1998;9(1):45-50.
72. Ho DH, Brown NS, Yen A, et al. Clinical pharmacology of polyethylene glycol-L-asparaginase. *Drug Metab Dispos*. 1986;14(3):349-352.
73. Raanani P, Ben-Bassat I. Immune-mediated complications during interferon therapy in hematological patients. *Acta Haematol*. 2002;107(3):133-144.
74. Wendtner CM, Ritgen M, Schweighofer CD, et al. Consolidation with alemtuzumab in patients with chronic lymphocytic leukemia (CLL) in first remission--experience on safety and efficacy within a randomized multicenter phase III trial of the German CLL Study Group (GCLLSG). *Leukemia*. 2004;18(6):1093-1101.
75. Leopold LH, Berger MS, Feingold J. Acute and long-term toxicities associated with gemtuzumab ozogamicin (Mylotarg) therapy of acute myeloid leukemia. *Clin Lymphoma*. 2002;2(suppl 1):S29-S34.
76. Byrd JC, Waselenko JK, Maneatis TJ, et al. Rituximab therapy in hematologic malignancy patients with circulating blood tumor cells: association with increased infusion-related side effects and rapid blood tumor clearance. *J Clin Oncol*. 1999;17(3):791-795.
77. Szebeni J, Alving CR, Savay S, et al. Complement activation-related pseudoallergy caused by liposomes, micellar carriers of intravenous drugs, and radiocontrast agents. *Crit Rev Ther Drug Carrier Syst*. 2001;18(6):567-606.
78. Markman M. Management of toxicities associated with the administration of taxanes. *Expert Opin Drug Saf*. 2003;2(2):141-146.
79. Champiat S, Lambotte O, Barreau E, et al. Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. *Ann Oncol*. 2016;27(4):559-574.
80. Schoenfeld JD, Nishino M, Severgnini M, et al. Pneumonitis resulting from radiation and immune checkpoint blockade illustrates characteristic clinical, radiologic and circulating biomarker features. *J Immunother Cancer*. 2019;7(1):112.
81. Costantini A, Fallet V, Corny J, et al. Nivolumab-refractory patients with advanced non-small-cell lung cancer. *Lung Cancer*. 2019;130:128-134.
82. Balaji A, Verde F, Suresh K, Naidoo J. Pneumonitis from anti-PD-1/ PD-L1 therapy. *Oncology (Williston Park)*. 2017;31(10):739-746, 754.
83. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med*. 2018;378(22):2093-2104.
84. Shaverdian N, Lisberg AE, Bornazyan K, et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary

analysis of the KEYNOTE-001 phase 1 trial. *Lancet Oncol*. 2017;18(7):895-903.
85. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med*. 2017;377(20):1919-1929.
86. Naidoo J, Wang X, Woo KM, et al. Pneumonitis in patients treated with anti-programmed death-1/programmed death ligand 1 therapy. *J Clin Oncol*. 2017;35(7):709-717.
87. Delaunay M, Cadranel J, Lusque A, et al. Immune-checkpoint inhibitors associated with interstitial lung disease in cancer patients. *Eur Respir J*. 2017;50(2).
88. Ijaz A, Khan AY, Malik SU, et al. Significant risk of graft-versus-host disease with exposure to checkpoint inhibitors before and after allogeneic transplantation. *Biol Blood Marrow Transplant*. 2019;25(1):94-99.
89. Cho JY, Kim J, Lee JS, et al. Characteristics, incidence, and risk factors of immune checkpoint inhibitor-related pneumonitis in patients with non-small cell lung cancer. *Lung Cancer*. 2018;125:150-156.
90. Khunger M, Rakshit S, Pasupuleti V, et al. Incidence of pneumonitis with use of programmed death 1 and programmed death-ligand 1 inhibitors in non-small cell lung cancer: a systematic review and meta-analysis of trials. *Chest*. 2017;152(2):271-281.
91. Nishino M. Immune-related response evaluations during immune-checkpoint inhibitor therapy: establishing a "common language" for the new arena of cancer treatment. *J Immunother Cancer*. 2016;4:30.
92. Blanchard A, Bouchard N. Pembrolizumab-induced obstructive bronchiolitis in a patient with stage IV non-small-cell lung cancer. *Curr Oncol*. 2019;26(4):e571-e573.
93. Komiya K, Nakamura T, Abe T, et al. Discontinuation due to immune-related adverse events is a possible predictive factor for immune checkpoint inhibitors in patients with non-small cell lung cancer. *Thoracic Cancer*. 2019;10(9):1798-1804.
94. Suresh K, Naidoo J. Lower survival in patients who develop pneumonitis following immunotherapy for lung cancer. *Clin Lung Cancer*. 2019.
95. Tone M, Izumo T, Awano N, et al. Treatment effect and safety profile of salvage chemotherapy following immune checkpoint inhibitors in lung cancer. *Lung Cancer Manag*. 2019;8(2).
96. Haanen J, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28(suppl 4):iv119-iv142.
97. Dougan M. Checkpoint blockade toxicity and immune homeostasis in the gastrointestinal tract. *Front Immunol*. 2017;8:1547.
98. Stroud CR, Hegde A, Cherry C, et al. Tocilizumab for the management of immune mediated adverse events secondary to PD-1 blockade. *J Oncol Pharm Pract*. 2019;25(3):551-557.
99. Del Castillo M, Romero FA, Arguello E, et al. The spectrum of serious infections among patients receiving immune checkpoint blockade for the treatment of melanoma. *Clin Infect Dis*. 2016;63(11):1490-1493.
100. Fujita K, Kim YH, Kanai O, et al. Emerging concerns of infectious diseases in lung cancer patients receiving immune checkpoint inhibitor therapy. *Respir Med*. 2019;146:66-70.
101. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med*. 2001;345(15):1098-1104.
102. Godfrey MS, Friedman LN. Tuberculosis and biologic therapies: anti-tumor necrosis factor-alpha and beyond. *Clin Chest Med*. 2019;40(4):721-739.
103. Kedia S, Mouli VP, Kamat N, et al. Risk of tuberculosis in patients with inflammatory bowel disease on infliximab or adalimumab is dependent on the local disease burden of tuberculosis: a systematic review and meta-analysis. *Am J Gastroenterol*. 2020.
104. Sousa M, Ladeira I, Ponte A, et al. Screening for latent tuberculosis in patients with inflammatory bowel disease under antitumor necrosis factor: data from a Portuguese center. *Eur J Gastroenterol Hepatol*. 2019;31(9):1099-1102.
105. Hanania AN, Mainwaring W, Ghebre YT, et al. Radiation-induced lung injury: assessment and management. *Chest*. 2019;156(1):150-162.
106. Marks LB, Yu X, Vujaskovic Z, et al. Radiation-induced lung injury. *Semin Radiat Oncol*. 2003;13(3):333-345.
107. Movsas B, Raffin TA, Epstein AH, Link CJ Jr. Pulmonary radiation injury. *Chest*. 1997;111(4):1061-1076.
108. Koenig T, Munden RF, Eramus JJ, et al. Radiation injury of the lung after three-dimensional conformal radiation therapy. *AJR Am J Roentgenol*. 2002;178:1383-1388.
109. Cornelissen R, Senan S, Antonisse IE, et al. Bronchiolitis obliterans organizing pneumonia (BOOP) after thoracic radiotherapy for breast carcinoma. *Radiat Oncol*. 2007;2(2):1-5.
110. Schweitzer V, Juillard G, Bajada C. Radiation recall dermatitis and pneumonitis in a patient treated with paclitaxel. *Cancer*. 1995;76:1069-1072.
111. Smith JC. Radiation Pneumonitis. Case report of bilateral reaction after unilaternal irradiation. *Am Rev Respir Dis*. 1964;89:264-269.
112. Schwarte S, Wagner K, Karstens JH, Bremer M. Radiation recall pneumonitis induced by gemcitabine. *Strahlenther Onkol*. 2007;183(4):215-217.
113. Abdel-Razeq H, Mansour A, Abdulelah H, et al. Thromboembolic events in cancer patients on active treatment with cisplatin-based chemotherapy: another look! *Thromb J*. 2018;16:2.
114. Papaxoinis G, Kamposioras K, Germetaki T, et al. Predictive factors of thromboembolic complications in patients with esophagogatric adenocarcinoma undergoing preoperative chemotherapy. *Acta Oncol*. 2018;57(6):790-798.
115. Awad R, Nott L. Radiation recall pneumonitis induced by erlotinib after palliative thoracic radiotherapy for lung cancer: case report and literature review. *Asia Pac J Clin Oncol*. 2016;12(1):91-95.
116. Clark D, Gauchan D, Ramaekers R, et al. Radiation recall pneumonitis during systemic treatment with everolimus. *Oncol Res*. 2014;22(5-6):321-324.
117. Ding X, Ji W, Li J, et al. Radiation recall pneumonitis induced by chemotherapy after thoracic radiotherapy for lung cancer. *Radiat Oncol*. 2011;6(24):1-6.
118. Forschner A, Zips D, Schraml C, et al. Radiation recall dermatitis and radiation pneumonitis during treatment with vemurafenib. *Melanoma Res*. 2014;24(5):512-516.
119. Ma LD, Taylor GA, Wharam MD, Wiley JM. "Recall" pneumonitis: Adriamycin potentiation of radiation pneumonitis in two children. *Radiology*. 1993;187(2):465-467.
120. Onal C, Abali H, Koc Z, Kara S. Radiation recall pneumonitis caused by erlotinib after palliative definitive radiotherapy. *Onkologie*. 2012;35(4):191-194.
121. Shibaki R, Akamatsu H, Fujimoto M, et al. Nivolumab induced radiation recall pneumonitis after two years of radiotherapy. *Ann Oncol*. 2017;28(6):1404-1405.
122. Yuasa T, Kitsukawa S, Sukegawa G, et al. Early onset recall pneumonitis during targeted therapy with sunitinib. *BMC Cancer*. 2013;13:3.
123. Cottin V, Frognier R, Monnot H, et al. Chronic eosinophilic pneumonia after radiation therapy for breast cancer. *Eur Respir J*. 2004;23(1):9-13.
124. Capizzi SA, Kumar S, Huneke NE, et al. Peri-engraftment respiratory distress syndrome during autologous hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2001;27(12):1299-1303.
125. Afessa B, Tefferi A, Litzow MR, et al. Diffuse alveolar hemorrhage in hematopoietic stem cell transplant recipients. *Am J Respir Crit Care Med*. 2002;166(5):641-645.

126. Soubani A, Miller K, Hassoun P. Pulmonary complications of bone marrow transplantation. *Chest*. 1996;109(4):1066-1077.
127. Spitzer TR. Engraftment syndrome following hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2001;27(9):893-898.
128. Afessa B, Tefferi A, Litzow MR, Peters SG. Outcome of diffuse alveolar hemorrhage in hematopoietic stem cell transplant recipients. *Am J Respir Crit Care Med*. 2002;166(10):1364-1368.
129. Yanik G, Hellerstedt B, Custer J, et al. Etanercept (Enbrel) administration for idiopathic pneumonia syndrome after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2002;8(7):395-400.
130. Panoskaltsis-Mortari A, Griese M, Madtes DK, et al. An official American Thoracic Society research statement: noninfectious lung injury after hematopoietic stem cell transplantation: idiopathic pneumonia syndrome. *Am J Respir Crit Care Med*. 2011 183(9):1262-1279.
131. Cao TM, Negrin RS, Stockerl-Goldstein KE, et al. Pulmonary toxicity syndrome in breast cancer patients undergoing BCNU-containing high-dose chemotherapy and autologous hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2000;6(4):387-394.
132. Chien JW, Martin PJ, Gooley TA, et al. Airflow obstruction after myeloablative allogeneic hematopoietic stem cell transplantation. *Am J Respir Crit Care Med*. 2003;168(2):208-214.
133. Kotloff RM, Ahya VN, Crawford SW. Pulmonary complications of solid organ and hematopoietic stem cell transplantation. *Am J Respir Crit Care Med*. 2004;170(1):22-48.
134. Afessa B, Litzow MR, Tefferi A. Bronchiolitis obliterans and other late onset non-infectious pulmonary complications in hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2001;28(5):425-434.
135. Soubani AO, Uberti JP. Bronchiolitis obliterans following haematopoietic stem cell transplantation. *Eur Respir J*. 2007;29(5):1007-1019.
136. Gupta V, Malone AK, Hari PN, et al. Reduced-intensity hematopoietic cell transplantation for patients with primary myelofibrosis: a cohort analysis from the center for international blood and marrow transplant research. *Biol Blood Marrow Transplant*. 2014;20(1):89-97.
137. Faiz SA, Jimenez CA, Fellman BM, et al. Incidence of bleeding complications with flexible bronchoscopy in cancer patients with thrombocytopenia. *J Bronchology Interv Pulmonol*. 2019;26(4):280-286.
138. Khalid M, Al Saghir A, Saleemi S, et al. Azithromycin in bronchiolitis obliterans complicating bone marrow transplantation: a preliminary study. *Eur Respir J*. 2005;25(3):490-493.
139. Afessa B, Peters SG. Major complications following hematopoietic stem cell transplantation. *Semin Respir Crit Care Med*. 2006;27(3):297-309.
140. Yoshihara S1, Yanik G CK, Mineishi S. Bronchiolitis obliterans syndrome (BOS), bronchiolitis obliterans organizing pneumonia (BOOP), and other late-onset noninfectious pulmonary complications following allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2007;13(7):749-759.
141. Nakasone H, Remberger M, Tian L, et al. Risks and benefits of sex-mismatched hematopoietic cell transplantation differ according to conditioning strategy. *Haematologica*. 2015;100(11):1477-1485.
142. Freudenberger TD, Madtes DK, Curtis JR, et al. Association between acute and chronic graft-versus-host disease and bronchiolitis obliterans organizing pneumonia in recipients of hematopoietic stem cell transplants. *Blood*. 2003;102(10):3822-3828.
143. Rasche L, Kapp M, Einsele H, Mielke S. EBV-induced post transplant lymphoproliferative disorders: a persisting challenge in allogeneic hematopoietic SCT. *Bone Marrow Transplant*. 2014;49(2):163-167.
144. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *JAMA*. 2005;293(6):715-722.
145. Murchison JT, Wylie L, Stockton DL. Excess risk of cancer in patients with primary venous thromboembolism: a national, population-based cohort study. *Br J Cancer*. 2004;91(1):92-95.
146. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. *Blood*. 2013;122:1712-1723.
147. Prandoni P1, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood*. 2002 100(10):3484-3488.
148. Bashoura L, Eapen GA, Faiz SA. Pulmonary manifestations of lymphoma and leukemia. *Clin Chest Med*. 2017;38(2):187-200.
149. Vu K, Luong NV, Hubbard J, et al. A retrospective study of venous thromboembolism in acute leukemia patients treated at the University of Texas MD Anderson Cancer Center. *Cancer Med*. 2015;4(1):27-35.
150. ten Wolde M, Kraaijenhagen RA, Prins MH, Buller HR. The clinical usefulness of D-dimer testing in cancer patients with suspected deep venous thrombosis. *Arch Intern Med*. 2002;162(16):1880-1884.
151. Konstantinides SV, Meyer G. The 2019 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2019;40(42):3453-3455.
152. Key NS, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update. *J Clin Oncol*. 2020;38(5):496-520.
153. Rali PM, Criner GJ. Submassive pulmonary embolism. *Am J Respir Crit Care Med*. 2018;198(5):588-598.
154. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med*. 2014;370(15):1402-1411.
155. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med*. 2018;378(7):615-624.
156. Agnelli G, Becattini C, Meyer G, et al. Apixaban for the treatment of venous thromboembolism associated with cancer. *N Engl J Med*. 2020;382(17):1599-1607.
157. McBane RD 2nd, Wysokinski WE, Le-Rademacher JG, et al. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: the ADAM VTE trial. *J Thromb Haemost*. 2020;18(2):411-421.
158. Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral factor Xa Inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). *J Clin Oncol*. 2018;36(20):2017-2023.
159. Connors J. Prophylaxis against venous thromboembolism in ambulatory patients with cancer. *N Engl J Med*. 2014;370(26):2515-2519.
160. Kahn SR1, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e195S-e226S.
161. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016;149(2):315-352.
162. Jasti N, Streiff MB. Prevention and treatment of thrombosis associated with central venous catheters in cancer patients. *Expert Rev Hematol*. 2014 7(5):599-616.
163. Carrier M, Khorana AA, Zwicker JI, et al. Management of challenging cases of patients with cancer-associated thrombosis including recurrent thrombosis and bleeding: guidance from the SSC of the ISTH: a reply to a rebuttal. *J Thromb Haemost*. 2014 12(1):116-117.
164. Trobaugh-Lotrario AD, Greffe B, Deterding R, et al. Pulmonary veno-occlusive disease after autologous bone marrow transplant

in a child with stage IV neuroblastoma: case report and literature review. *J Pediatr Hematol Oncol*. 2003;25(5):405-409.
165. Swift G, Gibbs A, Campbell I. Pulmonary veno-occlusive disease and Hodgkin's lymphoma. *Eur Respir J*. 1993;6:596-598.
166. Gagnadoux F, Capron F, Lebeau B. Pulmonary veno-occlusive disease after neoadjuvant mitomycin chemotherapy and surgery for lung carcinoma. *Lung Cancer*. 2002;36:213-215.
167. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53(1).
168. Dingli D, Utz JP, Krowka MJ, et al. Unexplained pulmonary hypertension in chronic myeloproliferative disorders. *Chest*. 2001;120:801-808.
169. Lee J, Kim Y, Lee K, Chung M. Tuberculous fibrosing mediastinitis: radiologic findings (letter). *AJR Am J Roentgenol*. 1996;167:1598-1599.
170. Lagerstrom C, Mitchell H, Graham B, Hammon JJ. Chronic fibrosisng mediastinitis and superior vena caval obstruction from blastomycosis. *Ann Thorac Surg*. 1992;54:764-765.
171. Mole T, Glover J, Sheppard M. Sclerosing mediastinitis: a report on 18 cases. *Thorax*. 1995;50:280-283.
172. Faiz SA, Iliescu C, Lopez-Mattei J, et al. Resolution of myelofibrosis associated pulmonary artery hypertension following allogeneic hematopoietic stem cell transplantation. *Pulmonary Circulation*. 2016.
173. Lopez-Mattei J, Verstovsek S, Fellman B, et al. Prevalence of pulmonary hypertension in myelofibrosis. *Ann Hematol*. 2020;99(4):781-789.
174. Brouns M, Jayaraju ST, Lacor C, et al. Tracheal stenosis: a flow dynamics study. *J Appl Physiol (1985)*. 2007;102(3):1178-1184.
175. Miller RD, Hyatt RE. Evaluation of obstructing lesions of the trachea and larynx by flow-volume loops. *Am Rev Respir Dis*. 1973;108(3):475-481.
176. Bibby AC, Dorn P, Psallidas I, et al. ERS/EACTS statement on the management of malignant pleural effusions. *Eur Respir J*. 2018;52(1):1800349.
177. Loddenkemper R. Thoracoscopy—state of the art. *Eur Respir J*. 1998;11(1):213-221.
178. Antony VB, Loddenkemper R, Astoul P, et al. Management of malignant pleural effusions. *Eur Respir J*. 2001;18(2):402-419.
179. Rodriguez-Panadero F, Borderas Naranjo F, Lopez Mejias L. Pleural metastatic tumours and effusions. Frequency and pathogenic mechanisms in a post-mortem series. *Eur Respir J*. 1989;2(4):366-369.
180. Sahn S. Pleural diseases related to metastatic malignancies. *Eur Respir J*. 1997;10:1907-1913.
181. Evans AL, Gleeson FV. Radiology in pleural disease: state of the art. *Respirology*. 2004;9(3):300-312.
182. Light RW. Clinical practice. Pleural effusion. *N Engl J Med*. 2002;346(25):1971-1977.
183. Arnold DT, De Fonseka D, Perry S, et al. Investigating unilateral pleural effusions: the role of cytology. *Eur Respir J*. 2018;52(5).
184. Grosu HB, Kazzaz F, Vakil E, Molina S, Ost D. Sensitivity of initial thoracentesis for malignant pleural effusion stratified by tumor type in patients with strong evidence of metastatic disease. *Respiration*. 2018;96(4):363-369.
185. Porcel JM, Vives M, Esquerda A, et al. Use of a panel of tumor markers (carcinoembryonic antigen, cancer antigen 125, carbohydrate antigen 15-3, and cytokeratin 19 fragments) in pleural fluid for the differential diagnosis of benign and malignant effusions. *Chest*. 2004;126(6):1757-1763.
186. O'Hara MF, Cousar JB, Glick AD, Collins RD. Multiparameter approach to the diagnosis of hematopoietic-lymphoid neoplasms in body fluids. *Diagn Cytopathol*. 1985;1(1):33-38.
187. Burrows CM, Mathews WC, Colt HG. Predicting survival in patients with recurrent symptomatic malignant pleural effusions: an assessment of the prognostic values of physiologic, morphologic, and quality of life measures of extent of disease. *Chest*. 2000;117(1):73-78.
188. Feller-Kopman D, Light R. Pleural disease. *N Engl J Med*. 2018;378(8):740-751.
189. Roberts ME, Neville E, Berrisford RG, et al Management of a malignant pleural effusion: British Thoracic Society Pleural Disease Guideline 2010. *Thorax*. 2010;65(suppl 2):ii32-40.
190. Lentz RJ, Lerner AD, Pannu JK, et al. Routine monitoring with pleural manometry during therapeutic large-volume thoracentesis to prevent pleural-pressure-related complications: a multicentre, single-blind randomised controlled trial. *Lancet Respir Med*. 2019;7(5):447-455.
191. Bertolaccini L, Viti A, Paiano S, et al. indwelling pleural catheters: a clinical option in trapped lung. *Thorac Surg Clin*. 2017;27(1):47-55.
192. Alinsonorin CY, Jimenez CA, Ersoy YM, et al. Indwelling pleural catheters for management of recurrent malignant pleural effusions. *Am J Respir Crit Care Med*. 2003;167(7 suppl):A901.
193. Shaw P, Agarwal R. Pleurodesis for malignant pleural effusions. *Cochrane Database Syst Rev*. 2004(1):Cd002916.
194. Bhatnagar R, Maskell NA. Delivery of talc for pleurodesis of malignant pleural effusions-reply. *JAMA*. 2020;323(18):1855-1856.
195. Bhatnagar R, Keenan EK, Morley AJ, et al. Outpatient talc administration by indwelling pleural catheter for malignant effusion. *N Engl J Med*. 2018;378(14):1313-1322.
196. Mares DC, Mathur PN. Medical thoracoscopic talc pleurodesis for chylothorax due to lymphoma: a case series. *Chest*. 1998;114(3):731-735.
197. Davidson JR, MacLean AW, Brundage MD, Schulze K. Sleep disturbance in cancer patients. *Social science & medicine (1982)*. 2002;54(9):1309-1321.
198. Tamakoshi A, Ohno Y. Self-reported sleep duration as a predictor of all-cause mortality: results from the JACC study, Japan. *Sleep*. 2004;27(1):51-54.
199. Davis S, Mirick DK, Stevens RG. Night shift work, light at night, and risk of breast cancer. *J Natl Cancer Inst*. 2001;93(20):1557-1562.
200. Schernhammer ES, Laden F, Speizer FE, et al. Rotating night shifts and risk of breast cancer in women participating in the Nurses' Health Study. *J Natl Cancer Inst*. 2001;93(20):1563-1568.
201. Schernhammer ES, Hankinson SE, Rosner B, et al. Job stress and breast cancer risk: the Nurses' Health Study. *Am J Epidemiol*. 2004;160(11):1079-1086.
202. Nieto FJ, Peppard PE, Young T, et al Sleep-disordered breathing and cancer mortality: results from the Wisconsin Sleep Cohort Study. *Am J Respir Crit Care Med*. 2012;186(2):190-194.
203. Ancoli-Israel S, Moore PJ, Jones V. The relationship between fatigue and sleep in cancer patients: a review. *Eur J Cancer Care (Engl)*. 2001;10(4):245-255.
204. Roehrs T, Hyde M, Blaisdell B, et al. Sleep loss and REM sleep loss are hyperalgesic. *Sleep*. 2006;29(2):145-151.
205. Farney RJ, Walker JM, Cloward TV, Rhondeau S. Sleep-disordered breathing associated with long-term opioid therapy. *Chest*. 2003;123(2):632-639.
206. Faiz SA, Sahay S, Jimenez CA. Pleural effusions in acute and chronic leukemia and myelodysplastic syndrome. *Curr Opin Pulm Med* :340-346.2014;20(4):340-346.
207. Bower JE, Ganz PA, Aziz N, Fahey JL. Fatigue and proinflammatory cytokine activity in breast cancer survivors. *Psychosomatic Med*. 2002;64(4):604-611.
208. Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. *J Clin Oncol*. 2001;19(3):895-908.
209. Savard J, Simard S, Blanchet J, et al. Prevalence, clinical characteristics, and risk factors for insomnia in the context of breast cancer. *Sleep*. 2001;24(5):583-590.

This page intentionally left blank

64 Cancer-Associated Thrombosis

Kelly A. Casteel
Michael H. Kroll

KEY CONCEPTS

- Venous thromboembolism (VTE) is common in patients with cancer and contributes to their morbidity and mortality.
- All hospitalized patients with cancer should be given pharmacologic thromboprophylaxis unless there is a contraindication.
- High-risk ambulatory patients with cancer receiving outpatient chemotherapy can be considered candidates for receiving prophylactic-dose apixaban or rivaroxaban.
- Cancer-associated VTE treatment with anticoagulation is associated with a higher rate of recurrence and bleeding compared with non–cancer-related VTE, so one must fastidiously review the risk–benefit ratio for each patient before beginning anticoagulation.
- Cancer-associated thrombotic microangiopathy is not caused by ADAMTS-13 autoantibodies and does not improve with plasma exchange.
- Routine anticoagulation or antiplatelet therapy for cancer patients with atrial fibrillation or coronary artery disease appears to be safe.

VENOUS THROMBOEMBOLISM

Scope of the Problem

Pulmonary embolism (PE) and deep vein thrombosis (DVT) are manifestations of venous thromboembolism (VTE). Approximately 20% of all VTEs are associated with cancer, and cancer increases the risk for VTE four- to sixfold. Surgery, chemotherapy, hormonal therapy, growth factors, angiogenesis inhibitors, immunomodulators, erythropoietic agents, and central venous catheters (CVCs) contribute to cancer-associated VTE.[1] The risk of VTE is associated with the type of cancer and its clinical stage, with glioblastoma, stomach cancer, pancreatic cancer, lung cancer, gynecologic cancer, and acute leukemia frequently associated with VTE and early-stage breast cancer, prostate cancer, and melanoma least commonly associated with VTE.[1] Cancer-associated VTE is rarely lethal within 6 months of diagnosis and treatment,[2] but it is often undiagnosed, and its onset can be associated with considerable mortality. VTE was the death certificate–attributed cause of death for 0.21% of patients with cancer in a large population-based death certificate review,[3] the objectively documented cause of death among 0.4% of all patients with cancer registered by our institution between 2000 and 2010 (unpublished data), and the cause of death for 5/141 (3.5%) deaths recorded among 4466 community hospital–treated ambulatory patients with cancer.[4]

Diagnosis

Clinical presentations of VTE are not specific. Most patients with DVT have unilateral leg swelling and tenderness, and most patients with PE have abrupt-onset dyspnea and pleuritic chest pain. VTE can be ruled out in about 97% of cases when there is a low Well's score in conjunction with normal D-dimer levels. A higher Well's score along with elevated D-dimers cannot, however, be used to diagnose VTE in patients with cancer, and radiographic studies are required for all patients in whom VTE cannot be ruled out using Well's criteria and D-dimer levels.[5] Doppler with compression ultrasound is the preferred method to diagnose DVT, although magnetic resonance imaging and

computed tomography (CT) may be required in special circumstances, such as internal iliac vein or vena cava thrombosis. CT angiography is the best method for diagnosing PE,[6] and it offers the advantage of providing additional information regarding synchronous thoracic pathology that may confound the diagnosis. Up to 5% of all routine chest CTs done for cancer staging, monitoring, and surveillance show asymptomatic or incidental PEs.[7]

Prevention

Pharmacologic VTE prophylaxis should be considered in every hospitalized patient with cancer for whom there is no contraindication.[8] Contraindications to pharmacologic anticoagulation are absolute (platelets <20,000/μL, recent central nervous system bleed, intracranial or spinal lesion at high risk for bleeding, or major active bleeding: >2 units transfused in 24 hours) or relative (chronic, clinically significant measurable bleeding >48 hours; platelets <50,000/μL; platelet dysfunction [uremia, medications, dysplastic hematopoiesis]; recent major operation at high risk for bleeding; underlying hemorrhagic coagulopathy; high risk for falls; neuraxial anesthesia/lumbar puncture). During hospitalization for nonsurgical patients with cancer, one could use enoxaparin 40 mg subcutaneously (SC) once per day, dalteparin 5000 IU SC once per day, fondaparinux 2.5 mg SC once per day or rivaroxaban 10 mg by mouth (PO) once per day. Another option is the direct oral anticoagulant rivaroxaban 10 mg PO once per extended post hospitalization for up to 31-39 days total.[9]

Patients with cancer undergoing abdominal or pelvic surgery should receive low-molecular-weight heparin (LMWH) prophylaxis extended for 4 weeks.[10] Routine pharmacologic prophylaxis in ambulatory patients with cancer receiving chemotherapy is recommended for patients with myeloma receiving thalidomide or lenalidomide as part of combination chemotherapy, although outpatient pharmacologic prophylaxis, including thromboprophylaxis with rivaroxaban 10 mg or apixaban 2.5 mg po twice a day (BID) can be considered in high-risk patients receiving systemic chemotherapy, such as those with glioblastoma multiforme, pancreatic cancer gastric cancer, or metastatic breast cancer beginning tamoxifen therapy.[8,11]

Treatment

Routine VTE induction followed by maintenance therapy is used to treat patients with symptomatic VTE or incidental PE. Incidental PEs, including those found in the subsegmental branches of the pulmonary artery, appear to have a recurrence risk similar to symptomatic PE and should be managed similarly.[12] There has been a preference for induction and maintenance therapy with a LMWH over warfarin—for example, enoxaparin 1 mg/kg/12 hours or dalteparin 200 IU/kg/24 hours—but most organizations now suggest that a direct oral anticoagulant (DOAC) can be considered. Edoxaban 60 mg PO once per day is begun as maintenance therapy after 5 days of LMWH.[13] Rivaroxaban 15 mg PO BID for 3 weeks followed by 20 mg once per every day[14,15] or apixaban 10 mg PO BID for 1 week followed by 5 mg PO BID[16] can be used during both induction and maintenance. Both edoxaban and rivaroxaban cause more bleeding than LMWH, with almost all major bleeding being gastrointestinal (GI) or genitourinary (GU). Therefore, these DOACs should be avoided in patients with luminal GI or GU malignancies or among those with overt or potential GI or GU hemorrhage.[17] Apixaban does not cause more bleeding than LMWH, and it appears to be the safest DOAC for patients with luminal GI or GU malignancies or GI or GU bleeding.[18]

Unfractionated heparin (UFH) followed by warfarin is preferred for patients with renal failure. Because it is rapidly reversible with a reliable antidote (Table 64–1), UFH is also preferred for patients with nonsevere hemorrhage and all patients with massive PE (defined as associated with systolic blood pressure <90 mm Hg lasting for more than 15 minutes) being evaluated for systemic or local thrombolytic therapy. Thrombolysis must be considered in all cases of massive PE. If thrombolysis is contraindicated, one must evaluate patients with massive PE for treatment with mechanical thrombectomy.[7]

An inferior vena cava (IVC) filter should be placed when anticoagulation is contraindicated. If the contraindication is temporary, a retrievable IVC filter is preferred. If a patient has bleeding that is not reversible or has cancer and is unlikely to survive for more than 6 months, a permanent IVC filter is preferred.[19]

Recurrence

Recurrence of VTE on anticoagulation therapy is common in patients with cancer. The Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) trial from 2003 showed a best-case scenario of 9% recurrence at 6 months among those treated with LMWH maintenance.[2] The Comparison of Acute Treatments in Cancer Hemostasis (CATCH) trial showed that we have not made great progress in the intervening decade: the recurrence rate was 6.9% at 6 months among patients receiving LMWH maintenance.[20] The only prospective analysis examining 12 months of anticoagulation (in

TABLE 64–1 Coagulation Reversal Recommendations

Vitamin K Antagonist	Reversal Agent	Dosage	Comments
	Vitamin K	Life-threatening bleed: 10 mg IV[62] INR >9 with no bleeding: 5–10 mg PO[62] INR >5 to <9 with no bleeding: 1–4 mg PO[62]	IV and PO are equally effective at 24 hours, but IV is more effective at 6–8 hours.[1] DO NOT administer SC.[1,11,12]
		Recommended for life-threatening bleeds or need for emergency surgery[a]	For prolonged reversal administer with vitamin K:[1] Duration: 12–24 hours[1] **Contraindications:** DIC, recent thrombotic event, HIT with a HIT episode in past 60 days
Warfarin (Coumadin) (Jantoven)	PCC (Kcentra)	**INR** / **Dose (units/kg)** / **Max Dose (units)** 2 to < 4 / 25 / 2500 4–6 / 35 / 3500 > 6 / 50 units/kg / 5,000 units	
Half-life[4]: 36–48 hours			
	FFP	If PCC not available, use FFP. Generally, 15 mL/kg (64,65)[a] 5–8 mL/kg if urgent reversal is required and INR is not supratherapeutic (See dosing calculation on page 9.)	Monitor for volume overload[1] Risk of transfusion complications[1] Thawing of product may result in administration delays[17] Time to normal hemostasis: 2–7 hours[4]
Heparin			
Half-life[4]: 60–90 min (IV) 3 hours (SC)	Protamine 1 mg protamine neutralizes 100 units of heparin	The anticoagulant effect of heparin IV infusion will not be present 3–4 hours after discontinuing IV infusion or 8–12 hours after SC UFH.[66] Administer 1 mg of IV protamine for every 100 units of IV heparin given over the last 2–2.5 hours. Give slowly over 10 minutes or as a continuous infusion over 30 minutes. Administration rates should not exceed 5 mg/min. Single doses **should not exceed** 50 mg. Neutralization of subcutaneously administered heparin may require a prolonged infusion of protamine sulfate because the half-life is longer. Half-life is 10 minutes, so repeat dosing may be needed.	Excessive dosing can potentially lead to increased bleeding. Increased risk for preformed antibodies against protamine sulfate and to have an allergic reactions, including anaphylaxis • Previously received protamine sulfate-containing insulin • Have undergone vasectomy • Have known sensitivity to fish **Possible side effects of protamine:** Severe hypotension, anaphylaxis, dyspnea, bradycardia, flushing, a feeling of warmth, especially when given too rapidly

(Continued)

TABLE 64–1 Coagulation Reversal Recommendations *(Cont.)*

LMWH	Reversal Agent	Dosage	Comments
		Administer 1 mg of IV protamine for each 1 mg of enoxaparin or 100 IU of dalteparin given in the past 8 hours[66] IV slowly over 10 minutes or as a continuous infusion over 30 minutes. Administration rates should not exceed 5 mg/min. Can repeat a second dose of 0.5 mg per 100 units if bleeding continues. Smaller doses of protamine can be given if the time since LMWH is >8 hours. Likely not useful if dose given >12 hours ago. Single doses of protamine **should not exceed** 50 mg. Half-life is 10 minutes, so repeat doing may be needed.	See comments for heparin above
	Protamine		
Enoxaparin (Lovenox) Half-life: 4.5–7 hours	Percent Xa activity neutralizes enoxaparin: 54.2%[2] Dalteparin: 74%[2]		**Possible side effects of protamine:** severe hypotension, anaphylaxis, dyspnea, bradycardia, flushing, a feeling of warmth, especially when given too rapidly
Dalteparin (Fragmin) Half-life: 4–8 hours			
		For refractory life-threatening bleed:	
	PCC (Kcentra)	25 units/kg (maximum, 2500 units) to 50 units/kg (maximum, 5000 units) Consider using ideal or adjusted body weight for obese patients.	**Contraindications:** DIC, recent thrombotic event, HIT with a HIT episode in past 60 days
Pentasaccharide	**Reversal Agent**	**Dosage**	**Comments**
Fondaparinux (Arixtra) Half-life[4]: 15–20 hours	PCC (Kcentra)	25 units/kg (maximum, 2500 units) to 50 units/kg (maximum, 5000 units) Consider using ideal or adjusted body weight for obese patients.	Contraindications: DIC, recent thrombotic event HIT with a HIT episode in past 60 days
	Recombinant factor VIIa (Novo-Seven) Half-life: 2.6–3.1 hours	20–90 mcg/kg IV for one dose[66] Repeat in 2 hours if needed. Round to the nearest 1 mg.	**Monitoring**: monitor for evidence of hemostasis; safe to use in Jehovah's Witness patients

(Continued)

TABLE 64–1 Coagulation Reversal Recommendations *(Cont.)*

<table>
<tr><th>Factor Xa Inhibitor</th><th>Reversal Agent</th><th>Dosage</th><th>Comments</th></tr>
<tr><td>Rivaroxaban (Xarelto)
Half-life[7]: 7–11 hours</td><td>Activated charcoal</td><td>25–50 g by mouth</td><td>If ingested within 2 hours</td></tr>
<tr><td></td><td></td><td>For life-threatening bleed with apixaban/rivaroxaban. Likely will not offer any benefit if normal renal function and last dose was >18 hours ago.[67]</td><td></td></tr>
<tr><td>Apixaban (Eliquis™)
Half-life: 8–15 hours</td><td>Andexanet alfa (Andexxa)</td><td>
<table>
<tr><th>Factor Xa Inhibitor</th><th>Factor Xa Inhibitor Last Dose</th><th colspan="2">Timing of Factor Xa Inhibitor Last Dose Before Andexanet alfa Initiation</th></tr>
<tr><td rowspan="2">Apixaban
Rivaroxaban</td><td rowspan="2">≤5 mg
>5 mg or unknown
≤10 mg
>10 mg or unknown</td><td><8 Hours or Unknown</td><td>≥8 Hours</td></tr>
<tr><td>Low dose
High dose
Low dose
High dose</td><td>Low dose</td></tr>
</table>
Low dose: 400 mg IV bolus administered at a rate of ~30 mg/min followed 2 minutes later by 4 mg/min IV infusion for up to 120 minutes
High dose: 800 mg IV bolus administered at a rate of ~30 mg/min followed 2 minutes later by 8 mg/min IV infusion for up to 120 minutes
</td><td>Modified form of the human Factor Xa molecule. Works by acting as a decoy for the factor Xa inhibitors.</td></tr>
<tr><td>Edoxaban (Savaysa)
Half-life: 10–14 hours</td><td></td><td></td><td></td></tr>
<tr><td></td><td>PCC (Kcentra)[6]</td><td>If andexanet alfa is not available, use PCC:

25 units/kg (maximum, 2500 units) to 50 units/kg (maximum, 5000 units)
Consider using ideal or adjusted body weight for obese patients.</td><td>Contraindications: DIC, recent thrombotic event, HIT with a HIT episode in past 60 days</td></tr>
</table>

(Continued)

TABLE 64–1 Coagulation Reversal Recommendations *(Cont.)*

Direct Thrombin Inhibitors	Reversal Agent	Dosage	Comments
Argatroban8 Half-life: 39–51 min Bivalirudin8 (Angiomax) Half-life: 25–45 min	Desmopressin acetate (DDAVP)	0.3 mcg/kg in 50 mL NS over 15 minutes; can repeat in 8–12 hours	Nonspecific prohemostatic agent that stimulates the release of factor VIII and VWF from the endothelium into the plasma[3] **Monitoring:** heart rate, blood pressure, sodium, risk of seizure (especially if younger than 2 years old[3] **Contraindication:** hyponatremia
	Aminocaproic acid (Amicar)	0.1–0.15 g/kg IV bolus over 30 minutes followed by 0.5–1 g/hour infusion	**Monitoring:** heart rate, blood pressure, CPK **Contraindications:** DIC , premature neonates (because of benzyl alcohol content)
	Tranexamic acid	10 mg/kg IV every 6–8 hours	**Monitoring:** heart rate, blood pressure Contraindications: active thrombotic disease, subarachnoid hemorrhage
Dabigatran (Pradaxa) Half-life (7): 12–17 hours	Activated charcoal	25–50 g by mouth	Only for acute ingestion within 1–2 hours
	Idarucizumab (Praxbind)	For life-threatening bleed or need for emergency surgery: 5 g IV once[67,68] Administer as two consecutive infusions of the 2.5-g vial by hanging vials or injecting both via a syringe. Flush line with 0.9% sodium chloride before and after infusion.	Humanized mAb that binds dabigatran with a higher affinity than thrombin
	Hemodialysis	62%–68% of drug is removed by 2–4 hours of hemodialysis	Charcoal hemoperfusion is able to remove 75%–80%.

A. Choose a Target INR[b]		B. Convert INR to Prothrombin Complex		
Clinical Situation	**Target INR**	**INR**	**INR**	**Approximate %**
Moderate risk for bleeding, high risk of thrombosis	2.0–2.1	Overanticoagulation	>5	5
Serious bleeding, moderate risk of thrombosis	1.5		4.0–4.9	10
Serious bleeding, moderate risk of thrombosis	1.0	Therapeutic range	2.6–3.2	15
			2.2–2.5	20
			1.9–2.1	25
		Subtherapeutic range	1.7–1.8	30
			1.4–1.6	40
		Complete reversal to normal	1.0	100

[a]Calculation of milliliters of plasma or international units of prothrombin complex concentrate (PCC) Used to reverse an elevated international normalized ratio (INR).
[b]Calculate dose of milliliters of plasma or IU or PCC: Target INR as a percentage from part B: Present INR as a percentage from part B × Body weight (kg).
CPK, creatine phosphokinase; DIC, disseminated intravascular coagulation; FFP, fresh-frozen plasma; HIT, heparin-induced thrombocytopenia; IV, intravenous; LMWH, low-molecular-weight heparin; mAb, monoclonal antibody; NS, normal saline; PO, oral; SC, subcutaneous; UFH, unfractionated heparin.
Data from Schulman S. Clinical practice. Care of patients receiving long-term anticoagulant therapy, *N Engl J Med* 2003 Aug 14;349(7):675-83.

>1000 patients with cancer) revealed a VTE recurrence rate at 12 months of about 8% in the DOAC (edoxaban) arm and about 11% in the LMWH (dalteparin) arm.

Optimal management of VTE recurrence remains uncertain. If a patient is using warfarin with in-range international normalized ratio (INR) or a DOAC for which monitoring is generally unavailable, one should switch to an LMWH. If a LMWH and an anti-FXa level drawn 4 hours after injection is not in the therapeutic range, the dose of LMWH should be adjusted, aiming toward the therapeutic peak anti–FXa level. If the anti-FXa level is therapeutic, one can increase the dose of LMWH by 20%, change to another anticoagulant, or place an IVC filter.[21]

Anticoagulation in Patients with Thrombocytopenia

Mild thrombocytopenia (platelets <50,000/μL) is presented as a relative contraindication for anticoagulation by the American Society of Clinical Oncology and the National Comprehensive Cancer Network despite the lack of data about the risk of anticoagulation in patients with thrombocytopenia. There are, however, fairly consistent data that thrombocytopenia preventing pharmacologic prophylaxis is a critical factor in the large risk of VTE and its recurrence among patients with acute leukemia[22] and after stem cell transplant (SCT).[23]

To address this conundrum, the Subcommittee on Haemostasis and Malignancy for the Scientific and Standardization Committee of the International Society of Thrombosis and Haemostasis has developed consensus guidelines.[24] One recommendation is that patients with chronic thrombocytopenia be given dose-adjusted LMWH, with full-dose LMWH when the platelet count is greater than 50,000/μL; half-dose LMWH when the platelet count is between 25,000 and 50,000/μL; and no anticoagulation when the platelet count is less than 25,000/μL. Such an approach can also be considered for patients with cyclical thrombocytopenia from chemotherapy.

Catheter Thrombosis

Catheter thrombosis may affect almost 50% of patients who have CVCs, although fewer than 5% of catheters are associated with symptomatic occlusive DVTs.[25] In addition to all the other risk factors for DVT development in patients with cancer, the catheter type (peripherally inserted central catheter > centrally inserted catheters > implanted ports) and location (femoral > jugular > subclavian) affect the risk of developing a catheter-related DVT.

There is no evidence that anticoagulation prevents catheter-associated thrombosis, and all guidelines currently recommend against it. The diagnosis and treatment of catheter-associated DVT are, however, similar to the diagnosis and treatment of lower extremity DVTs, with two special considerations. The first is that the catheter can be maintained in place during anticoagulation if it is functional and useful. In this case, therapeutic anticoagulation should be maintained for as long as the catheter is in place. The second is how to manage anticoagulation when a catheter has been removed because it is infected or no longer needed. Clinical guidelines recommend 3 months of anticoagulation after catheter removal.

Bleeding Complications

Bleeding while on anticoagulation is common. During the first 6 months of treatment, about 4% of all patients with cancer will have major bleeding (generally defined as a fall in hemoglobin of 2 g over 24 hours, the need for two units of packed red blood cell transfusion over 24 hours, or bleeding into a body cavity, vital organ or eye), and another 10% will have clinically relevant nonmajor bleeding.[13–18] After the first 6 months, bleeding events decrease, and after 1 year, they appear to remain at a stable level below 1% per year.[13,26]

Bleeding often develops unexpectedly at the beginning of treatment when LMWH unmasks a previously unrecognized bleeding threat.[8] When major bleeding occurs, it is essential to stop anticoagulation, reverse it when appropriate (Table 64–1), and place an IVC filter.

THROMBOTIC MICROANGIOPATHIES

Cancer-associated thrombotic microangiopathies (TMAs) are a group of disorders identified mainly by descriptive clinical characteristics, always involving the presence of circulating schistocytes associated with intravascular hemolysis (elevated lactate dehydrogenase and indirect bilirubin), anemia, thrombocytopenia and when the bone marrow is healthy, elevated reticulocytes. Anemia and thrombocytopenia are the principle clinical manifestations, but there may also be end-organ dysfunction from microvascular thrombosis, particularly in the kidneys. Cancer-associated TMAs are distinguished from disseminated intravascular coagulation (DIC) by normal coagulation studies and D-dimer levels.

Pathogenesis of Cancer-Associated Thrombotic Microangiopathy

The molecular pathogenesis of cancer-associated TMAs is barely understood, and ignorance about pathophysiological mechanisms is coupled to inadequate diagnostic measures and a paucity of effective evidence-based clinical therapeutics. Most of the approaches used derive from those used to manage

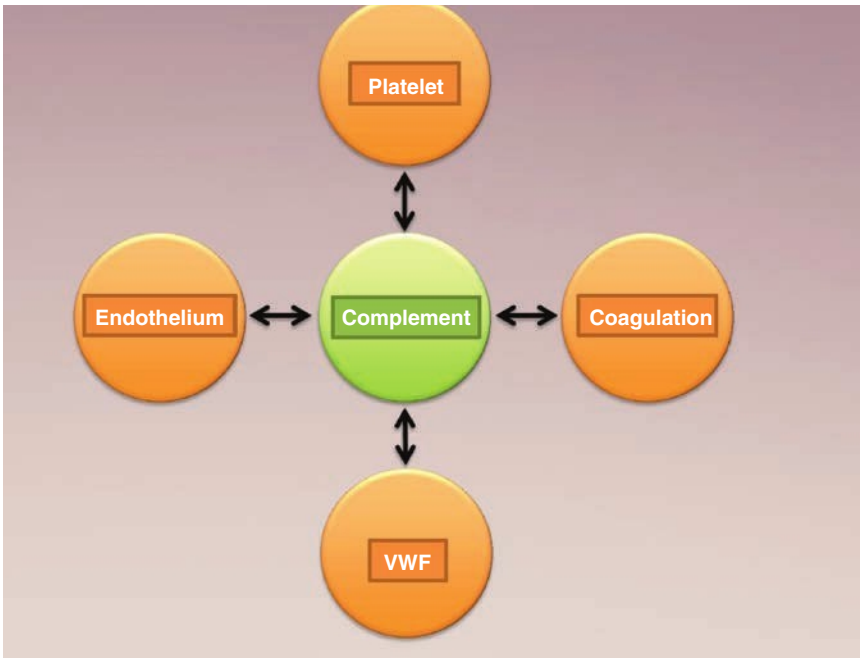


FIGURE 64–1 **Cancer-associated thrombotic microangiopathies represent a pathophysiological nexus involving von Willebrand factor (VWF), platelets, the soluble coagulation system, perturbed vascular endothelium, and the complement system. Identifying and ranking the major predisposing and triggering elements is the clinical challenge that one must confront with each individual case.**

patients with two of the well-characterized TMAs: de novo thrombotic thrombocytopenic purpura (TTP) and hereditary complement-mediated TMA (also referred to as familial atypical hemolytic uremic syndrome [aHUS]).[27] Because some forms of cancer-associated TMA almost certainly result from an overlap of pathophysiological elements present in TTP and complement-mediated TMA (Fig. 64–1), a brief overview of each is presented.

De Novo Thrombotic Thrombocytopenic Purpura

Thrombotic TTP is an autoimmune disorder leading to severely deficient (<10%) activity of the primary von Willebrand factor (VWF) cleaving protease ADAMTS-13 (the 13th member of the protein family designated "a disintegrin and metalloproteinase with thrombospondin-type 1 motif"). Anti-ADAMTS-13 antibodies cause its dysfunction or rapid clearance, and this results in absent cleavage of ultralarge VWF multimers that are synthesized and secreted by vascular endothelium. The ultralarge VWF multimers are excessively adhesive, and when they circulate systemically, they attach to platelet glycoprotein Ib in the microcirculation, leading to in vivo platelet activation and aggregation, microvascular thrombosis, and end-organ ischemia accompanied by microangiopathic hemolytic anemia. This is a hematologic emergency with considerable a mortality rate when it is unrecognized and untreated. Treatment targets the antibody (immune suppression with corticosteroids and urgent plasmapheresis) and restoring normal ADAMTS-13 activity (immediate plasma infusion). Factors separate from ADAMTS-13 def iciency (eg, numerous infections) are involved in triggering the onset and relapse of TTP, suggesting that there is more than a single pathophysiological element driving the development of this TMA.

Complement-Mediated Thrombotic Microangiopathy

aHUS is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and renal impairment. It is distinguished from typical hemolytic uremic syndrome by the absence of infection with Shiga-like toxin-producing bacteria.[28] The most common etiologic element in both inherited and sporadic aHUS is a deficiency of the alternative complement pathway regulatory protein factor H. Factor H binds indirectly to endothelial surfaces and engages C3b, serving as an essential allosteric cofactor for C3b cleavage by factor I. Factor I cleavage of C3b shuts down the proteolytic cascade of complement activation, thereby preventing the formation of the membrane attack complex on intact vascular endothelium. In the absence of factor H, there are unregulated complement activation and deposition of the membrane attack complex on the vascular

endothelium, leading to endothelial injury and its shift from an antithrombotic to a prothrombotic surface. The reason why the renal compartment is the primary target for thrombosis in aHUS is poorly understood, although one hypothesis is that the fenestrated endothelium of the glomerulus makes the kidney particularly vulnerable to complement attack.[28] The aHUS is treated with the anti-C5 antibody eculizumab or ravulizumab.

Cross Talk Between von Willebrand Factor, ADAMTS-13, and Complement

A story relevant to the pathogenesis of cancer-associated TMAs is rapidly developing: recent data indicate that de novo TTP involves complement activation and that aHUS involves abnormalities in the VWF–ADAMTS-13 axis.[29,30] Furthermore, mechanisms of cross talk between these two prototypical pathogenic elements have been identified and include direct interactions between factor H, VWF, and ADAMTS-13. These molecular interactions provide a conceptual framework from which to explore mechanisms of cancer-associated TMAs. Innovations in diagnosis and treatment will only become possible when pathogenic elements can be identified and their clinical significance elucidated and ranked.

Syndromes of Cancer-Associated Thrombotic Microangiopathy

There are rare but predictable clinical associations between TMA and some malignancies and their treatments. These may provide general clarity about pathogenesis, and their recognition often provides a useful management strategy for patients with microangiopathic hemolytic anemia and thrombocytopenia, particularly when the TMA is caused by a drug that can be replaced with an effective alternative agent.

Drugs

Several antineoplastic drugs have been repeatedly associated with TMA.[31] These include mitomycin C, gemcitabine, interferons, pentostatin, sunitinib, bevacizumab, oxaliplatin, and docetaxol. Also, TMA is predictably associated with drugs used routinely in the management of SCT: the calcineurin inhibitors cyclosporine and tacrolimus and the mTOR (mammalian target of rapamycin) inhibitors sirolimus and everolimus. End-organ injury, if it occurs, mainly involves the kidneys and is reversible after stopping the drug.[32]

Hematopoietic Stem Cell Transplantation

At least 3% of all recipients of SCT develop TMA, usually within the first year after SCT.[33] Risk factors include conditioning programs (total-body irradiation, busulfan, fludarabine, and platinum compounds), graft-versus-host disease, infections (especially *Aspergillus*, cytomegalovirus, and adenovirus), and medications (especially calcineurin inhibitors). The pathogenesis of post-SCT TMA focuses primarily on vascular endothelial injury (directly from drugs or irradiation or indirectly by inflammatory cytokines) as the trigger (see Fig. 64–1). Genetic or acquired abnormalities of the VWF–ADAMTS-13 axis or complement are theorized as predisposing factors that drive the development of overt TMA in susceptible individuals suffering a triggering event.

Diagnosis is based mainly on clinical judgement, although there are scoring systems that have been weakly validated.[34] Acute renal failure is the most threatening clinical consequence of post-SCT TMA. Treatment with plasma exchange or any other active intervention is rarely effective, but discontinuing a calcineurin inhibitor can often arrest (and sometimes reverse) kidney injury. The long-term prognosis of post-SCT TMA is unfavorable; there are increased risks of hypertension, chronic kidney disease, end-stage kidney disease, cardiac disease, and death.

Paraneoplastic Thrombotic Microangiopathy

Thrombotic microangiopathy may develop in patients with solid tumors. The most likely development pattern for patients is gastric > breast > prostate > lung > lymphoma > unknown primary cancer. Paraneoplastic TMA almost always develops in patients with bone marrow metastases and can involve a DIC-like coagulation picture. It rarely involves any end-organ injury and appears to be treatable only with effective chemotherapy, although plasma infusion followed by plasma exchange (if needed because of TMA progression despite plasma infusion) is often used along with anticancer therapy.[33,35]

Summary

In patients with cancer, TMAs are a heterogeneous group of diagnoses, almost all of which have common clinical correlates and a final common pathway of microvascular thromboses that threaten or injure the kidneys. Dissecting established pathophysiological elements of de novo TTP (VWF and ADAMTS-13) and aHUS (complement over activity), putative pathophysiological elements of chemotherapy and post-SCT TMA (direct endothelial toxicity and cytokine "storms"), and vague pathophysiological elements of paraneoplastic TMA (myelophthisis and coagulation system activation) may someday allow clinicians to establish diagnostic criteria and treatments that are based on a hierarchy of pathophysiological factors driving each individual case.

VASCULAR SYNDROMES

Chemotherapy-Induced Thrombosis

A number of medications used to treat patients with cancer have been documented to increase the risk of venous thromboembolic events. These are reviewed individually. It is worth noting, however, that the use of any chemotherapeutic agent has consistently been demonstrated to increase thrombotic risk. In 2008, Khorana et al[36] developed a predictive model for chemotherapy-associated thrombosis. In their derivation cohort of 2701 patients, 60 patients (2.2%) developed VTE; of these events, 75% of the VTEs occurred within the first two cycles of chemotherapy. A 2009 review identified systemic chemotherapy as carrying a two- to sixfold increased risk of VTE.[37]

The most common oncologic medications that carry an increased risk of thrombosis include tamoxifen, bevacizumab and other angiogenesis-inhibiting tyrosine kinase inhibitors (TKIs), lenalidomide or its derivatives when combined with steroids or chemotherapy, and L-asparaginase.

Tamoxifen, but not an aromatase inhibitor, raises the risk of thromboembolic events, particularly in the first 3 months of use; its procoagulant effect is amplified by coadministration with chemotherapy.[38] Bevacizumab and other angiogenesis-inhibiting TKIs have been associated with an increase in arterial thrombotic events; there are mixed data on whether the risk of venous thrombotic events is also increased.[39] Mechanistically, it is thought that these drugs disturb the endothelial lining of the vasculature, providing a nidus for thrombus formation. Given the risk for both thrombotic and hemorrhagic complications with these medications, prophylactic anticoagulation is not recommended. Thalidomide and its derivatives (lenalidomide, pomalidomide) increase the risk of VTE when administered in combination with steroids or chemotherapy; the highest risk is when thalidomide is combined with doxorubicin. This is thought to be caused by direct endothelial damage caused by both thalidomide and doxorubicin in addition to alterations in the coagulation cascade.[8] Thalidomide alone does not raise the risk of VTE. Patients with multiple myeloma treated with combination therapy containing thalidomide have a risk of VTE approaching 20%. Therefore, pharmacologic VTE prophylaxis is indicated with aspirin, LMWH, or warfarin. The Myeloma Working Group has proposed a risk stratification model, including factors such as obesity, recent surgery, history of VTE, and type of therapy (thalidomide combined with high-dose dexamethasone, doxorubicin, or multiagent cytotoxic chemotherapy) to determine which agent to use for VTE prophylaxis. Patients with no or one risk factor should receive aspirin (81 or 325 mg), and patients with two or more risk factors should receive LMWH (enoxaparin 40 mg subcutaneous daily).[40] L-asparaginase is often used to treat adult acute lymphoblastic lymphoma. Its use carries a small risk of arterial thrombosis but a large risk of VTE (up to one third of patients). The mechanism of these effects may be caused by decreased synthesis of the natural anticoagulant protein antithrombin.[41]

Myeloproliferative Neoplasm–Associated Thrombosis with Attention to Portal Vein Thrombosis and Budd-Chiari Syndrome

The Philadelphia chromosome–negative myeloproliferative neoplasms (Ph^- MPNs), including polycythemia vera (PV), essential thrombocytosis (ET), and primary myelofibrosis (PMF), are clonal disorders of myeloid lineage stem cells associated with *JAK2*, *MPL*, or *CALR* mutations. These disorders carry an increased risk of both arterial and venous thrombotic events, as well as increased risk of hemorrhagic events. The mechanism of thrombophilia in Ph^- MPN is complex. Proposed factors include increased total volume of erythrocytes, activated or adhesive platelets and erythrocytes, inflammation leading to endothelial damage, inhibition of anticoagulant pathways, and secretion of procoagulant factors.[42] Thrombotic events contribute significantly to disease-specific morbidity and mortality, causing 45% of all disease-specific fatal events.[43] Venous thrombosis in an unusual location (ie, portal vein thrombosis [PVT]) may be the presenting symptoms of Ph^- MPN, and *JAK2* mutation testing should be strongly considered in a patient presenting with a first thrombosis in an unusual location.[44]

A number of studies have sought to stratify patients with PV and ET into those with high- versus low-risk of thrombotic events, with conflicting results. Patients older than age 60 years or with a history of thrombosis are considered high risk. High-risk patients should be managed with low-dose aspirin, phlebotomy to a goal hematocrit of less than 45%, and cytoreduction with hydroxyurea or interferon alpha to normalize platelet count (for ET) or if phlebotomy alone is unable to produce the target hematocrit level (for PV).[45] Additional factors to be considered in evaluating the individual patient include *JAK2* mutation status and allele burden, leukocytosis, inflammatory markers, and any history of bleeding, particularly the presence of an acquired von Willebrand syndrome. Traditional risk factors for arterial and venous thrombotic events (smoking, hyperlipidemia, and diabetes and immobility, respectively) should be managed aggressively. The role of ruxolitinib and other *JAK* inhibitors in the prevention of thrombotic events is uncertain at this time.[46]

Management of the acute VTE in a patient with Ph^- MPN includes anticoagulation with LMWH, heparin, fondaparinux, warfarin, or a DOAC.[47,48] The duration

of anticoagulation remains controversial; a minimum of 3 to 6 months is required, with longer duration to be guided by the clinician's estimate of risk of recurrence. Risk of recurrence is influenced by MPN disease burden, advanced age, and prior history of VTE. Bleeding complications must also be considered. If the decision is made to continue anticoagulation beyond 6 months, the risk and benefit of anticoagulation should be reassessed frequently. Aggressive management of the MPN, with attention to achieving goal complete blood cell count values, is an integral component of the management of VTE in the patient with MPN. Concurrent use of anticoagulation and antiplatelet therapy increases the risk of bleeding events.[49] After VTE, monotherapy with an antiplatelet agent reduces the risk of both recurrent venous and arterial events; therefore, a reasonable course of action for the patient with MPN and a new VTE is 3 to 6 months of LMWH followed by long-term low-dose aspirin with optimal cytoreduction. Patient-specific factors (a life-threatening VTE or life-threatening bleeding) must always be considered.

As noted, the diagnosis of MPN may be heralded by development of a VTE in an unusual location, including the portal vein or the hepatic vein; the latter may result in venous congestion and hepatocyte damage (Budd-Chiari syndrome). The management of PVT is dictated by the acuity of the thrombus. Acute PVT, in which symptoms precede the diagnosis of PVT by less than 60 days and there is no evidence of cirrhosis, is managed with therapeutic anticoagulation. The diagnosis is made with abdominal ultrasound, which has a 90% negative predictive value.[50] Patients with chronic PVT should not be anticoagulated because the likelihood of recanalization of the blood vessel in this setting is low, and the sequelae of PVT-related portal hypertension (gastric and esophageal varices) increase the risk of life-threatening bleeding with anticoagulation. Making the diagnosis of MPN at the time of chronic PVT diagnosis may be hindered by portal hypertension causing GI blood loss or hypersplenism, resulting in platelet sequestration, falsely suppressing hematocrit and platelet levels; a high index of suspicion is required.

Budd-Chiari syndrome can be classified as fulminant, acute, subacute, or chronic. Unless there are clear contraindications, anticoagulation should be started promptly on diagnosis and continued indefinitely. Although a stepwise approach is warranted with medical management alone first, a number of interventions for patients with MPN-associated Budd-Chiari syndrome are available including endovascular stenting, transjugular intrahepatic portosystemic shunt, and even orthotopic liver transplant for patients with good-prognosis ET and PV.[50]

Paroxysmal Nocturnal Hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hematopoietic clonal disorder caused by mutation of the PIGA gene, leading to a deficiency of a glycosyl phosphatidylinositol anchor for several proteins, including the natural anticomplement proteins CD55 (membrane inhibitor of reactive lysis) and CD59 (decay accelerating factor).[51] This leads to chronic nonimmune intravascular hemolysis caused by complement activation on the red cell surface. It is diagnosed by blood flow cytometry revealing CD55 and CD59 deficiency on leukocytes and erythrocytes. PNH is associated with cytopenias from bone marrow failure. All patients with PNH have some degree of marrow failure, and about 50% of patients with aplastic anemia and 20% of patients with low-risk myelodysplastic syndrome have detectable CD55- and CD59-deficient blood cells. Thrombosis, particularly thrombosis in unusual sites, including cerebral venous thrombosis, portal venous thrombosis, and hepatic vein thrombosis, is common in patients with PNH, preceding the diagnosis in almost 10% of patients and developing during the course of the disease in about one third of all patients.[52] Management of acute thrombosis is routine anticoagulation, adding anticomplement therapy with eculizumab or ravulizumab for patients with clinically significant hemolysis. Anticoagulation should be continued indefinitely until the patient receives a SCT that eliminates the PIGA mutated clone.

Trousseau Syndrome

Trousseau's sign is the appearance of superficial thrombophlebitis heralding the diagnosis of malignancy, named after the French physician Armand Trousseau, who noted the phenomenon in 1865. Trousseau syndrome is used more broadly to describe the hypercoagulable state associated with malignancy, often described as low-grade DIC. The pathogenesis of Trousseau syndrome is multifactorial and likely to involve all three components of Virchow's triad (stasis of blood flow, activation of the coagulation cascade, and damage to endothelial cells of the blood vessel).[51,52] Mouse models of MET oncogene-driven hepatocellular carcinoma have demonstrated a relationship between MET-driven malignancies and the development of a thrombohemorrhagic phenotype similar to Trousseau syndrome, mediated by cyclooxygenase-2 and plasminogen activator type 1 genes.[53] When Trousseau syndrome appears to be causing microvascular thrombosis with digital, nasal, or earlobe ischemia, low-dose UFH or LMWH may be beneficial.[54]

ARTERIAL THROMBOSIS

Coronary Artery Disease

The management of patients with malignancy-associated thrombocytopenia and acute coronary syndrome

(ACS) poses a unique challenge; the cardioprotective effect of antiplatelet agents must be balanced with the increased risk of bleeding. Two retrospective analyses with a total of 188 patients with thrombocytopenia demonstrated marked improvement in 7-day survival when they received aspirin. Platelet counts in the thrombocytopenic groups ranged from 4000 to 100,000/μL, and no major bleeding events (defined as major GI bleeding, intracranial bleeding, or fatal bleeding) were reported.[55,56] In an appropriately monitored setting and in the absence of clear contraindications, aspirin should not be withheld from patients with malignancy-associated thrombocytopenia and ACS.

Atrial Fibrillation

There appears to be an increased risk of nonvalvular atrial fibrillation for patients with cancer: among all Danes older than 18 years, the incidence of atrial fibrillation was 17.4 per 1000 persons per year among patients with cancer versus 3.7 per 1000 persons per year among noncancer persons.[57] The reasons for this are not clear. Alleged reasons include treatment-induced effects, such as the familiar toxicities of mediastinal irradiation, anthracyclines, trastuzumab, and ibrutinib; heart trauma from surgery, such as lung cancer or esophageal cancer surgery; and recognition bias as the diagnosis of cancer brings individuals under more intense clinical scrutiny.[58] To date, there is no evidence that treatment of cancer-associated atrial fibrillation is associated with worse outcomes: the risk of thromboembolic stroke and anticoagulation-related bleeding appears similar in patients with and without cancer,[58] and cancer patients with atrial fibrillation treated with DOACs had rates of thromboembolism similar to those treated with warfarin with a lower risk of bleeding, including intracranial bleeding.[59]

MD ANDERSON PRACTICE TIPS

- A LMWH such as enoxaparin 40 mg SC or dalteparin 5000 units SC should be give once per day for 28 days to patients receiving abdominal or pelvic cancer surgery.
- These same LMWHs or rivaroxaban 10 mg PO every day can be given to nonsurgical cancer patients who are hospitalized. LMWH is used during hospitalization, but rivaroxaban is extended post discharge for a total of ~ 35 days.
- Consider using thromboprophylaxis with apixaban 2.5 mg PO BID or rivaroxaban 10 mg PO once per day for 6 months to prevent VTE in outpatients receiving treatment for pancreatic cancer, gastric cancer, glioblastoma multiforme, and breast cancer beginning a selective estrogen receptor modulator.
- Cancer-associated VTE can be treated with a DOAC, although edoxaban and rivaroxaban should be avoided in patients with any luminal GI or GU malignancies.
- Patients with thrombocytopenia can be given dose-adjusted anticoagulation, with full-dose anticoagulation when the platelet count is greater than 50,000/μL, half-dose when the platelet count is between 25,000 and 50,000/μL, and no anticoagulation when the platelet count is less than 25,000/μL.
- Patients with myeloproliferative disorder–associated acute splanchnic vein thrombosis should be treated with routine anticoagulation.

REFERENCES

1. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. *Blood*. 2013;122:1712-1723.
2. Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med*. 2003;349:146-153.
3. Stein PD, Beemath A, Meyers FA, et al. Pulmonary embolism as a cause of death in patients who died of cancer. *Am J Med*. 2006;119:163-165.
4. Khorana AA, Francis CW, Culakova E, et al. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J Thromb Haemost*. 2007;5:632-634.
5. ten Wolde M, Kraaijenhagen RA, Prins MH, et al. The clinical usefulness of D-dimer testing in cancer patients with suspected deep venous thrombosis. *Arch Intern Med*. 2002;162:1880-1884.
6. Di Nisio M, Lee AYY, Carrier M, et al. Diagnosis and treatment of incidental venous thromboembolism in cancer patients: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2015;13:880-883.
7. Agnelli G, Becattini C. Acute pulmonary embolism. *N Engl J Med*. 2010;363:266-274.
8. Key NB, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO Clinical Practice Guideline update. *J Clin Oncol*. 2020;38:496-520.
9. Cohen AT, Spiro TE, Büller HR, et al. Rivaroxaban for thromboprophylaxis after hospitalization for acute medical illness, *New Engl J Med*. 2013;368:513-523. Bergqvist D, Agnelli G, Cohen AT, et al.
10. Bergqvist D, Agnelli G, Cohen AT, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. *N Engl J Med*. 2002;346:975-980.
11. Connor JM. Prophylaxis against venous thromboembolism in ambulatory patients with cancer. *N Engl J Med*. 2014;370:2515-2519.
12. Kraaijpoel N, Bleker SM, Meyer G, et al. Treatment and long-term clinical outcomes of incidental pulmonary embolism in patients with cancer: an international prospective cohort study. *J Clin Oncol*. 2019;37:1713-1720.
13. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med*. 2018;378:615-624.
14. Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). *J Clin Oncol*. 2018;36:2017-2023.
15. Costa OS, Kohn CG, Kuderer NM, et al. Effectiveness and safety of rivaroxaban compared with low-molecular-weight heparin in cancer-associated thromboembolism. *Blood Adv*. 2020;4:4045-4051.
16. Wysokinski WE, Houghton DE, Casanegra AI, et al. Comparison of apixaban to rivaroxaban and enoxaparin in acute cancer-associated venous thromboembolism. *Am J Hematol*. 2019;11:1185-1192.
17. Kraaijpoel N, Di Nisio M, Mulder FI, et al. Clinical impact of bleeding in cancer-associated venous thromboembolism: results from the Hokusai VTE Cancer study. *Thromb Haemost*. 2018;118:1439-1449.
18. Agnelli G, Becattini C, Meyer G, at al. Apixaban for the treatment of venous thromboembolism associated with cancer. *N Engl J Med*. 2020;382:1599-1607.
19. Huang SY, Odisio BC, Sabir SH, et al. Development of a predictive model for 6 month survival in patients with venous thromboembolism and solid malignancy requiring IVC filter placement. *J Thromb Thrombolysis*. 2017;44:30-37.
20. Lee AYY, Kamphuisen PW, Meyer G, et al. A randomized trial of long-term tinzaparin, a low molecular weight heparin, versus warfarin for treatment of acute venous thromboembolism (VTE) in cancer patients—the CATCH study. *JAMA*. 2015;314:677-686.
21. Carrier M, Khorana AA, Zwicker J, et al. Management of challenging cases of patients with cancer-associated thrombosis including recurrent thrombosis and bleeding: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2013;11:1760-1765.
22. Vu K, Luong NV, Hubbard J, et al. A retrospective study of venous thromboembolism in acute leukemia patients treated at the University of Texas MD Anderson Cancer Center. *Cancer Med*. 2015;4(1):27-35.
23. Gerber DA, Segal JB, Levy MY, et al. The incidence of and risk factors for venous thromboembolism (VTE) transplantation: implications for VTE prevention and bleeding among 1514 patients undergoing hematopoietic stem cell transplantation. *Blood*. 2008;112:504-510.
24. Bannow BTS, Lee A, Khorana AA, et al. Management of cancer-associated thrombosis in patients with thrombocytopenia: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2018;16:1246-1249.
25. Geerts W. Central venous catheter-related thrombosis. *Hematology Am Soc Hematol Educ Program*. 2014;2014(1):306-311.
26. Chee CE, Ashrani AA, Marks RS, et al. Predictors of venous thromboembolism recurrence and bleeding among active cancer patients: a population-based cohort study. *Blood*. 2014;123:3972-3978.
27. George JN, Nester CM. Syndromes of thrombotic microangiopathy. *N Engl J Med*. 2014;371:654-666.
28. Noris M, Remuzzi G. Atypical hemolytic-uremic syndrome. *N Engl J Med*. 2009;361:1676-1687.
29. Feng S, Liang X, Cruz MA, et al. The interaction between factor H and Von Willebrand factor. *PLoS One*. 2013;8(8):e73715.
30. Feng S, Liang X, Kroll MH, et al. Von Willebrand factor is a cofactor in complement regulation. *Blood*. 2015;125(6):1034-1037.
31. Al-Nouri ZL, Reese JA, Terrell DR, et al. Drug-induced thrombotic microangiopathy: a systematic review of published reports. *Blood*. 2015;125(4):616-618.
32. Jhaveri KD, Shah HH, Calderon K, et al. Glomerular diseases seen with cancer and chemotherapy: a narrative review. *Kidney Int*. 2013;84:34-44.
33. Masias C, Vasu S, Cataland SR. None of the above: thrombotic microangiopathy beyond TTP and HUS. *Blood*. 2017;129:2857-2863.
34. Epperla N, Li A, Logan B, at al. Incidence, risk factors for and outcomes of transplant-associated thrombotic microangiopathy. *Br J Haematol*. 2020;189(6):1171-1181.
35. Lechner K, Obermeier HL. Cancer-related microangiopathic hemolytic anemia: clinical and laboratory features in 168 reported cases. *Medicine (Baltimore)*. 2012;91:195-205.
36. Khorana AA, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood*. 2008;111(10):4902-4907.
37. Khorana AA, Connolly GC. Assessing risk of venous thromboembolism in the patient with cancer. *J Clin Oncol*. 2009;27(29):4839-4847.
38. Walker AJ, West J, Card TR, et al. When are breast cancer patients at highest risk of venous thromboembolism? A cohort study using English health care data. *Blood*. 2016;127:849-857.
39. Zangari M, Fink LM, Elice F, et al. Thrombotic events in patients with cancer receiving antiangiogenesis agents. *J Clin Oncol*. 2009;27(29):4865-4873.
40. Palumbo A, Rajkumar SV, Dimopoulos MA, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. *Leukemia*. 2008;22:414-423.

41. Truelove E, Fielding AK, Hunt BJ. The coagulopathy and thrombotic risk associated with L-Asparaginase treatment in adults with acute lymphoblastic leukaemia. *Leukemia*. 2013;27:553-559.
42. Kroll MH, Michaelis LC, Verstovsek S. Mechanisms of thrombogenesis in polycythemia vera. *Blood Rev*. 2015;29:215-221.
43. Marchioli R, Finazzi G, Landolfi R, et al. Vascular and neoplastic risk in a large cohort of patients with polycythemia vera. *J Clin Oncol*. 2005;23(10):2224-2232.
44. Abbattista M, Capecchi M, Martinelli I. Treatment of unusual thrombotic manifestations. *Blood*. 2020;135:326-334.
45. Stein B, Martin K. From Budd-Chiari syndrome to acquired von Willebrand syndrome: thrombosis and bleeding complications in the myeloproliferative neoplasms. *Blood*. 2019;134(22):1902-1911.
46. Masciulli A, Ferrari A, Carobbio A, et al. Ruxolitinib for the prevention of thrombosis in polycythemia vera: a systematic review and meta-analysis. *Blood Adv*. 2020;4:380-386.
47. Naymagon L, Tremblay D, Zubizarreta N. The efficacy and safety of direct oral anticoagulants in noncirrhotic portal vein thrombosis. *Blood Adv*. 2020;4:655-666.
48. Sant'Antonio E, Guglielmelli P, Pieri L, et al. Splanchnic vein thromboses associated with myeloproliferative neoplasms: an international, retrospective study on 518 cases. *Am J Hematol*. 2020;95:156-166.
49. De Stefano V, Za T, Rossi E, et al. Recurrent thrombosis in patients with polycythemia vera and essential thrombocythemia: incidence, risk factors, and effect of treatments. *Haematologica*. 2008;93(3):372-380.
50. Menon KV, Shah V, Kamath PS. The Budd-Chiari syndrome. *N Engl J Med*. 2004;350(6):578-585.
51. Parker CJ. Update on the diagnosis and management of paroxysmal nocturnal hemoglobinuria. *Hematology Am Soc Hematol Educ Program*. 2016;2016:208-216.
52. Griffin M, Munir T. Management of thrombosis in paroxysmal nocturnal hemoglobinuria: a clinician's guide. *Ther Adv Hematol*. 2017;8:119-126.
53. Dammacco F, Vacca A, Procaccio P, et al. Cancer-related coagulopathy (Trousseau's syndrome): review of the literature and experience of a single center of internal medicine. *Clin Exp Med*. 2013;13(2):85-97.
54. Varki A. Trousseau's syndrome: multiple definitions and multiple mechanisms. *Blood*. 2007;110(6):1723-1729.
55. Boccaccio C, Sabatino G, Medico E, et al. The MET oncogene drives a genetic programme linking cancer to haemostasis. *Nature*. 2005;434(7031):396-400.
56. Ortel TL, Erkan D, Kitchens CS. How I treat catastrophic thrombotic syndromes. *Blood*. 2015;126:1285-1293.
57. Sarkiss MG, Yusuf SW, Warneke CL, et al. Impact of aspirin therapy in cancer patients with thrombocytopenia and acute coronary syndromes. *Cancer*. 2007;109(3):621-627.
58. Feher A, Kampaktsis PN, Parameswaran R, et al. Aspirin Is associated with improved survival in severely thrombocytopenic cancer patients with acute myocardial infarction. *Oncologist*. 2017;22:213-221.
59. Jakobsen CB, Lamberts M, Carlson N, et al. Incidence of atrial fibrillation in different major cancer subtypes: a nationwide population-based 12 year follow up study. *BMC Cancer*. 2019;19:1105.
60. Chu G, Versteeg HH, Verschoor AJ, et al. Atrial fibrillation and cancer—an unexplored field in cardiovascular oncology. *Blood Rev*. 2019;35:59-67.
61. Olesen KKW, Wheeler M, Eikelboom JW. Oral anticoagulant treatment in patients with atrial fibrillation and cancer. *Thromb Haemost*. 2020;120:194-196.
62. Schulman S, Bijsterveld NR. Anticoagulants and their reversal. *Transfus Med Rev*. 2007;21(1):37-48.
63. Rodgers GM. Prothrombin complex concentrates in emergency bleeding disorders. *Am J Hematol*. 2012;87(9):898-902.
64. Bhagirath VC, O'Malley L, Crowther MA. Management of bleeding complications in the anticoagulated patient. *Semin Hematol*. 2011;48(4):285-294.
65. Crowther MA, Berry LR, Monagle PT, Chan AK. Mechanisms responsible for the failure of protamine to inactivate low-molecular-weight heparin. *Br J Haematol*. 2002;116(1):178-186.
66. Schulman S. Clinical practice. Care of patients receiving long-term anticoagulant therapy. *N Engl J Med*. 2003 Aug 14;349(7):675-683.
67. Piran S, Schulman S. Bleeding complications in patients on anticoagulant therapy. *Blood*. 2019;133:425-435.
68. Pollack CV, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal—full cohort analysis. *N Engl J Med*. 2017;377:431-441.

Section XIV

Supportive and Palliative Care

Section Editor: Eduardo Bruera

65 Inpatient Supportive and Palliative Care

66 Integrated Outpatient Supportive Care

67 Rehabilitation

68 Pain Management and Symptom Control

This page intentionally left blank

65

Inpatient Supportive and Palliative Care

Ahsan Azhar
Ali Haider
Eduardo Bruera

KEY CONCEPTS

- Inpatient palliative or supportive care service is an interdisciplinary team of palliative care providers, including a physician, counselor, chaplain, social worker, pharmacist, palliative care nurses, and many others, who provide an integrated model of care to advanced cancer patients alongside the oncology teams.
- Supportive care consultation can help identify and manage complex symptom issues like missed delirium and refractory pain in patients with advanced cancer, as well as psychosocial, emotional, and spiritual distress, while reducing the amount of opioids and other psychotropic agents (polypharmacy).
- Early integration of supportive care has improved patient-reported outcomes and discharge outcomes, including an intensive care unit and overall hospital mortality, without increasing length of stay.
- An acute palliative and supportive care unit (PSCU) at a tertiary care hospital is different from an acute inpatient hospice facility, because patients with a prognosis of more than six months can be admitted to a PSCU for the management of physical symptoms and the psychosocial, emotional, and spiritual distress for both the patient and their family.
- An acute PSCU not only provides clinical care and education to the patient and family but also provides opportunities for education of the different disciplines involved in the patient's care as well as research geared toward improving the quality of life of patients, family, caregivers, and care providers.
- The supportive care team, when part of the care continuum, can proactively assist with early identification and clarification of goals of care and completion of advanced-care directives, as well as provide a smoother transition and/or discharge plan for patients with advanced cancer.
- An overwhelming majority of patients with cancer, as well as junior oncology colleagues, feel that they benefit from the integration of an interdisciplinary palliative and supportive care team.

Patients with advanced illnesses such as cancer often experience high physical and psychological symptoms that can affect them throughout the trajectory of their disease.[1–3] The literature has shown that patients with advanced cancer experience an average of 8 to 12 symptoms, suggesting that many symptoms are not recognized by their treating teams and often remain untreated.[1,4] In addition to physical and psychological needs, patients and caregivers often struggle with decision making.[4] Provision of specialized palliative and supportive care services has improved patients' physical, psychosocial, and spiritual well-being.[5–9] The World Health Organization has defined palliative care as:

"An approach that improves the quality of life of patients and their families facing the problem associated with a life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual. … Palliative care is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to understand better and manage distressing clinical complications."[10]

In the last few decades, palliative care has emerged as an interdisciplinary team specialty with expertise in complex symptom management, psychosocial

care, communication, complex decision making, and transition of care.[5] Despite mounting evidence on the effectiveness of palliative care services, the referral of patients often occurs late in their disease trajectory.[5,11] One crucial reason for late referrals is the misconception of palliative care as "end-of-life care"; therefore, oncologists are often reluctant to refer to preserve patients' hopes.[12,13] However, current evidence suggests that palliative care can function along with the oncologic care for improving quality of life.[8,9,14] To overcome some of these barriers, the term "supportive care" instead of palliative care has improved oncologists' comfort to refer patients early in the disease trajectory.[15–17]

MODELS OF PALLIATIVE CARE DELIVERY

Specialist palliative care is delivered by different models of care such as outpatient palliative care, inpatient palliative care that functions as consultative, acute palliative and symptom management units, community-based palliative care services, and hospice care.[5] These models have different structures, processes, location of services, and patient populations (Fig. 65–1).[5] In this chapter, we will discuss different inpatient palliative and supportive care structures, processes, and outcomes.

STRUCTURE AND PROCESSES OF INPATIENT PALLIATIVE AND SUPPORTIVE CARE SERVICES

Inpatient palliative and supportive care is the most prevalent model of palliative care service and is usually delivered in acute care hospitals.[5,18] In the United States, approximately 90% of the National Cancer Institute–designated centers have dedicated inpatient palliative care teams, and up to 56% of non–NCI-designated cancer centers have such services. A palliative care consultant team—including physicians, advanced practice providers, nurses, and members of the psychosocial

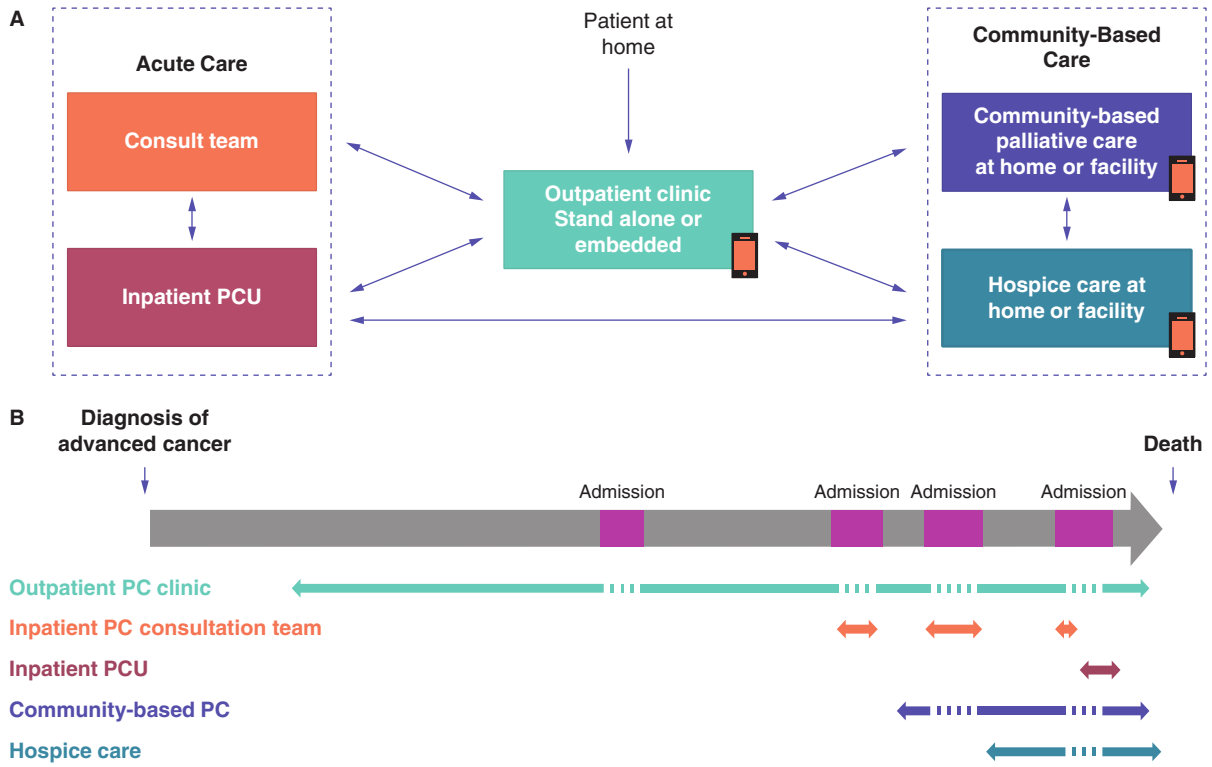


FIGURE 65–1 **Service models of specialist palliative care (PC). A. Care anywhere. Outpatient clinics facilitate access to palliative care in the ambulatory setting while coordinating care with the other models of PC. Inpatient consultation teams and PC units (PCUs) are available at acute care facilities, whereas community-based PC and hospice care allow patients to be cared for in the ambulatory and community setting. The smartphone icon indicates telehealth outreach. B. Care anytime. This figure highlights how the five service models complement one another to provide a comprehensive PC along the entire disease continuum for patients and their families. The arrows indicate the general time frame of patient engagement. (Reproduced with permission from Hui D, Bruera E. Models of Palliative Care Delivery for Patients With Cancer, *J Clin Oncol* 2020 Mar 20;38(9):852-865).**

team such as counselors, psychologists, and social workers—delivers this model of palliative care.[5] Access to palliative care teams in certain centers is available as inpatient consultation as well as outpatient, which provides opportunities for early referral.[19] Despite all this, patients continue to be referred to palliative care in low numbers and late in the trajectory of illness, at an average of 30 to 60 days before death.[19,20] Late referrals often undermine the ability of the palliative care interdisciplinary team to intervene, especially among patients with high symptom burden and caregivers' distress.[20] In a recent retrospective study, Heung et al examined 7322 patients who were referred to inpatient palliative care for the first time; 154 (2%) died within the 24 hours of referral but were found to have a significant amount of distress, indicating a missed opportunity for earlier palliative care intervention.[21]

OUTCOMES OF INPATIENT PALLIATIVE AND SUPPORTIVE CARE SERVICES

Inpatient palliative and supportive care consultation can help identify and manage complex symptom issues like missed delirium and refractory pain in patients with advanced cancer, as well as psychosocial, emotional, and spiritual distress, while reducing the amount of opioids and other psychotropic agents (polypharmacy).[7,22–24] In a recent study of 536 hospitalized patients with cancer, 239 (45%) who received timely palliative care had significantly less chemotherapy in the last two weeks of life and considerably fewer admissions to intensive care units (ICUs) in the last month of life.[25] Delgado et al compared 200 patients with advanced cancer who received palliative care services from the emergency center with those who received palliative care services during inpatient stay; patients who received palliative care had significantly earlier control of their symptoms and a shorter length of stay.[6] In the last decade, several randomized controlled trials have been conducted to examine the benefits of inpatient palliative care.[5,26,27] Grudzen et al examined hospitalized patients with advanced cancer who received palliative care versus the control group and found that the palliative care group was associated with significant improvement of quality of life at 12 weeks compared with the usual care.[26] Although the trend favored the palliative care group, no statistically significant difference was found in secondary outcomes such as rates of depression, ICU admissions, hospice discharge, and overall survival.[26]

Literature has highlighted the benefits of early integration of palliative care with standard transplant care among patients with hematologic care.[14,27] In a recent nonblinded, randomized clinical trial among 160 patients undergoing autologous/allogeneic stem cell transplant, El-Jawahri et al found that patients who received twice-weekly inpatient palliative care reported a smaller decrease in quality of life at two weeks post-transplant versus those who received standard care.[27] Moreover, patients in the concurrent care arm reported lower anxiety, less increase in depression, and less increase in overall symptom burden.[27] Patients' caregivers also reported significantly less depression and post-traumatic stress disorder at 6 months post-transplantation.[28]

According to the American Society of Clinical Oncology clinical practice guidelines, patients with advanced cancer and/or high symptom burden should be considered for a referral to an interdisciplinary palliative care team early in their disease trajectory concurrent with active cancer treatment.[29] More research is needed to find an optimal model of integration of early palliative care among hospitalized patients for symptom management, complex decision making, and survivorship care.

INPATIENT PALLIATIVE AND SUPPORTIVE SERVICE AT MD ANDERSON

Palliative and supportive care services at the MDACC was established 20 years ago and has seen constant growth in its clinical activity, including the inpatient model of delivery.[30] In recent years, most of the patients were initially consulted at the outpatient or inpatient non-ICU setting.[30] It is reassuring that a very low proportion of patients were consulted at the ICU setting, which is generally considered a late referral.[30] From 2011 to 2017, the proportion of first-time referral in the ICU setting has decreased from 2.3% in 2011 to 1% in 2017 versus the non-ICU setting from 97.7% in 2011 to 98% in 2017 ($P < .01$).[30] Unfortunately, despite the continued growth seen in many centers, the existing infrastructure is unable to accommodate universal referral of all hospitalized patients, especially in the oncologic setting.[5,18] The Center to Advance Palliative Care has published several criteria for referral of patients to inpatient palliative care (Table 65–1).[18] These criteria can serve as a general guideline to decide whether patients will benefit from palliative care integration.

HISTORY AND BACKGROUND OF THE INPATIENT PALLIATIVE CARE UNIT

Cicely Saunders, a nurse and a social worker who became a physician, having worked with patients with advanced cancer treating their pain and other symptoms from 1957

Table 65–1 Referral Criteria for Inpatient Palliative Care Consultation Teams for Patients with a Life-Limiting or Life-Threatening Condition

Primary Criteria[a]	Secondary Criteria[b]
The surprise question: You would not be surprised if the patient died within 12 months or before adulthood	Metastatic or locally advanced incurable cancer
Frequent admissions (eg, more than one admission for the same condition within several months)	Admission from long-term care facility or medical foster home
Admission prompted by difficult-to-control physical or psychological symptoms (eg, moderate to severe symptom intensity for 24–48 hours)	Elderly patient, cognitively impaired, with acute hip fracture
Complex care requirements (eg, functional dependency; complex home support for ventilator, antibiotics, and feedings)	Long-term home oxygen use
Decline in function, feeding intolerance, or unintended decline in weight (eg, failure to thrive)	Out-of-hospital cardiac arrest
	Current or past hospice program enrollee
	Limited social support (eg, family stress, chronic mental illness)
	No history of completing an advanced-care planning discussion/document

[a]Global indicators that represent the minimum that a hospital should use to screen patients at risk for unmet palliative care needs.
[b]More specific indicators of a high likelihood of unmet palliative care needs and should be incorporated into a systems-based approach to patient identification if possible.
Data from Weissman DE, Meier DE. Identifying patients in need of a palliative care assessment in the hospital setting: a consensus report from the Center to Advance Palliative Care, *J Palliat Med* 2011 Jan;14(1):17-23.

to 1967 at St. Joseph's Hospice, laid the foundation of the St. Christopher's Hospice in London in 1967. Saunders appreciated the importance of teaching and research in the hospice care setting and, on her advice, in 1974, Florence Ward, then the dean of the School of nursing at Yale University in New Haven, Connecticut, founded the Connecticut hospice.[31]

During the same time, the first hospital-based palliative care service was founded by a Urology Surgeon, Dr Balfour Mount, in 1974. This was part of the research and teaching structure at the Royal Victoria Hospital of McGill University in Montréal, Canada. Dr Mount was the first to use the term *palliative care*,[32] demonstrating the value of a hospital-based palliative care service, which he called the "palliative care unit." Its primary purpose at that time was to perform research and education for control of symptoms, mainly pain. Following the same model of inpatient palliative care in 1974, St Luke's Hospital in New York City created a working palliative consultation team.[31]

THE ACUTE PALLIATIVE AND SUPPORTIVE CARE UNIT AND HOW IT DIFFERS FROM A HOSPICE INPATIENT UNIT

An acute palliative and supportive care unit (PSCU) in a hospital setting (also known as a tertiary care Palliative Unit) differs in many ways from an inpatient hospice care unit. The main distinction is its being designed for the care of distressed patients with an advanced illness like cancer with poor prognosis (perhaps terminal; however, meaning more than six months and not necessarily actively dying patients).[33] It is a hospital inpatient facility with designated beds, where care is provided by a highly specialized interdisciplinary team lead by a palliative care physician (who works in conjunction with an inpatient palliative care program, including a consultation team with or without an outpatient clinic).[34,35]

The unit is considered an interdisciplinary care unit to meet the needs of patients and families while addressing complex problems: physical, psychosocial, and spiritual. It offers a full range of diagnostic and interventional procedures geared toward palliation of symptoms while providing access to different support services and specialty and subspecialty consultations. A *Do Not Resuscitate* (DNR) order may not be a prerequisite for admission to such a unit. However, it is of utmost importance to have clarity of goals of care between all parties involved about the intent and duration of the interventions being offered.

OBJECTIVES OF AN ACUTE PALLIATIVE AND SUPPORTIVE CARE UNIT

At its core, a PSCU is primarily a unit for clinical care of distressed patients[36] and families. Its primary role is to assess and treat the most complex patients with advanced cancer, considered terminal in most cases, with and without complex family dynamics (whole-person care). It may involve challenging discharge planning near the end of life.

Another critical role of such a unit is the education of physicians and other disciplines, along with research aimed at the identification and management

of complex situations in such patients. The role of an interdisciplinary team to care for this patient population is of paramount importance.

GUIDELINES FOR ADMISSION TO AN INPATIENT PALLIATIVE AND SUPPORTIVE CARE UNIT

The following two main categories of patients comprise the vast majority of patients with advanced illness, along with their families (Fig. 65–2). They may be candidates for transfer to the PSCU. They are mostly near the end of life (with advanced, refractory cancer with limited or no anticancer treatments available) but are not necessarily actively dying. These include patients and family members who are:

1. Extremely distressed, with refractory symptoms near the end of life.
2. Facing difficulty in transitioning to comfort or end-of-life care

The PSCU serves to control their special (and complex) symptoms and counseling needs. These patients and their families need to accept the role that the PSCU fulfills so that the problem of unfulfilled expectations is not created (ie, the focus of the PSCU is not to treat cancer but increase the quality of life and comfort of the patient and assist the family in coping). In addition, such patients with advanced cancer at the end of life do not benefit from attempts at resuscitation, so that "no CPR" (a DNR) would be appropriate. They do not have to agree to go to hospice; however, it may be helpful to explain that this is usually the option recommended for such patients.

3. The third category is a small, select groups of patients who are early in their disease trajectory, who may have special problems (usually refractory symptom control) that are not resolvable on the regular floor under the guidance of the mobile consult team and would be better addressed in the PSCU. The patients may wish to recieve full resusitation and return to the primary oncologist for further cancer-directed treatment. Such patients are an exception to the usual end-of-life care that the PSCU provides and benefit from the symptom control expertise and the interdisciplinary team approach present on the unit. This group is a tiny percentage of the total number of patients admitted to the unit served by our current palliative care model.

Generally, the following types of patients and families are not considered as candidates for transfer because the scope of the PSCU is limited in their case and they can be transitioned to comfort measures either on the primary floor or outside under hospice care:

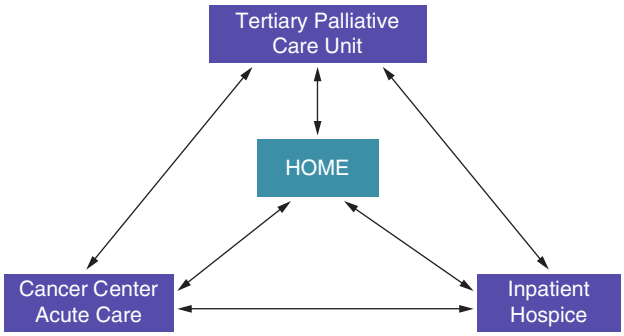


FIGURE 65–2 Service delivery locations for acute symptom management in patients with advanced cancer near the end of life.

1. Patients and families that are managing well and prefer to go directly to the hospice.
2. A comatose patient with a family who is coping well. If they were to be transferred to the PSCU, the team's only next step would be to transfer to hospice, which in the majority of cases can be offered and arranged directly from their primary oncology floor.
3. The patient is dying (or may soon be) and they wish to be "full code" despite ongoing discussions.
4. The patient is intubated and on a ventilator.
5. The patient is under 18 years of age.
6. The primary team does not agree with transferring the patient to the PSCU.

SERVICES AVAILABLE IN PALLIATIVE AND SUPPORTIVE CARE UNITS

In addition to the core interdisciplinary team (comprised mainly of a board-certified palliative care physician, junior physician or trainee, advanced practice provider, palliative nurse, nursing assistants/patient care technicians and Patient Scheduling Coordinators (PSCs), palliative pharmacist, chaplain, social worker, counselor, case manager, physical and occupational therapist, dietician, research staff, and volunteers), some other services available for the patient and their family may include Pets Are Wonderful Support, aromatherapy, music therapy, massage therapy, availability of artist-in-residence (legacy therapy), caregiver support groups and family care conferences.[37] The interdisciplinary team at the PSCU, which continually provides psychosocial, spiritual, and emotional support to the patient and family will recommend the involvement of different specialists for these additional services. Based on available resources, the patient's condition and tolerance, and goals of care discussions,

the interventions available may include but are not limited to palliative radiotherapy, limited duration of transfusion and antibiotics support, hydration, procedures for achieving palliation of symptoms like a colostomy, venting tube, intraperitoneal and intrapleural catheter, interventional pain procedures (cordotomy, nerve block, vertebroplasty), as well as oxygen supplementation, opioids, antiemetics, and laxatives.

SEVERE SYMPTOM DISTRESS: ROLE OF PALLIATIVE SEDATION NEAR THE END OF LIFE AND AN ACUTE PSCU

The interdisciplinary model of care in the PSCU under the leadership of the palliative physician, with specialty trained palliative nurses, plays an essential role in the delivery of interventions like palliative sedation for the management of refractory and distressing issues like terminal delirium, refractory dyspnea, and pain near the end of life, mainly for patients who are actively dying.[38–44]

ROLE OF THE PSCU IN IMPROVING PATIENT-REPORTED OUTCOMES AS WELL AS DISCHARGE OUTCOMES

Various studies have shown improvement in patient-reported outcomes when they are treated by an inpatient palliative care service, including an inpatient PSCU.[2,5,34,45–51] Mortality rates in the PSCU vary owing to multiple factors.[52–54] However, the role of the PSCU is of paramount importance in reducing inpatient hospital mortality because from 40% to 70 % of patients admitted to the PSCU are able to be discharged from the hospital (mostly to hospice care), which helps reduce emergency center readmissions and the ICU census.[48,54–57]

ROLE OF THE ENVIRONMENT

The acute PSCU is poised to provide a unique level of care,[34,35] mainly because of the interdisciplinary model of team integration, but also from the exceptional environment (with the incorporation of soothing, ambient lighting and music)[58–60] it provides to patients and families under care of the team. It offers opportunities for better assessment, improved symptom control, better family satisfaction with care, better bed utilization, and decreased cost of care.[34,53,61] Chai et al stated: "A dedicated unit offers direct control over the implementation of clinical recommendations, the presence of skilled interdisciplinary staff, and a care setting designed for the needs of seriously ill patients. Under circumstances of difficult-to-control symptom distress, family exhaustion, or lack of adequate community support services, a palliative care unit may provide the safest and highest quality of care."[62]

Patients with advanced cancer (and their families) near the end of life face many distressing symptoms and challenges.[45] Unfortunately, only a small proportion of comprehensive cancer centers and community-based cancer centers in the nation have inpatient PSCUs.[19,20] The acute PSCU can be a fantastic resource as an integral part of the inpatient palliative care service,[34,47] not just for managing complex and challenging situations but also for providing a platform on which to conduct sensitive clinical research[63–65] in this patient population, and to provide education and training for the various disciplines involved in the provision of such vital care.

MD ANDERSON PRACTICE TIPS

- Familiarity with the inpatient palliative or supportive care team structure and function can be useful for the referring teams. It is an interdisciplinary team of palliative care providers, including a physician, counselor, chaplain, social worker, pharmacist, palliative care nurses, and many others, alongside the oncology teams, who provide an integrated model of care to patients with advanced cancer.
- Consultation with inpatient supportive care service can help identify and manage complex symptom issues like missed delirium and refractory pain in patient with advanced cancer, as well as psychosocial, emotional, and spiritual distress, while reducing the amount of opioids and other psychotropic agents (polypharmacy).
- Early integration of supportive care has improved patient-reported outcomes and discharge outcomes, including ICU and overall hospital mortality without increasing length of stay.
- An acute PSCU at a tertiary care hospital is different from an acute inpatient hospice facility, because patients with a prognosis more than six months can be admitted to a PSCU for the management of physical symptoms and help navigating the psychosocial, emotional, and spiritual distress for the patient and their family.

MD ANDERSON PRACTICE TIPS

- An acute PSCU not only provides clinical care and education to the patient and family but also provides opportunities for education of the different disciplines involved in the patient's care, as well as research geared toward improving the quality of life of patients, family, caregivers, and care providers.
- The supportive care team, when part of the care continuum, can proactively assist with early identification and clarification of goals of care, completion of advanced-care directives, and providing a smoother transition and/or discharge plan for patients with advanced cancer.

REFERENCES

1. Portenoy RK, Thaler HT, Kornblith AB, Lepore JM, Friedlander-Klar H, Coyle N, et al. Symptom prevalence, characteristics and distress in a cancer population. *Qual Life Res.* 1994;3(3):183-189.
2. Hui D, de la Cruz M, Thorney S, Parsons HA, Delgado-Guay M, Bruera E. The frequency and correlates of spiritual distress among patients with advanced cancer admitted to an acute palliative care unit. *Am J Hosp Palliat Care.* 2011;28(4):264-270.
3. van den Beuken-van Everdingen MH, Hochstenbach LM, Joosten EA, Tjan-Heijnen VC, Janssen DJ. Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. *J Pain Symptom Manage.* 2016;51(6):1070-90 e9.
4. Whelan TJ, Mohide EA, Willan AR, Arnold A, Tew M, Sellick S, et al. The supportive care needs of newly diagnosed cancer patients attending a regional cancer center. *Cancer.* 1997;80(8):1518-1524.
5. Hui D, Bruera E. Models of palliative care delivery for patients with cancer. *J Clin Oncol.* 2020;38(9):852-865.
6. Delgado-Guay MO, Rodriguez-Nunez A, Shin SH, Chisholm G, Williams J, Frisbee-Hume S, et al. Characteristics and outcomes of patients with advanced cancer evaluated by a palliative care team at an emergency center. A retrospective study. *Support Care Cancer.* 2016;24(5):2287-2295.
7. Qian Y, Haider A, Lu Z, Naqvi S, Zhuang A, Nguyen K, et al. Factors associated with improvement in uncontrolled cancer pain without increasing the opioid daily dose among patients seen by an inpatient palliative care team. *J Palliat Med.* 2020;23(4):483-488.
8. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med.* 2010;363(8):733-742.
9. Zimmermann C, Swami N, Krzyzanowska M, Hannon B, Leighl N, Oza A, et al. Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. *Lancet.* 2014;383(9930):1721-1730.
10. World Health Organization. Palliative Care. Accessed May 16, 2021. http://www.who.int/cancer/palliative/definition/en/
11. Bandieri E, Banchelli F, Artioli F, Mucciarini C, Razzini G, Cruciani M, et al. Early versus delayed palliative/supportive care in advanced cancer: an observational study. *BMJ Support Palliat Care*. 2020;10(4):e32.
12. Hui D, Bruera E. Integrating palliative care into the trajectory of cancer care. *Nat Rev Clin Oncol.* 2016;13(3):159-171.
13. Freireich EJ, Kurzrock R. The role of investigational therapy in management of patients with advanced metastatic malignancy. *J Clin Oncol.* 2009;27(2):304-306.
14. El-Jawahri A, Nelson AM, Gray TF, Lee SJ, LeBlanc TW. Palliative and end-of-life care for patients with hematologic malignancies. *J Clin Oncol.* 2020;38(9):944-953.
15. Bruera E, Hui D. Integrating supportive and palliative care in the trajectory of cancer: establishing goals and models of care. *J Clin Oncol.* 2010;28(25):4013-4017.
16. Dalal S, Palla S, Hui D, Nguyen L, Chacko R, Li Z, et al. Association between a name change from palliative to supportive care and the timing of patient referrals at a comprehensive cancer center. *Oncologist.* 2011;16(1):105-111.
17. Rhondali W, Burt S, Wittenberg-Lyles E, Bruera E, Dalal S. Medical oncologists' perception of palliative care programs and the impact of name change to supportive care on communication with patients during the referral process. A qualitative study. *Palliat Support Care.* 2013;11(5):397-404.
18. Weissman DE, Meier DE. Identifying patients in need of a palliative care assessment in the hospital setting: a consensus report from the Center to Advance Palliative Care. *J Palliat Med.* 2011;14(1):17-23.
19. Hui D, De La Rosa A, Chen J, Dibaj S, Delgado Guay M, Heung Y, et al. State of palliative care services at US cancer centers: an updated national survey. *Cancer.* 2020;126(9):2013-2023.
20. Hui D, Elsayem A, De la Cruz M, Berger A, Zhukovsky DS, Palla S, et al. Availability and integration of palliative care at US cancer centers. *JAMA.* 2010;303(11):1054-1061.
21. Heung Y, Azhar A, Ali Akbar Naqvi SM, Williams J, Park M, Hui D, et al. Frequency and characteristics of first-time palliative care referrals during the last day of life. *J Pain Symptom Manage.* 2020.
22. Lim KH, Nguyen NN, Qian Y, Williams JL, Lui DD, Bruera E, et al. Frequency, outcomes, and associated factors for opioid-induced neurotoxicity in patients with advanced cancer receiving opioids in inpatient palliative care. *J Palliat Med.* 2018;21(12):1698-1704.
23. Ann-Yi S, Bruera E, Wu J, Liu DD, Agosta M, Williams JL, et al. Characteristics and outcomes of psychology referrals in a palliative care department. *J Pain Symptom Manage.* 2018;56(3):344-351.
24. de la Cruz M, Fan J, Yennu S, Tanco K, Shin S, Wu J, et al. The frequency of missed delirium in patients referred to palliative care in a comprehensive cancer center. *Support Care Cancer.* 2015;23(8):2427-2433.
25. Ledoux M, Rhondali W, Lafumas V, Berthiller J, Teissere M, Piegay C, et al. Palliative care referral and associated outcomes among patients with cancer in the last 2 weeks of life. *BMJ Support Palliat Care*. 2019;9(1):e16.
26. Grudzen CR, Richardson LD, Johnson PN, Hu M, Wang B, Ortiz JM, et al. Emergency department-initiated palliative care in advanced cancer: a randomized clinical trial. *JAMA Oncol.* 2016;2(5):591-598.
27. El-Jawahri A, LeBlanc T, VanDusen H, Traeger L, Greer JA, Pirl WF, et al. Effect of inpatient palliative care on quality of life 2 weeks after hematopoietic stem cell transplantation: a randomized clinical trial. *JAMA.* 2016;316(20):2094-2103.
28. El-Jawahri A, Traeger L, Greer JA, VanDusen H, Fishman SR, LeBlanc TW, et al. Effect of inpatient palliative care during hematopoietic stem-cell transplant on psychological distress 6 months after transplant: results of a randomized clinical trial. *J Clin Oncol.* 2017;35(32):3714-3721.
29. Ferrell BR, Temel JS, Temin S, Alesi ER, Balboni TA, Basch EM, et al. Integration of palliative care into standard oncology care: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol.* 2017;35(1):96-112.
30. Prado BL, Haider A, Naqvi S, Pestana RC, Williams JL, Dibaj S, et al. Changes in the care setting of first consults to palliative and supportive care over a seven-year period. *J Pain Symptom Manage.* 2019;57(1):86-92.
31. Walsh D. *Palliative Medicine*. Saunders/Elsevier; 2009.
32. Mount BM. The problem of caring for the dying in a general hospital; the palliative care unit as a possible solution. *CMAJ.* 1976;115(2):119-121.
33. Hui D, Elsayem A, Palla S, De La Cruz M, Li Z, Yennurajalingam S, et al. Discharge outcomes and survival of patients with advanced cancer admitted to an acute palliative care unit at a comprehensive cancer center. *J Palliat Med.* 2010;13(1):49-57.
34. Casarett D, Johnson M, Smith D, Richardson D. The optimal delivery of palliative care: a national comparison of the outcomes of consultation teams vs inpatient units. *Arch Intern Med.* 2011;171(7):649-655.
35. Bruera E, Hui D. Palliative care units: the best option for the most distressed. *Arch Intern Med.* 2011;171(17):1601; author reply -2.

36. Bruera E, Neumann C, Brenneis C, Quan H. Frequency of symptom distress and poor prognostic indicators in palliative cancer patients admitted to a tertiary palliative care unit, hospices, and acute care hospitals. *J Palliat Care.* 2000;16(3):16-21.
37. Yennurajalingam S, Dev R, Lockey M, Pace E, Zhang T, Palmer JL, et al. Characteristics of family conferences in a palliative care unit at a comprehensive cancer center. *J Palliat Med.* 2008;11(9):1208-1211.
38. Elsayem A, Curry Iii E, Boohene J, Munsell MF, Calderon B, Hung F, et al. Use of palliative sedation for intractable symptoms in the palliative care unit of a comprehensive cancer center. *Support Care Cancer.* 2009;17(1):53-59.
39. Beller EM, van Driel ML, McGregor L, Truong S, Mitchell G. Palliative pharmacological sedation for terminally ill adults. *Cochrane Database Syst Rev.* 2015;1:CD010206.
40. Cherny NI, Radbruch L, Board of the European Association for Palliative C. European Association for Palliative Care (EAPC) recommended framework for the use of sedation in palliative care. *Palliat Med.* 2009;23(7):581-593.
41. Del Fabbro E, Reddy SG, Walker P, Bruera E. Palliative sedation: when the family and consulting service see no alternative. *J Palliat Med.* 2007;10(2):488-492.
42. Eun Y, Hong IW, Bruera E, Kang JH. Qualitative study on the perceptions of terminally ill cancer patients and their family members regarding end-of-life experiences focusing on palliative sedation. *J Pain Symptom Manage.* 2017;53(6):1010-1016.
43. Maltoni M, Scarpi E, Rosati M, Derni S, Fabbri L, Martini F, et al. Palliative sedation in end-of-life care and survival: a systematic review. *J Clin Oncol.* 2012;30(12):1378-1383.
44. Morita T, Kiuchi D, Ikenaga M, Abo H, Maeda S, Aoyama M, et al. Difference in opinions about continuous deep sedation among cancer patients, bereaved families, and physicians. *J Pain Symptom Manage.* 2019;57(3):e5-e9.
45. Azhar A, Bruera E. Outcome measurement and complex physical, psychosocial and spiritual experiences of death and dying. *Ann Palliat Med*. 2018:S231-S243.
46. O'Mahony S, McHenry J, Blank AE, Snow D, Eti Karakas S, Santoro G, et al. Preliminary report of the integration of a palliative care team into an intensive care unit. *Palliat Med.* 2010;24(2):154-165.
47. Casarett D, Pickard A, Bailey FA, Ritchie C, Furman C, Rosenfeld K, et al. Do palliative consultations improve patient outcomes? *J Am Geriatr Soc.* 2008;56(4):593-599.
48. Elsayem A, Calderon BB, Camarines EM, Lopez G, Bruera E, Fadul NA. A month in an acute palliative care unit: clinical interventions and financial outcomes. *Am J Hosp Palliat Care.* 2011;28(8):550-555.
49. Gaertner J, Frechen S, Sladek M, Ostgathe C, Voltz R. Palliative care consultation service and palliative care unit: why do we need both? *Oncologist.* 2012;17(3):428-435.
50. Grundmann RT. [Palliative medicine and inpatient palliative care unit--functions, organisation forms and significance of surgery]. *Zentralbl Chir.* 2010;135(6):547-555.
51. Hui D, Park M, Liu D, Reddy A, Dalal S, Bruera E. Attitudes and beliefs toward supportive and palliative care referral among hematologic and solid tumor oncology specialists. *Oncologist.* 2015;20(11):1326-1332.
52. Elsayem A, Mori M, Parsons HA, Munsell MF, Hui D, Delgado-Guay MO, et al. Predictors of inpatient mortality in an acute palliative care unit at a comprehensive cancer center. *Support Care Cancer.* 2010;18(1):67-76.
53. Elsayem A, Swint K, Fisch MJ, Palmer JL, Reddy S, Walker P, et al. Palliative care inpatient service in a comprehensive cancer center: clinical and financial outcomes. *J Clin Oncol.* 2004;22(10):2008-2014.
54. Elsayem A, Smith ML, Parmley L, Palmer JL, Jenkins R, Reddy S, et al. Impact of a palliative care service on in-hospital mortality in a comprehensive cancer center. *J Palliat Med.* 2006;9(4):894-902.
55. Rigby A, Krzyzanowska M, Le LW, Swami N, Coe G, Rodin G, et al. Impact of opening an acute palliative care unit on administrative outcomes for a general oncology ward. *Cancer.* 2008;113(11):3267-3274.
56. Shin SH, Hui D, Chisholm GB, Kwon JH, San-Miguel MT, Allo JA, et al. Characteristics and outcomes of patients admitted to the acute palliative care unit from the emergency center. *J Pain Symptom Manage.* 2014;47(6):1028-1034.
57. El Majzoub I, Qdaisat A, Chaftari PS, Yeung SJ, Sawaya RD, Jizzini M, et al. Association of emergency department admission and early inpatient palliative care consultation with hospital mortality in a comprehensive cancer center. *Support Care Cancer.* 2019;27(7):2649-2655.
58. Sagha Zadeh R, Eshelman P, Setla J, Kennedy L, Hon E, Basara A. Environmental design for end-of-life care: an integrative review on improving the quality of life and managing symptoms for patients in institutional settings. *J Pain Symptom Manage.* 2018;55(3):1018-1034.
59. Lopez G, Christie AJ, Powers-James C, Bae MS, Dibaj SS, Gomez T, et al. The effects of inpatient music therapy on self-reported symptoms at an academic cancer center: a preliminary report. *Support Care Cancer.* 2019;27(11):4207-4212.
60. Perez-Cruz P, Nguyen L, Rhondali W, Hui D, Palmer JL, Sevy I, et al. Attitudes and perceptions of patients, caregivers, and health care providers toward background music in patient care areas: an exploratory study. *J Palliat Med.* 2012;15(10):1130-1136.
61. May P, Normand C, Morrison RS. Economic impact of hospital inpatient palliative care consultation: review of current evidence and directions for future research. *J Palliat Med.* 2014;17(9):1054-1063.
62. Chai E, Meier DE. Identifying the effective components of palliative care: comment on "The optimal delivery of palliative care". *Arch Intern Med.* 2011;171(7):655-656.
63. Bruera S, Chisholm G, Dos Santos R, Bruera E, Hui D. Frequency and factors associated with unexpected death in an acute palliative care unit: expect the unexpected. *J Pain Symptom Manage.* 2015;49(5):822-827.
64. Hui D, dos Santos R, Chisholm G, Bansal S, Silva TB, Kilgore K, et al. Clinical signs of impending death in cancer patients. *Oncologist.* 2014;19(6):681-687.
65. Hui D, Dos Santos R, Chisholm G, Bansal S, Souza Crovador C, Bruera E. Bedside clinical signs associated with impending death in patients with advanced cancer: preliminary findings of a prospective, longitudinal cohort study. *Cancer.* 2015;121(6):960-967.

This page intentionally left blank

66

Integrated Outpatient Supportive Care

Akhila Reddy
David Hui
Eduardo Bruera

KEY CONCEPTS

- Interdisciplinary palliative care improves the quality of life of patients and families by focusing on alleviation of physical, psychosocial, and spiritual distress.
- The literature consists of a variety of outpatient palliative care models with different team composition, the timing of referral, and the place of delivery.
- Outpatient palliative care provided by an interdisciplinary team and earlier in the disease trajectory is generally more beneficial than that provided by a single discipline or later in the disease trajectory.
- Automatic referrals to palliative care can increase both the volume and timeliness of referral.
- Standalone clinics are more suitable for larger centers than multiple embedded clinics.
- Ultimately, no one model fits all, and each institution needs to determine the optimal model based on patient population, infrastructure, staff, and resource availability.

Palliative care is "an approach that improves the quality of life of patients and their families facing the problem associated with a life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual."[1] According to the World Health Organization, palliative care "is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications."[1]

Palliative care first started in the community with the hospice movement. It evolved over the past six decades to offer care in acute care facilities by providing inpatient consultations and palliative care units.[2] In 1990s, Edmonton, Canada, established one of the first palliative care clinics, providing outpatient care to patients in the ambulatory setting.[3,4] This represented a significant shift in paradigm because patients at palliative care clinics generally had better performance status and fewer acute symptom distress than patients at other palliative care settings (ie, palliative care inpatient consultation teams, palliative care units, and home palliative care programs and hospices).[5] Palliative care clinics allowed patients to be referred earlier in the disease trajectory while they were actively receiving cancer treatments. As a result, these patients could be followed longitudinally by the palliative care team, with many more opportunities to optimize care. The focus of care also shifted from dealing with acute symptom crisis at the end-of-life care to anticipatory care to address chronic symptoms (eg, fatigue, nutrition, function) through education and monitoring, and timely serious illness conversations to enhance illness understanding and facilitate care planning.[6] As a result, an increasing number of cancer centers now offer outpatient palliative care services. For example, 67% of the National Cancer Institute (NCI)-designated cancer centers in the United States reported having outpatient palliative care clinics in 2009, and this number had increased to 98% in 2018.[7]

The literature for outpatient palliative care has grown substantially over time.[8] Timely referral of cancer patients to outpatient palliative care leads to

enhanced symptom management, decreased rates of depression, greater patient and caregiver satisfaction, better illness understanding, improved quality of end-of-life care, and overall survival compared with oncologic care alone.[9–11] This chapter covers three key aspects: (1) a synopsis of the literature on outpatient palliative care, (2) models of outpatient palliative care delivery, and (3) a description of the outpatient palliative care clinic at MD Anderson Cancer Center.

LITERATURE ON OUTPATIENT PALLIATIVE CARE

In 2004, Rabow et al conducted a controlled trial comparing the outcomes of 50 patients seen by an outpatient palliative care team with 40 control patients seen by an outpatient general internal medicine clinic over 12 months.[12] Patients were eligible if they had a diagnosis of cancer (33%), advanced chronic obstructive pulmonary disease or heart failure, and a life expectancy of 1 to 5 years. The palliative care team consisted of three physicians, a social worker, nurse, chaplain, pharmacist, psychologic art therapist, and volunteer coordinator. The primary outcome was pain, which did not differ between the study groups. However, dyspnea, sleep, anxiety, and spiritual well-being improved in the palliative care group and decreased in the control group. There were also significantly fewer urgent care visits.

In 2009, the Project ENABLE II study was published by Bakitas et al. This randomized clinical trial assigned 322 patients with advanced solid tumors to either a telephone-based nurse-led palliative care intervention or usual care alone.[13] The three coprimary outcomes were the quality of life, symptom burden, and resource use. The telephone-based nurse-led palliative care intervention was associated with a significant improvement in the quality of life and mood, but not symptom burden or resource use. Of note, a small proportion of patients in both the intervention group (26%) and usual care group (32%) received a referral to specialist palliative care.

In 2010, Temel et al reported the findings of a groundbreaking clinical trial that randomly assigned 151 patients with metastatic non–small-cell lung cancer to specialist outpatient palliative care or usual care provided by an oncology team.[14] Patients were eligible if they were within 8 weeks of cancer diagnosis and had a performance status of 0 to 2. The palliative care intervention included monthly clinic appointments provided by palliative care physicians and advanced practice nurses. At 12 weeks, patients in the palliative care group had a significantly higher quality of life, lower depression scores, and improved quality of end-of-life care compared with usual oncologic care. There was also a significant overall survival benefit in post-hoc analysis. In a subsequent secondary analysis, the palliative care group was also found to have greater illness understanding, which was associated with less chemotherapy use at the end of life.[15]

These findings were consistent with a large cluster-randomized trial by Zimmermann and colleagues in 2014.[16] Four-hundred sixty-one patients with cancer from 24 medical oncology clinics were enrolled and randomly assigned to oncologic care with or without outpatient palliative care. The palliative care intervention involved monthly followed by a palliative care physician and nurse in a standalone clinic. At 3 months, there was a trend toward improvement in the quality of life (Functional Assessment of Chronic Illness Therapy–Spiritual Well-Being Scale [FACIT-Sp]) and symptom burden (Edmonton Symptom Assessment Scale [ESAS]) favoring the palliative care group, which became statistically significant at 4 months.[16] Palliative care was also associated with increased patient satisfaction. A secondary analysis found that patients with higher symptom burden were more likely to benefit from palliative care (personal communication).

In 2014, Tattersall et al randomly assigned 120 patients with metastatic cancer and a life expectancy of less than 12 months to usual care with or without a palliative care nurse consultant.[17] It is important to note that the intervention only consisted of a brief introduction to palliative care services with limited follow-up. The investigators found no significant difference in the primary outcome of quality of life over 12 months; moreover, patients in the palliative care group had worse physical symptom scores, worse psychological distress scores, and worse survival compared with the control group.

Bakitas et al reported findings from the Project ENABLE III study in 2015 that involved 207 patients with advanced cancer to examine the effect of a telephone-based nurse-led palliative care intervention.[18] Compared with the Project ENABLE II study, this study had a waitlist design, and the structured intervention included an initial in-person visit and more weekly sessions. Neither quality of life nor mood differed between the palliative care intervention and usual care groups. Interestingly, a greater proportion of patients in the palliative care group were still alive at the one-year survival marker.

In 2016, Temel et al published a confirmatory trial that included 191 patients with metastatic lung cancer and 159 with incurable noncolorectal gastrointestinal malignancies.[19] It adopted a similar design to their original trial with the same palliative care team intervention. The primary outcome (Functional Assessment of Cancer Therapy—General [FACT-G]) had a nonstatistically significant improvement at 12 weeks in the palliative care group compared with usual care, which became

significant at 24 weeks. Subgroup analysis revealed that patients with lung cancer had a greater benefit than patients with gastrointestinal malignancies.

Maltoni et al from Italy also reported their findings in 2016.[20] This randomized clinical trial assigned 207 patients with advanced pancreatic cancer to either palliative care or usual oncology care.[20] It had a similar design to the original Temel trial; however, palliative care was delivered by physicians only instead of by an interdisciplinary team (IDT). Quality of life at 3 months was the primary outcome and was significantly better in the palliative care group compared with the control group. Secondary outcomes, including depression, anxiety, a majority of the end-of-life care metrics, and overall survival did not differ significantly between the two groups.[21]

Another European trial was reported in 2017.[22] This Danish study by Groenvold et al enrolled patients with high symptom burden and randomly assigned them to palliative care intervention or usual care. The palliative care intervention involved physicians, nurses, and allied health professionals providing a consultation but limited follow-up visits. The primary outcome, palliative care need, did not differ significantly between groups; however, this measure has not been validated. The secondary outcomes also did not differ significantly, except for nausea.

In Brazil, do Carmo et al conducted a three-arm randomized trial in 2017 comparing palliative care plus a psychology intervention, palliative care, and usual care alone.[23] However, this study was terminated prematurely after enrolling 63 of 150 planned patients, and no difference in study outcomes was reported.

Vanbutsele et al from Belgium conducted a randomized study in 2018. Both outpatients and inpatients were eligible for this study, provided they were within 3 months of a diagnosis of advanced solid tumor or progression and had a life expectancy of 6 to 24 months.[24] One-hundred eighty-six patients were enrolled. The palliative care intervention was predominantly nurse based, and palliative care physicians were only available on an as-needed basis. At 24 weeks, the palliative care group had a statistically significant improvement in the primary outcome, quality of life at 12 weeks (global health status in European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 [EORTC-QLQ-C30]). Secondary outcomes including overall survival, symptoms, mood, and illness understanding did not differ between groups.

The Italian group reported the findings of a randomized study involving advanced gastric cancer in 2018.[25] With 186 patients enrolled, no significant differences were found between the two study arms in quality of life, mood, the aggressiveness of care near the end of life, and survival.[25]

MODELS OF OUTPATIENT PALLIATIVE CARE DELIVERY

Taken together, the above clinical trials varied widely in regard to the patient population, intensity of intervention, and outcomes. This diversity in the literature helps to inform which elements of outpatient palliative care delivery are more essential.[26] In this section, we will discuss the three key elements of outpatient palliative care clinics, including team composition, the timing of referral, and location of care.

Team Composition

No clinical trials have directly compared interdisciplinary and single-disciplinary palliative care teams. However, studies that included an interdisciplinary palliative care team providing in-person longitudinal care were generally associated with more consistent and positive outcomes relative to nurse-led telephone-based interventions[13,18] and physician-only interventions.[20,25] What is the definition of an IDT? In an international Delphi study, the consensus was that an interdisciplinary palliative care team should consist of at least physicians, nurses, and psychosocial professionals (eg, psychologist, social worker, chaplain).[27]

Palliative care delivered by an IDT is likely more beneficial versus that of a single discipline because patients' supportive care needs are interconnected, necessitating an IDT to address the multidimensional aspects of suffering. For example, total pain may have physical, emotional, social, spiritual, and informational components.[28] To manage pain effectively, a team approach may include physicians to make the proper diagnosis and prescribe appropriate therapies, nurses to provide education and nonpharmacologic strategies, physical and occupational therapists to improve function, psychologists and counselors to provide psychotherapy to alleviate emotional distress and to strengthen coping strategies, chaplains to discuss sources of spiritual pain, and social workers to provide financial support and maximize care access. However, it is important to note that different interventions may be appropriate in different settings. For instance, it may be difficult for patients in rural areas to attend an outpatient palliative care clinic when the closest is hundreds of miles away. In a resource-limited setting, a telephone-based nurse-led intervention would be the most appropriate model to provide outpatient palliative care.

Timing of Care

A majority of the randomized trials above showed that patients referred to specialist palliative care earlier in the disease trajectory generally had better outcomes than patients who either had delayed or no palliative

care. For example, a study at MDACC found that timelier referral (>6 months before death) was associated with lower rates of hospitalization, emergency department visits, and intensive care unit (ICU) admissions in the last 30 days of life compared with later referrals.[29] A systematic review in patients with cancer also showed that earlier referral was associated with improved outcomes.[10] However, it is currently not possible to universally refer patients within the first few months of their advanced cancer diagnosis to specialist palliative care because of the limited palliative care workforce. Furthermore, some patients with cancer may have limited supportive care needs and/or they have been adequately addressed by the oncology team.

In contrast to *early* palliative care, *timely* palliative care involves identifying patients with the greatest supportive care needs and referring them to palliative care in a timely fashion.[6] Theoretically, this approach has several advantages. First, it would align care needs with the provision of specialist palliative care, thus allowing the timing of involvement to be more personalized. Second, it would triage scarce palliative care resources. Third, it may uncover supportive care needs during initial screening. Fourth, it could help to streamline the processes of care while ensuring equal access. Four key components are needed for automatic referral to facilitate timely palliative care[30]:

(1) Systematic screening of supportive care needs in the oncology outpatient clinic. For example, symptom assessments can be conducted using the ESAS, which documents the intensity of 10 or more symptoms using 0–10 numeric rating scales.[31] ESAS is validated, available in different languages, and simple to use, making it an ideal tool for rapid screening.

(2) Referral criteria that both the oncology and palliative care teams agree can be used to identify patients most appropriate for specialist palliative care intervention. An international consensus panel has identified 11 criteria that could be useful to trigger a referral (Table 66–1).[32] Interestingly, nine of these criteria were needs-based, and two were time-based criteria. This set of criteria may represent a starting point for institutions to further tailor based on the availability of palliative care services and the desired level of supportive care services. In a retrospective study, the use of these criteria improved the timing of referral by approximately 2 months to more than 1 year.[33]

(3) Finally, successful application of these criteria will result in more and earlier referrals. Thus, the outpatient palliative care programs should have adequate staffing, space, and resources to support sustainable growth.

Table 66–1 International Consensual Referral Criteria for Outpatient Palliative Care[30,32]

Criteria
1. Severe physical symptom(s), eg, pain ≥7/10
2. Severe emotional symptom(s), eg, depression ≥7/10
3. Request for hastened death
4. Spiritual or existential crisis
5. Assistance with decision making/care planning
6. Patient request
7. Delirium
8. Brain or leptomeningeal metastases
9. Spinal cord compression or cauda equina
10. Within 3 months of diagnosis of advanced/incurable cancer for patients with median survival 1 year or less
11. Diagnosis of advanced cancer with progressive disease despite second-line systemic therapy (incurable)

Location of Care

In addition to team composition and timing of referral, another variation of outpatient palliative care delivery involves the location of delivery: patients may be seen at a standalone outpatient palliative care clinic, a palliative care clinic embedded within an oncology clinic, or remotely via telehealth. In a 2018 survey of NCI-designated cancer centers in the United States, 83% of the existing palliative care programs reported having standalone clinics, and 39% had embedded clinics. In contrast, 41% and 30% had standalone clinics and embedded clinics at non–NCI designated cancer centers.[7]

Standalone palliative care clinics represent the standard of care. To date, randomized controlled trials of outpatient palliative care clinics have mostly tested this model of care.[7,34] Standalone clinics allow all the palliative care resources to be consolidated in one place, providing centralized access to patients referred from different oncology services. Patients with cancer can access comprehensive supportive care services all in one location. However, unlike in embedded clinics, an encounter with palliative care is separated in space and time from the oncology visit. This can be partially addressed by booking the palliative care appointment on the same day as an oncology visit. The outpatient palliative care clinic at MDACC has successfully operated under this model of care, which is described in detail below.

A large proportion of cancer centers in the US offer embedded clinics, defined as "the palliative care team and the oncology team sharing the same clinic space and seeing the same patients on the same day."[26] Embedded clinics offer several advantages over standalone clinics, including convenience for patients and more opportunities for communication and collaboration between the oncology team and the palliative care team. To date, no randomized controlled trial has compared the outcomes

between embedded specialist palliative care clinics and standalone clinics or usual care. Several retrospective cohort studies have reported mixed outcomes compared with historical data or concurrent control.[35–39] In general, embedded clinics were associated with increased referral and timelier access to palliative care.[36,37,39] These embedded clinics are generally staffed by one to two members of the palliative care team, such as a physician,[36,39] a nurse practitioner,[35,38] and/or a psychosocial team member.[37] Embedded clinics are likely more suitable for smaller cancer centers because it is difficult to place a palliative care team in every oncology clinic (eg, thoracic, breast, gastrointestinal, genitourinary, gynecologic etc). Moreover, it is not often feasible to ensure the presence of a large interdisciplinary palliative care team at an oncology clinic because of limited space.

Telehealth has the potential to bring even more outpatient palliative care access to patients via video conference technology.[26] Compared with in-person visits or home visits, they can minimize the need for travel for patients and palliative care teams, respectively, thus cutting time and cost. It should be noted that telehealth technologies are mostly used to augment, instead of replace, in-person visits. Variations of telehealth interventions include video visits with or without remote physical examination capabilities, smartphone apps, and remote symptom monitoring.[40,41] Some setups involve patients (mostly in rural areas) attending a telehealth facility, and other programs can be delivered at home. Several nurse-led palliative care telehealth interventions discussed above have shown some benefits in randomized trials as discussed above.[13,18] However, there remains a paucity of studies examining outcomes associated with telehealth interventions by an interdisciplinary palliative care team.[42] A large noninferiority randomized trial is underway that compares palliative care delivered by either telehealth (with the first consultation being in person) with standard in-person visits.[43]

MD ANDERSON OUTPATIENT PALLIATIVE CARE PROGRAM

The Supportive Care Center (SCC) in MDACC was started in 1999 by Dr Eduardo Bruera, Chair, Palliative, Rehabilitation, and Integrative Medicine. The last few years have seen increased integration of supportive/palliative care with routine oncologic care in the US.[7] This increase is driven by growing evidence that early integration of palliative care can improve quality of life, symptom management, patient/family satisfaction, and patient experience while reducing aggressive end-of-life care and emergency room and ICU visits, and decreasing cost of care.[10] The increased integration has also been quite significant at MDACC, as demonstrated by our growth and steady increase in the total number of referrals every year.[44] To sustain the growth and to be able to accommodate the consults within 2 weeks of the request, a satellite supportive care center was started in 2014.

STRUCTURE OF THE SUPPORTIVE CARE CENTER

The SCC is staffed by 10 Registered Nurses (RNs), 4 Medical Assistants (MAs), 7 Patient Service Coordinators (PSCs), 3 counselors, a social worker, and a pharmacist. Other members of the IDT, such as the nutritionist, chaplain, and case manager, are available to assist as needed. There are a total of four physician templates daily, and an additional physician is available to help with phone calls, triages, and walk-ins, and also fulfills the role of the physician on call for the SCC. The SCC is not staffed with any advanced practice providers.

The SCCs have a total of 17 examination rooms along with a family counseling room. Because of the symptom distress experienced by the patients referred to the SCC, each of the examination rooms are furnished with a hospital bed, two comfortable chairs for visitors, and a computer and stool for the clinician (Fig. 66–1). It must be noted that the supportive care team does not use the computer in the room. A survey conducted showed that our patients (72%) preferred their doctors not to use the computer in the room.[45] The waiting room in the SCC is seldom used because many patients experience symptom distress or body image issues, or they use assistive devices and are promptly taken into the comfortable examination rooms rather than remain in the outside waiting room.

The SCC also has lights that have a pink hue, known to alleviate anxiety, and soft, soothing music is always played to help keep the patients relaxed and at ease. More than 70% of our patients surveyed preferred music in patient care areas.[46] The examination rooms have television screens with content displaying the SCC staff and clinicians they will see that day, and personal information such as "favorite food," "favorite movie," or "favorite book" listed underneath their picture and title. Patients have expressed that seeing this information on the screens while waiting for the provider to come in helps ease their anxiety related to the visit.

Along with the staff and clinician bios, the patients also watch 2-minute educational videos regarding exercise, cancer pain management, opioid use, constipation management, spirituality, preparation of advanced-care directives, and so on, while waiting for their clinical team. The patients and caregivers also have access to restrooms within a few steps



FIGURE 66–1 Examination room at MD Anderson Cancer Center's Supportive Care Center.

of the examination rooms. Because of the sensitive nature of specific discussions and to allow for split visits, a large family counseling room is available. During these split visits, the clinicians or counselors or other members of the IDT can meet separately with the caregivers to counsel them for emotional distress or end-of-life care planning or direct hospice referral.

The SCC welcomes same-day/walk-in patients and caregivers in severe distress, and they are seen without an appointment. New patient consults are also seen the same day for symptom distress after a physician-to-physician referral from other primary oncology centers. Approximately 30% of the patients seen in the SCC are those without any prior appointments. Allowing walk-in visits is vital in preventing avoidable visits to the emergency department, or even hospitalization, and also to help alleviate any distress in patients, both physical and psychosocial.[47,48] In addition, a total of 80 to 100 phone calls, messages, faxes, and prior authorization requests are received daily and promptly addressed by two dedicated telephone nurses.[49] Telephone calls by nurses and calls and telehealth visits by our counselors are also conducted proactively for any patients and families in high distress.[41]

The SCC successfully piloted video visits between physicians and patients during the Covid-19 pandemic in 2020, serving approximately 1000 patients within 2 months of implementation.

DELIVERY OF CARE AT THE SUPPORTIVE CARE CENTER

The SCC receives patients from medical oncology, radiation oncology, gynecological oncology, surgical oncology, and also from other downstream centers.[50] A patient visit to the SCC involves an interdisciplinary approach to care.[51] First, the medical assistant takes the patient to a room after recording the patient's vital signs. The RN then conducts a comprehensive assessment of symptoms using the Edmonton Symptom Assessment Scale- Financial and Spiritual (ESAS-FS) as a guiding tool.[31,52–54] The ESAS-FS is a symptom assessment scale where 12 primary physical, psychosocial, and spiritual symptoms are scored by the patient on a scale of 0–10. The RN also administers the Memorial Delirium Assessment Scale to screen for delirium, which is highly prevalent in patients with advanced cancer.[55] Other tools administered by the RN are the Cut-down Guilty Annoyed and Eye-Opener-Adapted to Include Drugs (CAGE-AID) questionnaire and Screener and Opioid Assessment for Patients with Pain (SOAPP), which are validated tools to screen for alcohol and substance abuse and enable the team to evaluate the risk for opioid abuse.[56] The RN also conducts an assessment of performance status based on the patient's reported functional ability.[57] Included in the RN's evaluation is a brief overview of coping strategies, sources of physical and emotional support for the patient, any worries/fears, presence of anhedonia or suicidal thoughts, medication review, falls assessment, and presence or absence of advanced-care directives. After receiving a report from the RN, the physician then visits with the patient and determines a plan, which may include extensive opioid and other medication management, counseling, and the involvement of other members of our IDT, such as the counselor, pharmacist, dietician, social worker, or chaplain.

Approximately 54 appointments are scheduled daily between the four physicians, and the walk-in physician sees an additional 8 to 12 walk-in patients. The counselors are involved in 15 to 20 patient visits and the pharmacist in about 8 to 10 patient visits daily. More than 50% of the patients visiting the SCC are seen by our counselor at least once, and 30% are seen more than once. Counselors conduct home outreach telephone/video follow-up counseling for patients, especially for those with transportation and distance barriers.[41]

At the end of every visit, the patient is provided with our contact information, including our after-hours and

weekend on-call pager information. Patients calling with severe symptom distress are asked to walk into the clinic the same day or the following day if adjustments and assistance are not feasible over the phone. About 30% of our patients use the phone triaging program; uncontrolled pain, nausea, constipation, and counseling are the main reasons.[51]

All follow-ups are scheduled in coordination with other appointments at MDACC, so the patient and family can minimize transportation efforts. This is especially important because the majority of our patients have advanced cancer and rely on instrumental aid and caregivers to bring them to their appointments. To accommodate a patient on a day and time best suited for them, the focus is on providing easy access rather than continuity with the same physician. Patients are informed that they may not be able to see the same supportive care physician for follow-up, although they have the choice of seeing the same physician if they return on their clinic day. However, because of the uniform practice guidelines in the SCC, lack of continuity is not foreseen as a significant concern by both patients and physicians.

Our SCC has a specialized interdisciplinary program called Compassionate High Alert Team (CHAT), which aims to address nonmedical opioid use in patients, assist clinicians, and ensure patient safety.[58] Advances in cancer treatments, improved cancer survival rates, and early referrals to supportive care can result in more patients receiving opioids, and for a longer duration, which may increase the risk for aberrant opioid use among patients. Our SCC has an elaborate screening process to include clinical interviews and tools like CAGE-AID and SOAPP. Along with these tools, a review of national prescription drug monitoring programs and random urine drug testing is part of routine care.[56,59] If aberrant opioid behavior is recognized, the CHAT is activated. Members of CHAT include physician, nurse, pharmacist, counselor, patient advocate, and social work. A team approach that emphasizes patient safety is followed. Our CHAT approach has resulted in significantly reduced frequency in aberrant behavior and aberrant opioid use among patients.[58] This successful CHAT approach is now being implemented in other centers in the US.[60]

Our SCC also has a clinic that aims to identify patients at risk for cachexia early and to intervene using a multidisciplinary approach.[61,62] Our SCC provides an ideal platform to train palliative care, medical oncology, and internal medicine trainees, along with introducing our way of care delivery to numerous observers and visitors from around the world.[63] For many trainees, our SCC is the first exposure to palliative care. Trainees that experienced a rotation with our palliative care team were more knowledgeable with a higher understanding of palliative care principles and strongly believed in referring patients to us early in the disease course.[64] In addition, our SCC is the home for an extensive palliative care research program, enrolling patients in multiple clinical trials and surveys, and is the most academically productive team in the field of palliative and supportive care in patients with cancer.

Despite increased integration and high utilization of SCC, 21% of our patients surveyed perceived that their consult to SCC happened late or too late.[65] Patients experience a significant decrease in numerous symptoms even after a single visit with the SCC team.[66] Patients referred early to outpatient supportive care at MDACC have significantly fewer emergency department visits, hospital admissions, ICU admissions, and hospital deaths.[29] An SCC must be an integral part of all cancer centers to deliver high-quality, patient-centered care to patients with cancer and their families.[67]

MD ANDERSON PRACTICE TIPS

- Consult supportive care for all patients with metastatic/advanced cancer and those with limited-stage cancer that has a poor prognosis.
- Consult supportive care for all patients with physical and psychosocial symptom distress irrespective of the cancer stage or prognosis.
- Supportive care can help not only distressed patients but also their caregivers and family.
- Patients exhibiting signs of aberrant opioid use will need an urgent referral to supportive care for specialized interdisciplinary care.
- Supportive care can help in goals-of-care discussions and timely referrals to hospice. Communication between the primary oncologist and palliative care team, along with the documentation in the electronic health record by the primary oncologist outlining the goals of treatment and prognosis, is beneficial.
- A referral to supportive care can improve patient and family satisfaction with care, patient experience, quality of life, physical and emotional symptoms, and healthcare utilization outcomes at the end of life.

REFERENCES

1. World Health Organization. Palliative Care. Accessed March 27, 2019. http://www.who.int/cancer/palliative/definition/en/.
2. Clark D. From margins to centre: a review of the history of palliative care in cancer. *Lancet Oncol.* 2007;8(5):430-438.
3. Oneschuk D, Fennell L, Hanson J, Bruera E. The use of complementary medications by cancer patients attending an outpatient pain and symptom clinic. *J Palliat Care.* 1998;14(4):21-26.
4. Bruera E, Michaud M, Vigano A, Neumann CM, Watanabe S, Hanson J. Multidisciplinary symptom control clinic in a cancer center: a retrospective study. *Support Care Cancer.* 2001;9(3):162-168.
5. Rabow MW, Petersen J, Schanche K, Dibble SL, McPhee SJ. The comprehensive care team: a description of a controlled trial of care at the beginning of the end of life. *J Palliat Med.* 2003;6(3):489-499.
6. Hui D, Hannon BL, Zimmermann C, Bruera E. Improving patient and caregiver outcomes in oncology: team-based, timely, and targeted palliative care. *CA Cancer J Clin.* 2018;68(5):356-376.
7. Hui D, De La Rosa A, Chen J, et al. State of palliative care services at US cancer centers: an updated national survey. *Cancer.* 2020;12699):2013-2023.
8. Smith AK, Thai JN, Bakitas MA, et al. The diverse landscape of palliative care clinics. *J Palliat Med.* 2013;16(6):661-668.
9. Gaertner J, Siemens W, Meerpohl JJ, et al. Effect of specialist palliative care services on quality of life in adults with advanced incurable illness in hospital, hospice, or community settings: systematic review and meta-analysis. *BMJ.* 2017;357:j2925.
10. Haun MW, Estel S, Rucker G, et al. Early palliative care for adults with advanced cancer. *Cochrane Database Syst Rev.* 2017;6:Cd011129.
11. Kavalieratos D, Corbelli J, Zhang D, et al. Association between palliative care and patient and caregiver outcomes: a systematic review and meta-analysis. *JAMA.* 2016;316(20):2104-2114.
12. Rabow MW, Dibble SL, Pantilat SZ, McPhee SJ. The comprehensive care team: a controlled trial of outpatient palliative medicine consultation. *Arch Intern Med.* 2004;164(1):83-91.
13. Bakitas M, Lyons KD, Hegel MT, et al. Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: the Project ENABLE II randomized controlled trial. *JAMA.* 2009;302(7):741-749.
14. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med.* 2010;363(8):733-742.
15. Temel JS, Greer JA, Admane S, et al. Longitudinal perceptions of prognosis and goals of therapy in patients with metastatic non-small-cell lung cancer: results of a randomized study of early palliative care. *J Clin Oncol.* 2011;29(17):2319-2326.
16. Zimmermann C, Swami N, Krzyzanowska M, et al. Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. *Lancet.* 2014;383(9930):1721-1730.
17. Tattersall MHN, Martin A, Devine R, et al. Early contact with palliative care services: a randomized trial in patients with newly detected incurable metastatic cancer. *J Palliat Care Med.* 2014;4(170):1-6.
18. Bakitas M, Tosteson T, Li Z, et al. Early versus delayed initiation of concurrent palliative oncology care: patient outcomes in the ENABLE III randomized controlled trial. *J Clin Oncol.* 2015;33(13):1438-1445.
19. Temel JS, Greer JA, El-Jawahri A, et al. Effects of early integrated palliative care in patients with lung and gi cancer: a randomized clinical trial. *J Clin Oncol.* 2016;35(8):834-841.
20. Maltoni M, Scarpi E, Dall'Agata M, et al. Systematic versus on-demand early palliative care: results from a multicentre, randomised clinical trial. *Eur J Cancer.* 2016;65:61-68.
21. Maltoni M, Scarpi E, Dall'Agata M, et al. Systematic versus on-demand early palliative care: A randomised clinical trial assessing quality of care and treatment aggressiveness near the end of life. *Eur J Cancer.* 2016;69:110-118.
22. Groenvold M, Petersen MA, Damkier A, et al. Randomised clinical trial of early specialist palliative care plus standard care versus standard care alone in patients with advanced cancer: The Danish Palliative Care Trial. *Palliat Med.* 2017;31(9):814-824.
23. do Carmo TM, Paiva BSR, de Oliveira CZ, Nascimento MSA, Paiva CE. The feasibility and benefit of a brief psychosocial intervention in addition to early palliative care in patients with advanced cancer to reduce depressive symptoms: a pilot randomized controlled clinical trial. *BMC Cancer.* 2017;17(1):564.
24. Vanbutsele G, Pardon K, Van Belle S, et al. Effect of early and systematic integration of palliative care in patients with advanced cancer: a randomised controlled trial. *Lancet Oncol.* 2018;19(3):394-404.
25. Scarpi E, Dall'Agata M, Zagonel V, et al. Systematic vs. on-demand early palliative care in gastric cancer patients: a randomized clinical trial assessing patient and healthcare service outcomes. *Support Care Cancer.* 2019;27(7):2425-2434.
26. Hui D, Bruera E. Models of palliative care delivery for patients with cancer. *J Clin Oncol.* 2020;38(9):852-865.
27. Hui D, Bansal S, Strasser F, et al. Indicators of integration of oncology and palliative care programs: an international consensus. *Ann Oncol.* 2015;26(9):1953-1959.
28. Hui D, Bruera E. A personalized approach to assessing and managing pain in patients with cancer. *J Clin Oncol.* 2014;32(16):1640-1646.
29. Hui D, Kim SH, Roquemore J, Dev R, Chisholm G, Bruera E. Impact of timing and setting of palliative care referral on quality of end-of-life care in cancer patients. *Cancer.* 2014;120(11):1743-1749.
30. Hui D, Mori M, Meng YC, et al. Automatic referral to standardize palliative care access: an international Delphi survey. *Support Care Cancer.* 2018;26(1):175-180.
31. Hui D, Bruera E. The Edmonton Symptom Assessment System 25 years later: past, present and future developments. *J Pain Symptom Manage.* 2017;53(3):630-643.
32. Hui D, Masanori M, Watanabe S, et al. Referral criteria for outpatient specialty palliative cancer care: an international consensus. *Lancet Oncol.* 2016;17(12):e552-e559.
33. Hui D, Anderson L, Tang M, Park M, Liu D, Bruera E. Examination of referral criteria for outpatient palliative care among patients with advanced cancer. *Support Care Cancer.* 2019.
34. Hui D, Elsayem A, De la Cruz M, et al. Availability and integration of palliative care at US cancer centers. *JAMA.* 2010;303(11):1054-1061.
35. Prince-Paul M, Burant CJ, Saltzman JN, Teston LJ, Matthews CR. The effects of integrating an advanced practice palliative care nurse in a community oncology center: a pilot study. *J Support Oncol.* 2010;8(1):21-27.
36. Muir JC, Daly F, Davis MS, et al. Integrating palliative care into the outpatient, private practice oncology setting. *J Pain Symptom Manage.* 2010;40(1):126-135.
37. Einstein DJ, DeSanto-Madeya S, Gregas M, Lynch J, McDermott DF, Buss MK. Improving end-of-life care: palliative care embedded in an oncology clinic specializing in targeted and immune-based therapies. *J Oncol Pract.* 2017;13(9):e729-e737.
38. Walling AM, D'Ambruoso SF, Malin JL, et al. Effect and efficiency of an embedded palliative care nurse practitioner in an oncology clinic. *J Oncol Pract.* 2017;13(9):e792-e799.
39. Rabow M, Small R, Jow A, et al. The value of embedding: integrated palliative care for patients with metastatic breast cancer. *Breast Cancer Res Treat.* 2018;167(3):703-708.
40. Calton BA, Rabow MW, Branagan L, et al. Top ten tips palliative care clinicians should know about telepalliative care. *J Palliat Med.* 2019;22(8):981-985.

41. Guzman D, Ann-Yi S, Bruera E, et al. Enhancing palliative care patient access to psychological counseling through outreach telehealth services. *Psychooncology.* 2020;29(1):132-138.
42. Hancock S, Preston N, Jones H, Gadoud A. Telehealth in palliative care is being described but not evaluated: a systematic review. *BMC Palliat Care.* 2019;18(1):114.
43. Chua IS, Zachariah F, Dale W, et al. Early integrated telehealth versus in-person palliative care for patients with advanced lung cancer: a study protocol. *J Palliat Med.* 2019;22(S1):7-19.
44. Dalal S, Bruera S, Hui D, et al. Use of palliative care services in a tertiary cancer center. *Oncologist.* 2016;21(1):110-118.
45. Haider A, Tanco K, Epner M, et al. Physicians' compassion, communication skills, and professionalism with and without physicians' use of an examination room computer: a randomized clinical trial. *JAMA Oncol.* 2018;4(6):879-881.
46. Perez-Cruz P, Nguyen L, Rhondali W, et al. Attitudes and perceptions of patients, caregivers, and health care providers toward background music in patient care areas: an exploratory study. *J Palliat Med.* 2012;15(10):1130-1136.
47. Azhar A, Wong AN, Cerana AA, et al. Characteristics of unscheduled and scheduled outpatient palliative care clinic patients at a comprehensive cancer center. *J Pain Symptom Manage.* 2018;55(5):1327-1334.
48. Delgado-Guay MO, Kim YJ, Shin SH, et al. Avoidable and unavoidable visits to the emergency department among patients with advanced cancer receiving outpatient palliative care. *J Pain Symptom Manage.* 2015;49(3):497-504.
49. Pimentel LE, Yennurajalingam S, Chisholm G, et al. The frequency and factors associated with the use of a dedicated Supportive Care Center Telephone Triaging Program in patients with advanced cancer at a comprehensive cancer center. *J Pain Symptom Manage.* 2015;49(5):939-944.
50. Prado BL, Haider A, Naqvi S, et al. Changes in the care setting of first consults to palliative and supportive care over a seven-year period. *J Pain Symptom Manage.* 2019;57(1):86-92.
51. Pimentel LE, De La Cruz M, Wong A, Castro D, Bruera E. Snapshot of an outpatient supportive care center at a comprehensive cancer center. *J Palliat Med.* 2017;20(4):433-436.
52. Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. *J Palliat Care.* 1991;7(2):6-9.
53. Delgado-Guay M, Ferrer J, Rieber AG, et al. Financial distress and its associations with physical and emotional symptoms and quality of life among advanced cancer patients. *Oncologist.* 2015;20(9):1092-1098.
54. Delgado-Guay MO, Chisholm G, Williams J, Frisbee-Hume S, Ferguson AO, Bruera E. Frequency, intensity, and correlates of spiritual pain in advanced cancer patients assessed in a supportive/palliative care clinic. *Palliat Support Care.* 2016;14(4):341-348.
55. Breitbart W, Rosenfeld B, Roth A, Smith MJ, Cohen K, Passik S. The Memorial Delirium Assessment Scale. *J Pain Symptom Manage.* 1997;13(3):128-137.
56. Yennurajalingam S, Edwards T, Arthur JA, et al. Predicting the risk for aberrant opioid use behavior in patients receiving outpatient supportive care consultation at a comprehensive cancer center. *Cancer.* 2018;124(19):3942-3949.
57. Kim YJ, Hui D, Zhang Y, et al. Differences in performance status assessment among palliative care specialists, nurses, and medical oncologists. *J Pain Symptom Manage.* 2015;49(6):1050-1058.e1052.
58. Arthur J, Edwards T, Reddy S, et al. Outcomes of a specialized interdisciplinary approach for patients with cancer with aberrant opioid-related behavior. *Oncologist.* 2018;23(2):263-270.
59. Arthur J, Lu Z, Nguyen K, et al. Random vs targeted urine drug testing among patients undergoing long-term opioid treatment for cancer pain. *JAMA Oncol.* 2020;6(4):580-581.
60. Arthur J, Bruera E. Balancing opioid analgesia with the risk of nonmedical opioid use in patients with cancer. *Nat Rev Clin Oncol.* 2019;16(4):213-226.
61. Del Fabbro E, Hui D, Dalal S, Dev R, Nooruddin ZI, Bruera E. Clinical outcomes and contributors to weight loss in a cancer cachexia clinic. *J Palliat Med.* 2011;14(9):1004-1008.
62. Dev R, Wong A, Hui D, Bruera E. The evolving approach to management of cancer cachexia. *Oncology (Williston Park).* 2017;31(1):23-32.
63. Reddy SK, Tanco K, Yennu S, et al. Integration of a mandatory palliative care education into hematology-oncology fellowship training in a comprehensive cancer center: a survey of hematology oncology fellows. *J Oncol Pract.* 2019;15(11):e934-e941.
64. Wong A, Reddy A, Williams JL, et al. ReCAP: attitudes, beliefs, and awareness of graduate medical education trainees regarding palliative care at a comprehensive cancer center. *J Oncol Pract.* 2016;12(2):149-150; e127-137.
65. Wong A, Vidal M, Prado B, et al. Patients' perspective of timeliness and usefulness of an outpatient supportive care referral at a comprehensive cancer center. *J Pain Symptom Manage.* 2019;58(2):275-281.
66. Yennurajalingam S, Urbauer DL, Casper KL, et al. Impact of a palliative care consultation team on cancer-related symptoms in advanced cancer patients referred to an outpatient supportive care clinic. *J Pain Symptom Manage.* 2011;41(1):49-56.
67. Bruera E. Relieving physical and psychosocial pain in patients with cancer-the search for enlightened academic medical leaders. *JAMA Oncol.* 2019;5(10):1401-1402.

This page intentionally left blank

67 Rehabilitation

Brian Fricke
An Ngo-Huang
Ekta Gupta

KEY CONCEPTS

- Cancer rehabilitation is a medical subspecialty practiced by physical medicine and rehabilitation (PM&R) physicians, also known as physiatrists. Cancer physiatrists practice in a variety of settings to address a wide array of diagnoses and impairments, with the end goals of optimizing independent function and quality of life.
- The four phases of cancer rehabilitation as described by Dietz in 1980 are: preventive, restorative, supportive, and palliative. These concepts help cancer physiatrists frame their functional assessment and treatment goals when working with cancer patients and their treating oncologic teams.
- The Karnofsky Performance Scale and Eastern Cooperative Oncology Group Scale of Performance Status are widely used as overall functional assessment tools but are limited by overgeneralization and poor correlation with cognitive status. The Functional Independence Measure or the Boston University Activity Measure for Post-Acute Care used by rehabilitation professionals are more comprehensive tools to assess current function and changes over time.
- Neurorehabilitation broadly includes any impairment or functional deficit that results from compromise of the central nervous system (CNS) resulting from direct tumor invasion or as a byproduct of cancer treatment. These can include cognitive deficits, motor impairments, neuropathy, apraxia, ataxia, dysphagia, aphasia, spasticity, or bowel/bladder dysfunction. Depending on the severity or complexity of the impairment, comprehensive evaluation by a cancer rehabilitation physician may be beneficial.
- Musculoskeletal rehabilitation broadly includes any impairment or functional deficit that results from compromise of the musculoskeletal system (bone and/or surrounding soft tissue) resulting from primary, secondary, or metastatic tumor invasion, or as a byproduct of cancer treatment. Topics addressed include amputee care, radiation fibrosis, general musculoskeletal diagnosis and treatment, wound care, bone health, and exercise guidance. Depending on the severity or complexity of the impairment, comprehensive evaluation by a cancer rehabilitation physician may be beneficial.
- There is a growing body of evidence demonstrating that moderate to vigorous exercise confers some protection against several different types of cancer. Along these same lines, "prehabilitation" is an emerging field of interest in oncology. By improving physical function, optimization of nutrition, gaining muscle mass and strength, improving body composition, providing tobacco and/or alcohol cessation counseling, and managing mood before planned cancer treatment, studies have shown improved patient outcomes and reduction in healthcare costs by decreasing length of stay, reducing post-treatment complications, and reducing hospital readmission rates.

GENERAL PRINCIPLES

Cancer and its treatments are a major cause for impairments and disability. As cancer treatments have become increasingly successful and have improved survival, there has been an increasing focus on quality of life and rehabilitation in particular. Cancer rehabilitation is practiced by physical medicine and rehabilitation (PM&R) physicians, also known as physiatrists, in a variety of clinical settings including outpatient clinics, oncology wards, inpatient rehabilitation units, skilled nursing facilities, nursing homes, long-term acute care centers, palliative care units, and hospices. Common diagnoses addressed include asthenia, deconditioning, hemiplegia, spinal cord injury, peripheral neuropathy, somatic and neuropathic pain, steroid myopathy, lymphedema, bowel/bladder management, limb amputation, and limb dysfunction.

The major goal of cancer rehabilitation is to improve quality of life by minimizing the disability caused by cancer and its treatments and decreasing the "burden of care" needed by patients with cancer and their caregivers. The more patients can do for themselves, the less assistance they will require from those around them, and thus they are able to maintain more personal dignity.

In 1978, Justus Lehmann, supported by the National Cancer Institute screened 805 randomly selected patients with cancer, identifying multiple problems in the cancer patient population amenable to rehabilitation interventions along with barriers limiting the delivery of rehabilitation care. More than 40 years later, many of Lehmann's remediable cancer rehabilitation problems and barriers to rehabilitation care remain the same (Table 67–1).[1]

These problems are familiar to physiatrists because many are also found in traditional rehabilitation patients without cancer. Lehmann also described major barriers to the delivery of cancer rehabilitation care including the lack of identification of these problems by oncologists and the lack of referral to rehabilitation professionals for intervention. In addition, there are multiple patient-related factors that can affect the successful rehabilitation of the patient with cancer. Several reported by DeLisa include reduced life expectancy, extensive comorbidities, degree of pain, the dynamic nature of cancer lesions, the demands of anticancer therapies, and the desire to spend remaining time with loved ones.[2]

Phases of Cancer Rehabilitation

In 1980, Dietz categorized cancer rehabilitation into four stages: preventive, restorative, supportive, and palliative.[3] Preventive rehabilitation, more recently coined "prehabilitation," occurs before an intended treatment with the aim of preventing loss of function or disability. In 2001, Courneya described a similar concept called "buffering," whereby a patient with cancer performs exercises and undergoes therapies to increase their physical and functional reserves before cancer treatment.[4] Although the concept of prehabilitation is not unique to cancer, research in the field of oncologic surgery has intensified and results suggest better medical and surgical outcomes with prehabilitation programs.[5–9] An example of prehabilitation would include exercise and nutrition counseling, pre-amputation residual limb care education, and practicing ambulation with a walker for a patient with a lower-extremity sarcoma pending surgical intervention.

Restorative rehabilitation occurs in patients who are believed to be disease free or will have an anticipated relatively stable disease course. In the previous example, a patient with lower-extremity sarcoma with no known metastatic disease after amputation undergoes prosthetic rehabilitation. These first two stages are not significantly different from conventional non-oncologic rehabilitation. Fortunately, as survivorship has increased, restorative rehabilitation has become more prominent in addressing issues in this population, including disability, return to work, and lymphedema management.

For patients in whom we are unable to achieve or maintain a state of remission, supportive rehabilitation is performed to sustain function and provide symptom management. Similar to the example above, a patient with metastatic sarcoma may be provided therapies and durable medical equipment (DME) to promote functional independence while receiving chemoradiation.

Unfortunately, patients may succumb to their malignancy or its accompanying morbidities, and efforts to maximize function may require a transition to focusing on quality of life. Palliative rehabilitation

Table 67–1 Remediable Rehabilitation Problems and Barriers to Delivery of Care[1]

Remediable Rehabilitation Problems		Barriers to Delivery of Rehabilitation Care
Psychological/psychiatric impairments	Lymphedema management	Lack of identification of patient problems
Generalized weakness	Musculoskeletal difficulties	Lack of appropriate referral by physicians unfamiliar with the concept of rehabilitation
Impairments in activities of daily living	Swallowing dysfunction	Patient too ill to participate
Pain	Impaired communication	Patient denies need
Impaired gait/ambulation	Skin management	Cancer prognosis too limited
Disposition/housing issues	Vocational assessments	Rehabilitation unavailable
Neurologic impairments	Impaired nutrition	No financial resources
Vocational assessments	Lymphedema management	
Impaired nutrition		

is provided to reduce discomfort and improve independence in patients with advanced disease. Again, an example scenario is a patient with sarcoma, and advancing metastatic disease may have failed multiple treatment regimens and now requires rehabilitation to return home with some degree of assistance. The emphasis of palliative rehabilitation is typically to get the patient home into a safe environment, focusing on family and transfer training. Higher-level goals such as performing household chores and mobility for longer distances should be addressed as an outpatient.

The last two stages described by Dietz[3] are relatively unique to cancer rehabilitation. The typical course for a patient in conventional rehabilitation (for example post-stroke) is continued improvement after the inciting event. In the cancer patient with persistent disease, however, the battle continues with brief victories followed by declines as the disease progresses (Fig. 67–1).[10]

Multiple studies have established a need for rehabilitation in the cancer patient population.[11,12] Functional improvements of cancer rehabilitation patients have been demonstrated in a number of settings including inpatient[13–16] and palliative care,[17,18] on a consultation basis,[19] in a hospice setting,[20,21] and for outpatient settings.[22] The maintenance of physical activity and exercise has been implicated in increasing survival, with the greatest quantity of evidence in patients with breast or colon cancer. Multiple mechanisms may exist, and some have proposed these findings to be related to levels of insulin/c-peptide, along with the positive effects of buffering on physiologic reserves, potentially allowing for more treatment.[23,24] Cancer physiatrists must also address medical sequelae and complications that are unique to this patient population. These comorbidities may serve as a significant challenge and require frequent communication between the primary oncology and rehabilitation teams as the transfer rate from inpatient rehabilitation to acute care teams has been shown to be quite high compared with other rehabilitation diagnoses.[25]

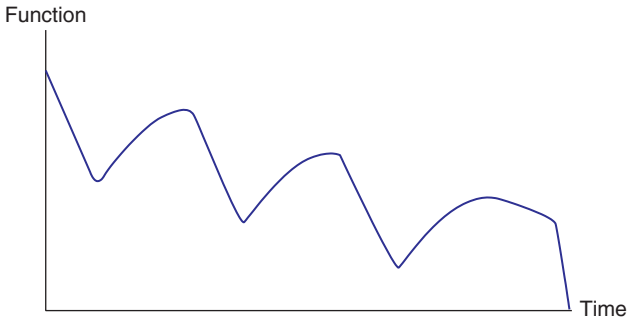


FIGURE 67–1 Functional changes over time typically seen in patients receiving cancer treatment.



FIGURE 67–2 The interdisciplinary rehabilitation team.

Rehabilitation often begins when a patient is admitted into the hospital. As a holistic medical specialty that accounts for medical needs while focusing on a patient's functional issues, physiatrists will ask a series of detailed social questions of patients and their caregivers. This comprehensive evaluation identifies a patient's current functional level, strength, cognition, availability of supervision or assistance upon discharge, accessibility of home conditions, and financial resources. Based on the patient's impairments and the aforementioned practical considerations, realistic and suitable rehabilitation goals are set. If a patient is medically stable with unmet functional and safety goals, their activity tolerance and performance trajectory are used to guide determination of the appropriate intensity and setting for additional rehabilitation.

Rehabilitation goals are formulated and fulfilled by a comprehensive interdisciplinary team of health care professionals, including the physiatrist, rehabilitation nurse, physical therapist, occupational therapist, speech-language pathologist (SLP), dietitian, pharmacist, chaplain, social worker, and case manager. Each member of the team has specific expertise to support the patient with a care plan of maximizing medical stability, function, financial resources, and caregiver involvement for a discharge that is as safe and meaningful as possible (Fig. 67–2).

Rehabilitation at MD Anderson

At MDACC, the cancer rehabilitation practice includes eight physiatrists, and a rehabilitation therapy staff consisting of SLPs and more than 100 physical therapy (PT) and occupational therapy (OT) clinicians. Rehabilitation therapists see more than 300 inpatients and 100 outpatients per day. Patients with a variety of tumor types are seen—the most common being brain, spine, lung, breast, hematologic, genitourinary, gastrointestinal, and head and neck tumors. The most common inpatient rehabilitation diagnoses include asthenia, gait abnormality, dyspnea, hemiparesis, spinal cord injury, and neurogenic bowel and bladder.

Common outpatient rehabilitation diagnoses include lymphedema, myofascial pain, rotator cuff dysfunction, peripheral neuropathy, radiation fibrosis, and low back pain. Inpatient and outpatient electromyograms are performed for neuropathic and myopathic diagnoses. Spasticity management with oral medications and chemodenervation using botulinum toxin injections is also a major focus.

Functional Metrics

When describing a cancer patient's functional status, the Karnofsky Performance Scale (KPS)[26] or Eastern Cooperative Oncology Group Scale of Performance Status[27] are often used. These scales have historically been the most widely used scales in oncology patients both clinically and in research, with various ways in which the scales have been mapped to correlate with each other. They are quick and easy generalized measurements of a patient's function. Weaknesses of these scales include overgeneralization (unable to measure specific tasks) and poor correlation with cognition.[28,29]

In rehabilitation, the outcome scale most often used is the Functional Independence Measure (FIM) (Fig. 67–3). This multidimensional scale addresses 18 items from a scale of 1 (total assistance) to 7 (complete independence). Items are subdivided into self-care, sphincter control, transfers, locomotion, communication, and social cognition. Subscale or aggregate scores are also often useful. It is a common language used in inpatient rehabilitation settings, and it is used to measure changes in functional status during the course of rehabilitation. Criticisms of the scale include that it is too long, too general, and omits items that are important for specific populations, such as those with spinal cord injuries.[30] The Boston University Activity Measure for Post-Acute Care (AM-PAC), developed in 2004, is being used more widely in rehabilitation setttings.[31] The Six-Clicks Basic Mobility and Daily activity are currently used in the MDACC inpatient setting. The Computer Adaptive Test version of this scale selects items from three main domains of basic mobility, daily activity, and applied cognition to match a patient's functional ability, thereby reducing the total number of items on the assessment while increasing the measure's validity.[32]

NEUROLOGICAL CANCER REHABILITATION

Although comprising a relatively small subset of the overall cancer population, patients with malignancy involving the brain or spinal cord often have considerable rehabilitation needs and make up a significant portion of cancer rehabilitation practice. These groups closely resemble their noncancer counterparts in terms of impairments and functional deficits that physiatrists commonly manage. Several key factors must be considered during rehabilitation of the patient with malignancy involving the central nervous system (CNS).

BRAIN TUMORS

Primary brain tumors, although they account for less than 2% of all malignancies, are the second leading cause of death from neurologic disorders after stroke.[33] One-half to two-thirds of intracranial tumors have been reported to be primary tumors.[34] In addition to primary brain tumors, brain metastases are estimated to occur in 20% to 40% of patients with cancer. Most of the metastases are located in the cerebral hemispheres, followed by the cerebellum, and then the brainstem. The incidence of brain tumor metastases is rising possibly because of the increasing length of survival in patients with cancer,[35] increasing ability to diagnose a tumor with improved radiographic imaging,[36] and possibly recent chemotherapy agents that may weaken the blood brain barrier.[37]

Normal brain parenchyma can be destroyed or compressed by the tumor, and the location of the tumor determines the resultant neurologic deficit. Surgical resection may exacerbate these deficits by creating inflammation or peritumoral infarct.[38] Radiation treatment has long been an integral part of brain tumor treatments and often results in collateral damage. Early acute radiation leukoencephalopathy is likely caused by increased cerebral edema. Late-delayed radiation reactions include focal cerebral radiation necrosis, diffuse cerebral radiation injury, and combined-therapy diffuse white matter injury/leukoencephalopathy. Clinical diffuse cerebral radiation injury has been reported in 2% to 5% of patients with metastases and 19% of 1-year survivors after whole brain radiation.[39,40]

Another etiology of significant neurologic deficits that can be challenging to diagnose and manage is leptomeningeal disease (LMD). Leptomeningeal metastases have been reported to occur in up to 10% of breast and lung cancer, melanoma, and acute lymphoblastic and myeloid leukemias, and up to 20% of primary CNS or ocular lymphomas, and non-Hodgkin lymphomas.[41] The presence of LMD is often a poor prognostic indicator of survival, and rehabilitation goals should be set accordingly. However, it has been demonstrated that patients with LMD can still benefit from comprehensive inpatient rehabilitation.[41]

The most common neurologic deficits in patients with brain tumors include impaired cognition (80%), weakness (78%), visual-perceptual deficits (53%), sensory loss (38%), and bowel/bladder dysfunction (37%). Other less common deficits include cranial

FIM™ Instrument

Levels		
	7 Complete Independence (timely, safely) 6 Modified Independence (device)	**No helper**
	Modified Dependence 5 Supervision (subject = 100%) 4 Minimal Assistance (subject = 75%+) 3 Moderate Assistance (subject = 50%+) **Complete Dependence** 2 Maximal Assistance (subject = 25%+) 1 Total Assistance (subject = less than 25%+)	**Helper**

	Admission	Discharge	Follow-up
Self-Care			
A. Eating	☐	☐	☐
B. Grooming	☐	☐	☐
C. Bathing	☐	☐	☐
D. Dressing - Upper Body	☐	☐	☐
E. Dressing - Lower Body	☐	☐	☐
F. Toileting	☐	☐	☐
Sphincter Control			
G. Bladder Management	☐	☐	☐
H. Bowel Management	☐	☐	☐
Transfers			
I. Bed, Chair, Wheelchair	☐	☐	☐
J. Toilet	☐	☐	☐
K. Tub, Shower	☐	☐	☐
Locomotion			
L. Walk/Wheelchair	☐ W Walk C Wheelchair B Both	☐ W Walk C Wheelchair B Both	☐ W Walk C Wheelchair B Both
M. Stairs	☐	☐	☐
Motor Subtotal Score	☐	☐	☐
Communication			
N. Comprehension	☐ A Auditory V Visual B Both	☐ A Auditory V Visual B Both	☐ A Auditory V Visual B Both
O. Expression	☐ A Auditory V Visual B Both	☐ A Auditory V Visual B Both	☐ A Auditory V Visual B Both
Social Cognition			
P. Social Interaction	☐	☐	☐
Q. Problem Solving	☐	☐	☐
R. Memory	☐	☐	☐
Cognitive Subtotal Score	☐	☐	☐
Total FIM™ Score	☐	☐	☐

Note: Leave no blanks. Enter 1 if patient is not testable due to risk.

FIGURE 67–3 **The Function Independence Measure (FIM) is a rehabilitation outcome measure used to record a patient's functional level. (Copyright © 1997 Uniform Data System for Medical Rehabilitation, a division of UB Foundation Activities, Inc. Reprinted with permission.)**

nerve palsy, dysarthria, dysphagia, aphasia, ataxia, and diplopia. Approximately 75% of patients with brain tumors have three or more concurrent neurologic deficits, and 39% have five or more deficits.[42] Because of the diverse nature of these neurologic deficits and their impact on functional performance and activities of daily living (ADLs), comprehensive multidisciplinary inpatient rehabilitation is often necessary.

Patients with brain tumors have similar efficiencies of functional improvement when compared with their traumatic brain injury and stroke counterparts, without much variability between tumor types. Lengths of stay tend to be shorter among patients with brain tumors, potentially because of a need to return patients home sooner given their shorter life expectancies.[43–47] Nonetheless, patients with brain tumors often have progressive disease resulting in gradual functional decline and present unique challenges for physiatrists.

CANCER-RELATED SPINAL CORD INJURY

Primary spinal cord tumors such as meningiomas, neurofibromas, and gliomas are relatively rare, and the majority of tumors involving the spinal cord are metastatic. Ninety-five percent of metastatic lesions are extradural, often arising from the vertebral body and compressing the anterior spinal cord. Most spinal cord metastases originate from primary tumors of the breast, lung, and prostate. Other tumors that metastasize to the spine include renal, melanoma, myeloma, and thyroid. Approximately 70% of spinal metastases occur in the thoracic spine, which has higher vascular flow and a smaller ratio of canal-to-cord diameter than the other two major spinal segments,[48] making it uniquely vulnerable to metastatic lesions.

Common presenting symptoms include pain worse at night and lying in the supine position. Weakness and sensory loss, along with the development of bowel or bladder incontinence, may indicate spinal cord compromise. Rapid progression of paraparesis over only a few hours indicates arterial compromise by tumor invasion or pressure; slowly evolving symptoms suggest gradual cord impingement and may respond to systemic steroids and/or radiotherapy, potentially alleviating pain and improving neurologic function.[49]

If a tumor involves two or three columns of the spine, spinal stability is of concern and initial treatment is aimed at stabilization of the spinal column. Surgical consultation is prudent in cases of neurologic compromise, pathologic fracture and dislocation/spondylolisthesis, failure of radiation therapy, and rapidly progressive myelopathy. If operative intervention is not recommended, prescription of an appropriate spinal orthosis may limit the degree of movement at various spinal levels.

Once spinal stabilization is achieved, comprehensive inpatient rehabilitation can address the impairments, functional limitations, and disabilities associated with spinal cord compression and injury caused by cancer. Individuals with nontraumatic spinal cord injuries can achieve significant gains in FIM scores during inpatient rehabilitation.[16] It has also been suggested that because of the limited prognosis of cancer patients with spinal cord compression, an expedited inpatient rehabilitation stay with the focus on family training and home safety should be emphasized.

Neurologic Motor Impairment

Motor impairment with hemiparesis, paraparesis, quadriparesis, ataxia, and apraxia may yield an unsafe gait pattern, increased risk for falls, and a need for inpatient rehabilitation. During inpatient rehabilitation, PTs provide hands-on analysis and treatment of a patient's bed and wheelchair mobility, transfers, and gait with or without an assistive device (eg, single-point cane, quad cane, rolling walker, hemi-walker, and wheelchair). Occupational therapists simultaneously aid vital recovery of other activity limitations, commonly addressing basic ADLs including dressing, bathing, toileting, grooming, and eating. Once a patient is functionally safe with or without an assistive device, they may be discharged home with outpatient rehabilitation prescribed to maximize functional gains and advance patient goals.

The stroke recovery pattern is often used as a guide for patients with brain tumors but does not always correlate. In stroke patients, the recovery of strength occurs in a proximal-to-distal fashion, with flaccidity and decreased muscle tone progressing to spasticity and increased muscle tone. Spasticity of affected limbs can evolve into flexor or extensor synergy patterns, and recovery of movement may plateau at any stage or progress to isolated coordinated volitional motor movement.[50,51] Neuromuscular facilitation techniques applied by PTs and OTs promote working with or against these patterns to optimize functional recovery of impaired extremities.

In cases of moderate neuromuscular weakness, functional electrical stimulation can be incorporated into a rehabilitation program. Using a low-level electrical current to stimulate motor or reflex sensory nerves, coordinated muscle contraction may produce purposeful, functional movements in paretic or paralytic muscles.[52] In addition, orthotic devices may be prescribed to support weak limbs and prevent secondary complications. An example would be an ankle-foot orthosis provided to prevent falls by stabilizing the ankle and knee during ambulation in a patient with ankle dorsiflexor weakness (foot drop). Another example would

be a lapboard while a hemiparetic patient is seated[53] to prevent painful shoulder subluxation caused by loss of motor control of the shoulder stabilizers including the deltoid and supraspinatus muscles.[54]

Apraxia and Hemispatial Neglect

Apraxia, hemisensory deficit, and homonymous hemianopsia may also be seen with hemiparesis. Visual or somatic hemineglect is more frequently seen when the nondominant cerebral hemisphere is affected and has a negative effect on sitting balance, visual perception, wheelchair mobility, safety awareness, and risk of falling. Patients with neglect have difficulty with hygiene and self-care activities, especially on the affected side. Rehabilitation programs must address the issues of apraxia and hemispatial neglect through focused measures led by SLPs, OTs, and PTs. Family training and education are important in this setting as well.

Ataxia

Cerebellar ataxia may be seen with mass effect within the posterior fossa, paraneoplastic cerebellar degeneration, and with high-dose administration of cytarabine or 5-fluorouracil.[55,56] Involvement of the cerebellum can produce intention tremors, dysmetria, and dysdiadochokinesis as patients lose the ability to coordinate agonist and antagonist muscle groups.[57] Response to pharmaceutical management is often poor; consequently, PT and OT are often mainstays of treatment. Therapies may include the teaching of compensatory techniques, weighted tools or wraps to reduce oscillations, and gait training with appropriate assistive devices for balance and safety.[58]

Aphasia

Depending on its location, a tumor may be associated with deficits in speech, which can vary in severity and type. SLP practitioners can diagnose the type of aphasia from a comprehensive neurologic examination including speech comprehension, fluency, and repetition. These include Broca, Wernicke, anomic, global, conduction, and the transcortical motor and sensory aphasias. A speech pathologist may implement treatment approaches including melodic intonation therapy, Amer-Ind Code treatment, functional communication treatment, stimulation approach, and Promoting Aphasics' Communication Effectiveness therapy.[59]

Cognitive Deficits

Cognitive deficits often are more problematic than motor deficits and may vary significantly. They can arise from direct injury to the brain tissue as a result of the tumor itself, from surgical resection, radiation, chemotherapy, depression/anxiety, and medications such as steroids, analgesics, and anticonvulsants.[36] Impairments most commonly seen involve limited memory and attention, decreased initiation, and psychomotor retardation.[60]

The physiatrist evaluates cognition as part of their examination, formulating a rehabilitation program involving all therapy disciplines. Specific deficits in language and cognition can be further delineated through specific testing performed by a SLP. The occupational therapist may also incorporate cognitive rehabilitation as part of a patient's plan of care. In some cases, formal neuropsychological testing may be of great value, especially if a patient wishes to return to work.

Dysphagia

A disruption in the swallowing process may also occur in patients with brain tumors or head and neck cancer caused by either direct tumor burden or as a byproduct of treatment. It is important to diagnose dysphagia because serious potential complications, such as malnutrition and aspiration pneumonia, can be devastating if dysphagia remains undetected. If dysphagia is suspected, a speech pathologist is consulted for bedside evaluation, and daily swallowing exercises are incorporated. Additional treatments include dietary modifications and facilitation techniques.[61] Video fluoroscopic evaluation may help guide food and liquid consistency restrictions (for example, puree, semisolid, or solid foods; or liquids with various degrees of thickening agents).

Compensatory strategies include proper head and trunk positioning, which for most patients is to be seated upright with head midline, trunk erect, and the neck slightly flexed forward. Other techniques include the chin-tuck method and head turning and tilting during swallowing. Regular follow-up to assess for dysphagia improvement is required and may be done by clinical examination or radiographic study. If improvement is noted, the diet may be advanced appropriately.

Spasticity

Spasticity is defined as velocity-dependent resistance to passive movement across a joint. It is an abnormality involving increased muscle tone and is one of the positive findings of upper motor neuron syndrome that can affect patients with brain tumors and cancer-related spinal cord injury. Spasticity must be distinguished from soft tissue contractures, which can result from chronic scar tissue formation and may arise from various causes, including uncontrolled spasticity. Spasticity can affect a patient's gait pattern, ADLs, and hygiene performance, and in severe cases may cause

pain and joint contracture. In some cases, however, spasticity may be beneficial, as when a patient may use knee extensor spasticity to assist in transferring from a sitting to a standing position. Goals of spasticity treatment include decreasing pain, improving hygiene, enhancing the efficiency of gait and transfers, minimizing contractures, and improving self-care.

Treatment measures for spasticity include physical and medical interventions. Proper positioning, passive range-of-motion exercises, serial casting, splints, and braces are some of the physical interventions used in treating spasticity. Oral medication options may include tizanidine, dantrolene sodium, and baclofen, but dosing is often limited by the side effects of excessive drowsiness and cognitive changes.[62] Localized treatment options such as botulinum toxin injections, phenol injections, or implantable intrathecal baclofen pumps may be useful if skilled physicians and follow-up resources are available.

Bladder Management

For all cancer patients with neurologic involvement and those with profound deconditioning, it is prudent to evaluate for signs of bladder dysfunction. One should maintain a low clinical threshold for working up a urinary tract infection. Furthermore, postvoid residual bladder scans can be performed to evaluate for complete bladder emptying.

If the pontine micturition center is preserved, patients with brain tumors and spinal cord injuries often have upper motor neuron bladder dysfunction, which is characterized by bladder hyper-reflexia, low postvoid residual volumes, high bladder pressures, diminished bladder compliance, reflex or urge incontinence, and complete emptying.[63] Persistent areflexia and retention may occur with bilateral brainstem lesions[61] or lesions involving the sacral micturition center, resulting in overflow incontinence and lower motor neuron bladder dysfunction. Patients with complete spinal cord lesions may have reflex incontinence and incomplete voiding caused by detrusor-sphincter dyssynergia.[63] In many cases, a mixed picture of the aforementioned bladder dysfunctions may occur. In complex cases that are difficult to manage, a urology consult for a formal urodynamics study should be considered.

Treatment should be directed at the cause of bladder dysfunction. Using a bedside commode or urinal is of benefit for patients with weakness or a limited ability to safely ambulate to the bathroom. A timed voiding program is useful for those with functional incontinence caused by hyper-reflexic urgency. An intermittent catheterization program may be necessary if postvoid residual volumes are persistently elevated above 150 mL. Anticholinergic medications such as oxybutynin or tolterodine tartrate or β-3 adrenergic agonists such as mirabegron can be used for persistent incontinence in the setting of a hyper-reflexic detrusor[61] to decrease detrusor tone and allow for greater bladder storage capacity; then an intermittent catheterization program can be instituted. Trial of an α-adrenergic agent (such as tamsulosin or terazosin) may be conducted in patients with urinary retention, but resting and orthostatic blood pressures should be monitored upon initiation and dose titration.

An intermittent catheterization program initially involves daily measurements of postvoid residuals (volume of urine remaining in the bladder after a void). If postvoid volumes are elevated, the patient is catheterized every 4 hours. Goals may vary but catheterized volumes should not exceed 500 mL. If the volumes remain consistently low, the frequency of catheterization can be decreased to every 6 hours.

It is important to note that in the cancer population, life expectancy often plays a part in rehabilitation management. Intermittent catheterization may be the preferred method of management for many patients, but an indwelling catheter, or a condom catheter for men, is sometimes used for ease and comfort in patients with limited prognosis or difficulty catheterizing themselves.

Bowel Management

Typically, with lesions above the conus medullaris, an upper motor neuron bowel dysfunction is present, with the muscles of the external anal sphincter and pelvic floor becoming spastic. The connection between the spinal cord and the colon remains intact, and stool can be propelled by reflex activity. With lesions below the conus medullaris, an areflexic lower motor neuron bowel dysfunction is present, with the myenteric plexus intrinsically moving stool slowly.[64]

A complicating matter in patients with cancer is opioid-induced constipation. This and other premorbid factors and current bowel function must be ascertained before instituting a bowel program. Often a plain radiograph of the abdomen is obtained to assess for obstipation before beginning a bowel program. If obstipation is present, suppositories or enemas can be given to clean out the bowels and evacuate the rectal vault.

The goals of a bowel program are to prevent fecal impaction and to facilitate efficient bowel evacuation on a routine schedule compatible with one's daily activities. A bowel program begins with a proper diet, including adequate amounts of fluid and fiber order to create soft, bulky stools that can decrease bowel transit time. In contrast, fatty foods can increase transit time. Medication options may include stimulant or osmotic laxatives, as well as adjunctive suppositories and enemas.

In stepwise fashion, a sample bowel program begins with an abdominal radiograph to determine whether evacuation by enema is necessary; then an appropriate diet is begun, along with stool softeners or stimulants. To take advantage of the gastrocolic reflex, the patient is transferred to a commode or toilet approximately 30 minutes after a meal, preceded by placement of a suppository 10 minutes before. In addition, manual digital stimulation 20 minutes after suppository insertion can be incorporated to induce the rectocolic reflex.[63]

MUSCULOSKELETAL CANCER REHABILITATION

Bone and Soft Tissue Tumors

Primary bone tumors are rare, with the majority arising in the lower limbs. Osteogenic sarcoma is the most common primary bone tumor, representing 20% of all malignant primary bone tumors, with 75% occurring in children.[65] Survival rates have increased from 20% to 70% with the implementation of chemotherapy and limb-sparing surgeries.[65] Grade of severity is based on biopsy results.[66] Anatomic setting and metastases are evaluated by imaging, with lung metastases being most common; based on this information, a surgical plan is devised.[66] No difference in survival has been shown between neoadjuvant chemotherapy followed by surgery versus surgery and adjuvant chemotherapy.[66] Notably, osteogenic sarcoma tends to be less radiation-sensitive as well.[66]

Primary malignant chondrosarcomas are not chemotherapy-sensitive, and wide excision is the treatment of choice.[66] These patients may undergo several types of surgery, including allografts and endoprostheses. Hemipelvectomy and sacrectomy are less common but are often seen at MDACC. There are two types of hemipelvectomy—internal and external—and four types of pelvic resection: iliac (type I), periacetabular (type II), pubic bone (type III), and sacrum (type IV), with combined resections possible.[67] Complications such as hematoma, delayed skin healing, and/or orthostasis caused by delayed mobility may be seen. It is key to communicate with the surgical teams regarding weight-bearing and range-of-motion precautions because this will impact a patient's rehabilitation course and length of stay.[68] Depending on musculature and nerves affected, as well as type of reconstruction, rehabilitation diagnoses may include lower limb weakness, sensory impairment, and neurogenic bowel and bladder. Multiple studies have shown that sparing of S3 spinal nerves results in less bowel dysfunction and sparing of L5/S1 spinal nerves results in improved motor function.[68,69]

Bony Metastases

Bony metastases are most common in the axial skeleton, followed by long bones, skull, ribs, and pelvis.[70] Skeletal-related events include pain, pathologic fracture, hypercalcemia, and spinal cord compression caused by bony metastases; this can result in significant loss of quality of life and function.[66] Bony metastases must be on the differential diagnosis in a patient complaining of localized bone pain. Lytic lesions can be seen with multiple myeloma, renal, lung, and thyroid cancers.[66,70] Blastic lesions can be seen with prostate cancer and mixed lesions with breast cancer.[66,70] Imaging recommendations are based on the type of cancer and location of pain, with magnetic resonance imaging preferred for spine and radiograph preferred for multiple myeloma lytic lesions, but definitive diagnosis requires biopsy. Treatment can be operative for impending pathologic fractures or nonoperative to halt progress and prevent fractures. Systemic hormones, chemotherapy, radiation therapy (often the treatment of choice for radiosensitive tumors), protected weight bearing, and external immobilization are all nonoperative interventions.[66,70] Except for lymphoma and some testicular germ cell tumors, treatment is generally palliative to relieve pain, prevent fractures, prolong survival, and improve quality of life.[66,70]

Rehabilitation of Bone Lesions

These patients often undergo PT and OT, and the physician needs to provide appropriate weight-bearing precautions, range-of-motion restrictions, positioning recommendations, and what resistance exercises to avoid (for instance, axial loading is generally preferred over eccentric exercise). By using an assistive device such as a walker, the patient may be able to offload weight to allow them to ambulate more independently without increasing fracture risk. Spinal precautions are recommended in those at risk for or with pathologic fractures and include no bending, lifting greater than 5 pounds, or twisting. A thoracic lumbar sacral spinal orthosis may need to be considered. It is also important to educate patients and family on the risks of immobility, including pressure ulcers, thromboembolic events, muscle contracture/weakness/atrophy, and osteopenia or osteoporosis.[66,70]

Amputee Care

Depending on the level of involvement of a bony tumor, amputation may be considered the best option for resection of the tumor. Amputation may provide the best outcome for the patient with bone or soft tissue sarcomas, but generally less than 10% of patients will require amputation.[66] Often, primary bone sarcomas

with fracture require immediate amputation to control tumor spread, especially in patients who present with advanced spread.[66] Below-knee amputation may be performed for distal lower-extremity tumors because of its superior function and decreased residual disability.[66] In addition, infection, limited or nonresponse to treatment, necrosis, or inadequate tissue for limb salvage may lead to amputation. In general, the more proximal the amputation, the more energy expenditure is required to ambulate with a prosthesis. After amputation, a patient generally remains non–weight bearing on the affected limb for 6 weeks, depending on wound healing. During this time, patients should receive PT and OT under the supervision of a physiatrist and orthopedist to focus on building independence, strengthening muscles for pregait and weight-bearing activities, and education on appropriate range of motion. Edema and residual limb shaping for prosthetic fitting is achieved first by wraps and then shrinker socks once appropriate. Patients may report phantom sensation and/or phantom pain. This can be treated by pharmacologic interventions, such as gabapentin, duloxetine, and pregabalin, as well as nonpharmacologic techniques, such as desensitization, edema management, and mirror therapy. Central pain syndrome may occur in patients as well. Neuromas may develop at distal limb sites and can be treated with anesthetic blocks to provide relief. Patients who have undergone external hemipelvectomy or sacrectomy may require additional education on sitting balance and use a prosthesis for sitting. Rotationplasty is primarily seen in children with growth potential to avoid above-the-knee amputation.[66] These patients may require later limb-lengthening surgeries and coordinated care with orthopedics, prosthetics, physiatry, and PT. For the upper extremity, forequarter amputation is removal of the shoulder and ipsilateral arm.[66] Postoperative care requires significant work on balance and ADLs with OT. An upper-extremity prosthesis can provide significant cosmetic and functional benefit to the patient.[66]

Radiation Fibrosis

Radiation fibrosis occurs as a result of tissue damage from radiation therapy.[71] Radiation fibrosis syndrome (RFS) is defined as the "clinical manifestations of progressive fibrotic sclerosis that can result from radiation treatment."[72] Because of abnormal accumulation of thrombin in extravascular and intravascular compartments, there may be tissue sclerosis in skin, muscle, nerve, viscera, tendon, ligament, and bone.[72] RFS may occur differently in each person because of susceptibility of underlying tissues to the effects of radiation.[72] Much of the literature has been focused on radiation-induced fibrosis in those who received mantle radiation for Hodgkin lymphoma as well as in breast cancer patients who received chest wall and supraclavicular radiation, but symptoms are also seen in patients with gastrointestinal and lung cancer. Patients with head and neck cancer also exhibit significant morbidity from radiation-induced fibrosis with neck posturing (such as dystonia or torticollis), trismus, and shoulder impairment. Temporally, effects can be seen during or immediately after radiation (acute), up to 3 months from completion (early-delayed), or more than 3 months from completion (late-delayed).[73] Patients can present with "myelo-radiculo-plexo-neuro-myopathy" caused by the significant impact on each respective component of the neuromuscular chain.[72] Patients may experience lower-extremity weakness and spasticity with myelopathy; upper or lower-extremity radiculopathy; plexopathy involving the trunk, divisions, or cords; peripheral neuropathy related to terminal branches involved; and myopathy affecting local muscles within the radiation field.[72] Electromyography/nerve conduction studies and magnetic resonance plexus imaging may be helpful in evaluating the extent of involvement. Unfortunately, RFS is not reversible, with prevention being the first step to avoiding it.[74] As technology continues to improve, the frequency of radiation-induced fibrosis may decrease. Treatments aimed at targeting matrix synthesis and use of biologics to prevent fibrosis are being explored.[74] Pentoxifylline with vitamin E has been shown to improve tissue compliance in patients with breast cancer.[75] Research is ongoing for hyperbaric oxygen and anticoagulation.[66] Most of all, education must be provided to patients by physiatrists, PT, and OT focused on stretching the involved muscles, strengthening both affected and unaffected sides, and orthoses. SLP treatments for patients with trismus include progressive jaw-opening exercises and orthoses. Botulinum toxin injections can treat spasticity and spasms of muscle, including cervical dystonia, trismus, chest wall and paraspinal spasms, and focal neuropathic pain disorders.[66]

REHABILITATION OF GENERALIZED DECONDITIONING AND ASTHENIA

Generalized weakness, deconditioning, and asthenia are common problems in patients with cancer that can require cancer rehabilitation intervention. Asthenia is a combination of weakness and decreased exercise tolerance arising from several factors including muscle wasting, disuse atrophy, malnutrition, anemia, and cardiac or pulmonary comorbidities. Functional impacts of asthenia can include difficulty with transfers, ambulation, ADLs, and balance, as well as a risk for falls.

Rehabilitation treatment can begin with increased sitting time and gentle range-of-motion exercises. This is followed by a progressive increase in physical activity

dose, duration, and intensity, along with instruction in energy conservation and balance training. It is also important to address other potential contributing medical conditions, such as anemia, malnutrition, sleep, pain, and mood disorders. Short-term inpatient rehabilitation can be effective in improving functional status after an acute decline. Outpatient rehabilitation may help maintain or more gradually improve functional performance. However, if the primary malignancy progresses, functional performance will likely deteriorate.

Muscle Atrophy

Muscle atrophy commonly occurs in patients with cancer. There are three types of muscle fibers. Type I muscle fibers are the slow-twitch oxidative metabolism fibers, which have slow fatigability and are used for prolonged activity. Type IIB fibers are the fast-twitch fibers, which use glycolytic anaerobic metabolism and have rapid fatigability. Type IIA is an intermediate fiber.

Prolonged bed rest can result in muscle atrophy and weakness. In a classic study by Muller, the muscles of a person on strict bed rest can lose approximately 1.0% to 1.5% of their initial muscle strength per day of bed rest, corresponding to approximately a 10% loss of strength per week.[76] Antigravity muscles like the gastrocnemius and back extensor muscles tend to lose strength disproportionately, with larger muscles losing strength more quickly than smaller muscles, often leaving handgrip strength unaffected.[77,78] Type I fibers are more affected than type II fibers.[79]

These effects on muscles can be counteracted by a daily stretching program, which delays muscle atrophy.[80] In addition, daily isometric muscle contractions of 10% to 20% of maximal tension for 10 seconds can help maintain muscle strength.[76] Electrical stimulation of muscles can also be used. In general, it may take two or more times as long as the period of immobilization to recover muscle strength.[81]

Cardiovascular Effects

There are deleterious cardiovascular effects from prolonged bed rest as well. Cardiac deconditioning may lead to resting tachycardia. After a period of bed rest, the heart rate can increase by about one-half beat per minute each day for the first 3 to 4 weeks of immobilization.[82] In addition, there are decreased diastolic filling times. This results in decreased myocardial perfusion, decreased stroke volume with submaximal and maximal exercises, decline in cardiac output at submaximal exercise, and deleterious hemodynamic and orthostatic changes.

The treatment of adverse cardiovascular effects from prolonged immobilization is mainly aimed at prevention. Sitting in a chair prevents deterioration of maximum oxygen consumption and orthostatic intolerance. Isometric exercise minimizes decreases in maximum oxygen consumption.[83] Cardiovascular deconditioning can be reversed by progressive increase in activity and regaining of upright posture. Orthostatic intolerance can be helped by range-of-motion exercises, abdominal strengthening, leg exercises to reverse venous stasis, and progressive ambulation. In addition, supportive treatments for orthostatic intolerance include the use of a tilt table, compressive garments such as leg stockings and abdominal binders, and medications such as ephedrine, midodrine, and fludrocortisone acetate.

Thrombotic complications, such as the development of a deep venous thrombosis (DVT) or a pulmonary embolism (PE), are also risks of immobility. Virchow's triad of hypercoagulability, endothelial injury, and stasis of blood flow are factors that acutely ill or postoperative cancer patients share that can contribute to clot formation. At times, rehabilitation begins after a prolonged state of immobility and it is imperative that we take measures to prevent DVT or PE development. Patients should be mobilized, encouraged to ambulate, provided with external intermittent leg compression devices, and administered low-dose anticoagulation when contraindications are not present.[84]

Joint Contractures

Another risk of prolonged bed rest and immobility is joint contracture, an abnormal limitation of passive joint range of motion. Typical contractures from immobilization include hip and knee flexion, ankle plantarflexion, elbow flexion, and internally rotated shoulder contractures. Contractures are treated with stretching, range-of-motion exercises, and soft tissue manipulation. For more severe cases, deep heating followed by range-of-motion exercises and serial casting may be necessary. One goal of nursing and inpatient rehabilitation services should be to prevent joint contractures before they occur. Hip flexion contractures can be prevented by occasionally lying in a prone position and avoiding overly soft mattresses. Dorsiflexion exercises, pressure relief ankle-foot orthoses, and footboards can help prevent ankle plantarflexion contractures.

Bone Health

Immobilization can also affect the bones. Wolff's law states that the ratio of formation to resorption is influenced by the stresses to which bones are subjected. The primary stress on most bones is weight bearing, which results in buildup of bone; a lack of stress on bones leads to a predominance of bone resorption. When a patient is immobilized in bed, extended periods of

non–weight bearing can lead to disuse osteoporosis. This is best treated with preventive measures such as active muscle contraction and active weight-bearing exercises. Exercises conducted in bed are not particularly effective and out-of-bed-to-chair activities are encouraged as soon as possible.[84]

Return to Primary Acute Care Service

It has been shown that cancer rehabilitation inpatients are transferred back to the primary acute care service more frequently than noncancer patients.[85] The medical fragility of these patients has led to interest in identifying predictors of medical complications while on inpatient rehabilitation. Published research has identified several factors in general oncology patients[25,86] and more specific groups including patients with lymphoma,[87] leukemia,[88] and hematopoietic stem cell transplant.[89] The presence of antimicrobial agents, elevated creatinine, and thrombocytopenia at the time of inpatient rehabilitation transfer have been identified as possible predictors of transfer back to the primary acute care service. These issues highlight the importance of maintaining continuous open communication with oncologists and surgeons during inpatient rehabilitation.[25]

EXERCISE IN CANCER

In the past, treatment algorithms for cancer patients did not incorporate physical exercise as an important component of care. Recently, studies have emerged substantiating the short- and long-term benefits of a well-constructed exercise program. Along the time spectrum of cancer prevention, treatment, and survivorship, patients benefit from an individualized exercise regimen at each stage.

As the prevalence of cancer grows, researchers have emphasized prevention strategies. According to the International Agency for Research on Cancer, obesity and a sedentary lifestyle may contribute to a quarter of new cancer cases. Women are at greatest risk with nearly three times the rate of overweight- and obesity-related cancers.[90]

In addition to reducing the burden of primary risk factors, physical activity may serve as a cancer prevention strategy by improving musculoskeletal strength, endurance, balance, and flexibility, while indirectly enhancing the performance of the body's cardiovascular, pulmonary, neurologic, and immune systems. Previously, the strongest evidence for cancer risk reduction via physical activity had been for colon cancer; a systematic review cited a 40% to 50% risk reduction with exercise.[91–93] The Physical Activity Guidelines Committee from the US Department of Health and Human Services in 2018 identified six additional cancers that may have reduced incidence with increased physical activity: breast, renal, endometrial, bladder, esophageal (adenocarcinoma), and gastric.[94,95] The World Cancer Research Fund/American Institute for Cancer Research concluded that there was strong to probable evidence for risk reduction in colon, postmenopausal breast, and endometrial cancers with moderate to vigorous physical activity, and probable evidence in premenopausal breast cancer with vigorous physical activity.[96] Thus, the emerging evidence demonstrating the protective properties of moderate to vigorous physical activity reinforces the importance of public education and execution of this risk-reducing strategy. The American Cancer Society updated their Diet and Physical Activity Guidelines in 2020, in which they again recommend that adults engage in 150 to 300 minutes of moderate-intensity aerobic activity per week, 75 to 150 minutes of vigorous-intensity aerobic activity, or an equivalent combination for cancer prevention. They also note that achieving or exceeding the upper limit is optimal. Children and adolescents should engage in at least one hour of moderate or vigorous physical activity weekly.[97]

In addition, there is an increasing body of research demonstrating improved cancer- and treatment-related symptoms with moderate increases in activity.[1] Rehabilitation regimens including a combination of aerobic and resistance training have demonstrated improvements in body weight, body composition, flexibility, strength, fatigue, depression, anxiety, self-esteem, perception of well-being, lymphedema, bone health, sleep, functional capacity, and health-related quality of life including role functioning and social functioning.[98–102] Many patients with cancer experience significant weight loss, particularly loss of lean muscle mass. This problem may be exacerbated by hormone or chemotherapy treatments and contribute to generalized weakness and fatigue. Sixty-three men with prostate cancer receiving androgen-deprivation therapy were enrolled in a randomized controlled trial; participants performed at least 150 minutes of moderate-intensity aerobic and resistance exercise training during a 3-month period. Compared with the control group, the exercise group had preserved appendicular lean mass and prevented gains in whole-body fat and trunk fat mass. Between-group analyses also demonstrated significant improvements in peak oxygen consumption, muscle strength, cholesterol levels, sexual function, and fatigue.[100]

Exercise may also improve cancer survival. Preliminary epidemiologic data comparing high versus low physical-activity levels has shown 40% to 50% relative risk reductions in mortality in breast, colon, and prostate cancers.[95] In patients with metastatic colorectal cancer, exercise volumes of more than 9 metabolic equivalent hours per week was associated with reduced treatment complications and exercise volumes of at

least 18 metabolic equivalent hours per week was associated with improved progression-free survival.[103] In a prospective trial that enrolled 1340 patients with breast cancer, patients who met the Physical Activity Guidelines before and 1 year after diagnosis had significant reductions in hazards of recurrence and mortality.[104] Even lower to moderate volumes of exercise were associated with improved survival.[104] In a 17-year survival study conducted in a cohort of 830 patients with stage II–IV prostate cancer, postdiagnosis total activity (high vs low) was associated with a significantly lower all-cause mortality risk and postdiagnosis recreational activity (high vs low) was associated with a significantly lower prostate cancer–specific mortality risk.[105] Furthermore, in another trial examining the associations of pre- and postdiagnosis recreational physical activity in 5807 patients with cancer, those who were habitually active had a 39% decreased hazard of all-cause mortality and a 36% decreased hazard of cancer-specific mortality. Moreover, patients who were previously inactive and began exercising after treatment also had a survival advantage.[104]

Safety of Exercise in Cancer

Although the reasons may be multifactorial, patients may not partake in regular exercise activity because of patient and provider fears.[106] Cheville interviewed a group of patients with advanced non–small-cell lung cancer and identified exercise barriers, which included fear of harm and a lack of direction from their physician.[106] Patients were less receptive to guidance from ancillary health professionals, but an early expert consultation with a physiatrist may prove helpful in formulating an individualized rehabilitation program with medical monitoring, identifying and managing impairments and psychosocial barriers, and therapy (if needed) oversight.

Rehabilitation programs involving exercise are generally safe and with proper precautions, adverse events are limited to musculoskeletal injuries, which are typically treated conservatively. Breast cancer survivors are among the most common population studied for exercise and in this group, there is concern that resistance exercise causes exacerbation of lymphedema.[107] However, the evidence suggests that breast cancer survivors undergoing a strength-training protocol demonstrate a reduced risk of lymphedema exacerbations, while improving strength and bone mineral density.[108,109]

Prescribing Exercise in Cancer

With increasing data supporting the benefits of exercise along the cancer diagnosis and treatment continuum, there has been an emerging need for expert clinical exercise guidelines. In 2018, the American College of Sports Medicine (ACSM) International Multidisciplinary Roundtable on Physical Activity and Cancer Prevention and Control brought together experts from 20 international organizations.[101] These experts found that the 2010 ACSM exercise guidelines may have been unachievable for cancer survivors with physical limitations and that health benefits could be achieved with a lower dose of exercise. Thus, the updated guidelines recommend that cancer survivors engage in at least 30 minutes of moderate-intensity aerobic exercise at least three times per week, for at least 8 to 12 weeks. In addition, cancer survivors should engage in strengthening exercises at least two times per week, using at least two sets of 8 to 15 repetitions of weights at 60% or more of their one-repetition maximum. Figure 67–4 outlines programming models on how exercise can be administered.[110] Unfortunately, the literature supporting specific exercise prescriptions for different cancer types is limited, but the updated 2018 ACSM exercise guidelines provide for structure and flexibility in formulating exercise programs for cancer survivors with functional impairment, to ones who are currently physically active.

In recent years, the literature has demonstrated improved cancer outcomes in patients participating in an exercise program. Exercise has been shown to be safe and effective in managing symptoms, body composition, strength, endurance, and well-being. Future steps in exercise oncology include testing different exercise prescriptions and determining the optimal doses of aerobic and strengthening exercise to further improve oncology outcomes.

PREHABILITATION

Prehabilitation, also known as "pretreatment optimization" or "pretreatment conditioning," is an emerging field in oncology. Patients with cancer are fraught with fatigue, muscle wasting, and functional impairments, which are caused by the cancer itself or sequelae of cancer treatment. Cancer prehabilitation is the initial and essential segment in the cancer rehabilitation continuum of care.[111] The goals of prehabilitation may include improving physical function, optimization of nutrition, gaining muscle mass and strength, improving body composition, tobacco and/or alcohol cessation counseling, and managing mood (stress, anxiety, depression). Thus, the prehabilitation period is an ideal time to document patients' baseline level of function, identify impairments, and formulate an individualized plan to minimize anticipated treatment-related declines in function. Figure 67–5 shows how prehabilitation may be unimodal in its goal and treatment outcome, or multimodal, depending on the needs of the patient population. Oncology prehabilitation programs have typically included any combination of exercise,

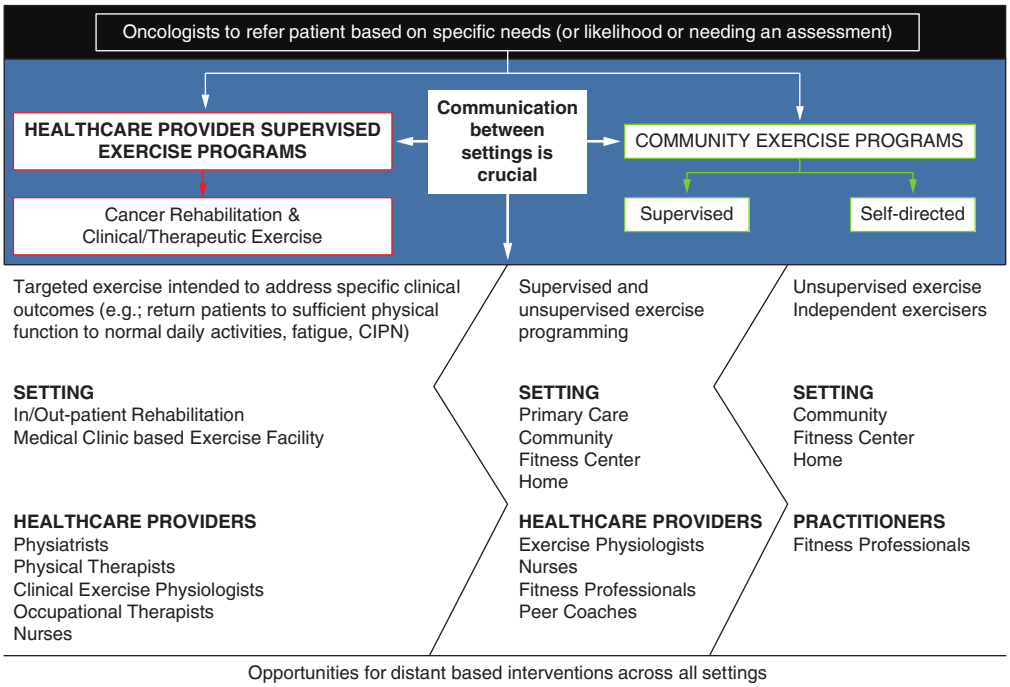


FIGURE 67–4 Different programming models for the referral of patients and delivery of exercise prescriptions.[110] CIPN, chemotherapy-induced peripheral neuropathy. (Reproduced with permission from Schmitz KH, Campbell AM, Stuiver MM, et al: Exercise is medicine in oncology: Engaging clinicians to help patients move through cancer, *CA Cancer J Clin* 2019 Nov;69(6):468-484.)

nutrition, and/or psychology, including stress-reduction strategies. Because of the multimodal programming and because patients often have functional impairment, it is beneficial to have physiatrist oversight for prehabilitation. At MDACC, prehabilitation is offered to patients who may have impairments or are at high risk of functional decline with treatment. Referrals are made to the PM&R, clinic where patients are evaluated by a physiatrist, physical therapist, and if indicated, a counselor (Fig. 67–6). In general, exercise interventions may be delivered by a physical therapist, occupational therapist, certified exercise trainer, or exercise physiologist. The exercise prescription should include a combination of aerobic and strengthening exercises and should often follow, and may exceed, the ACSM exercise guidelines for cancer survivors.[101] In a single-arm study demonstrating feasibility of exercise in 50 patients with potentially resectable pancreatic cancer, preoperative exercise resulted in improved functional capacity and lower limb strength, and physical activity was associated with improved health-related quality of life.[112]

Along with improving patient outcomes, prehabilitation may improve healthcare costs by decreasing length of stay, reducing post-treatment complications, and reducing hospital readmission. In a randomized trial that enrolled 101 patients with lung cancer in a 7-day high-intensity inpatient prehabilitation exercise program, the intervention group had a significantly lower incidence of postoperative pulmonary complications, shorter length of stay, and shorter postoperative stay when compared with the control group.[113] In a multidisciplinary prehabilitation program for elderly patients (≥75 years of age) with stage I–III colorectal cancer compared with historical controls, prehabilitation was associated with reduced cardiac postoperative complications, shorter length of stay, and trend toward lower 1-year mortality.[114] In a small cohort of patients with locally advanced esophageal cancer undergoing multimodal prehabilitation (physical exercise, nutrition optimization, and psychosocial support), patients had fewer admissions during neoadjuvant treatment and reduction in the hospital readmission rate.[115]

Because of improved cancer detection and increasingly effective cancer therapies, there is a growing population of cancer survivors who benefit from optimization of physical activity throughout the continuum of their cancer care via prehabilitation or rehabilitation programs.

PRACTICAL ASPECTS OF CANCER REHABILITATION

Lymphedema

Malignancy (including breast, melanoma, gynecologic, lymphoma, and urologic cancers) is the most common cause of secondary lymphedema in the United States. Lymphedema can be caused by a combination of the patient's cancer, along with its surgical and radiation

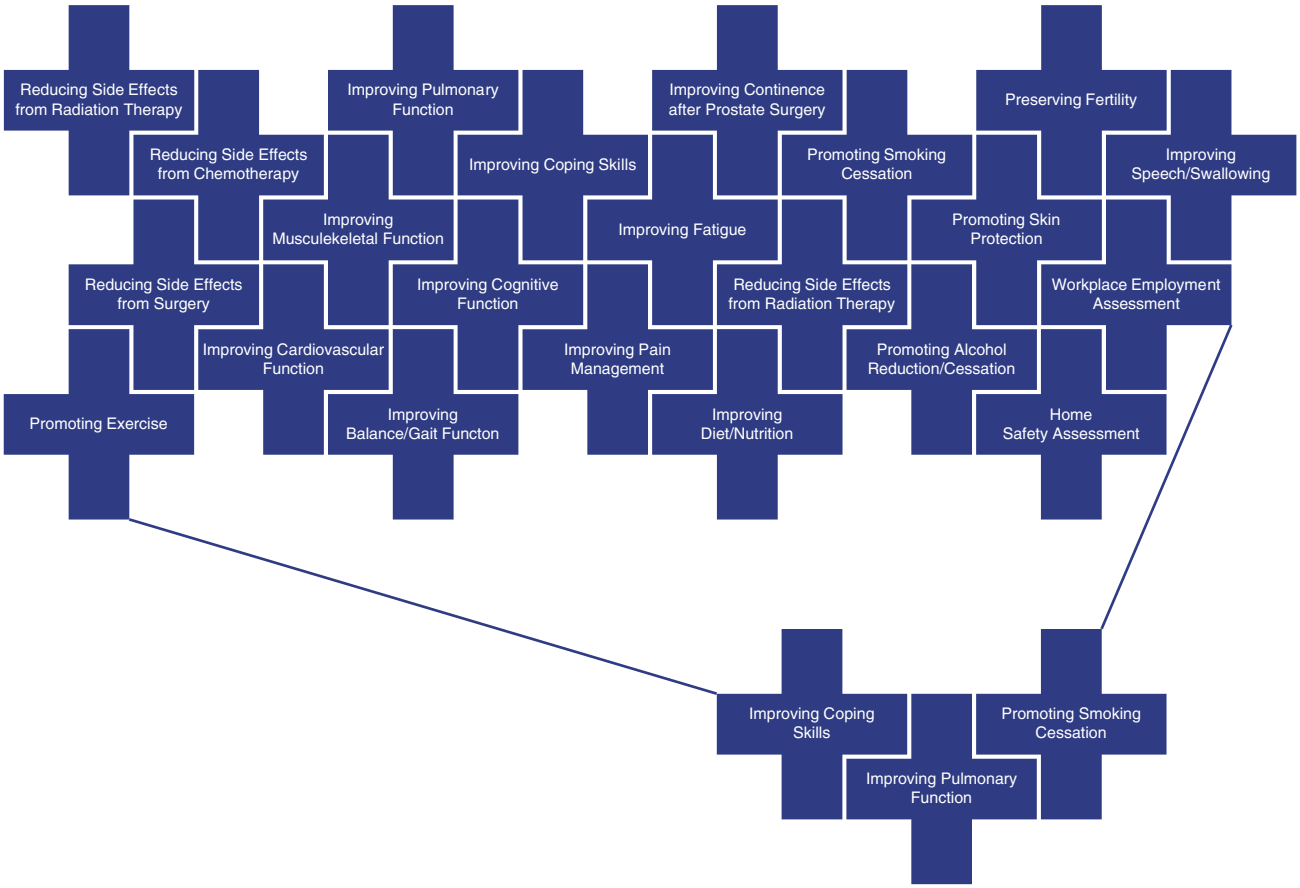


FIGURE 67–5 Examples of components of unimodal or multimodal prehabilitation programs. Pieces of this puzzle can be put together to design a prehabilitation program addressing the specific needs of the patient. (Reproduced with permission from Silver JK, Baima J. Cancer prehabilitation: an opportunity to decrease treatment-related morbidity, increase cancer treatment options, and improve physical and psychological health outcomes, *Am J Phys Med Rehabil* 2013 Aug;92(8):715-727.)

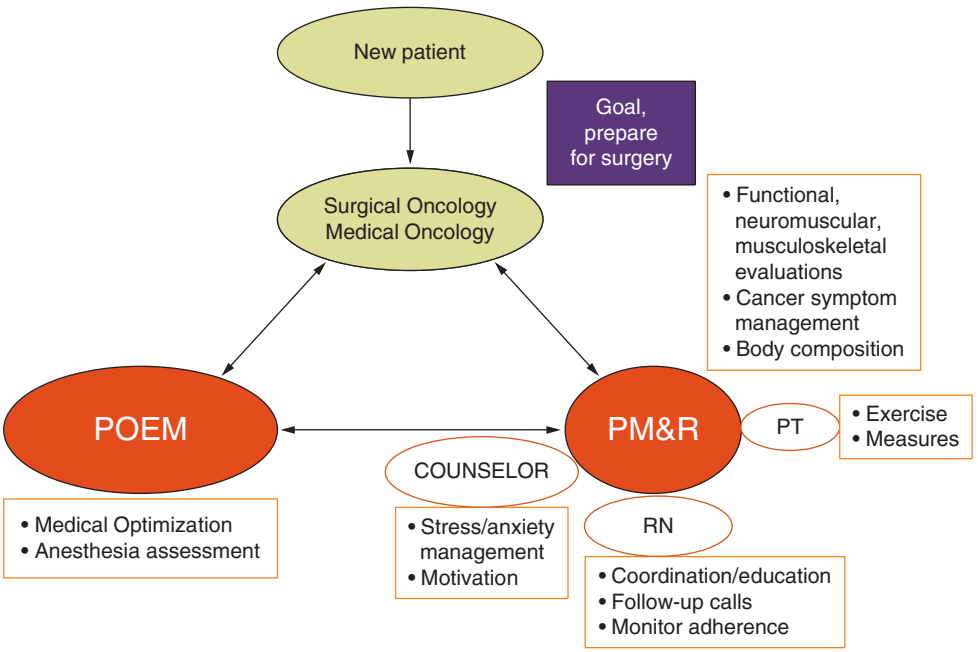


FIGURE 67–6 The MDACC model of prehabilitation with oversight by PM&R to address functional issues to prepare patients for their cancer treatments. PM&R, physical medicine and rehabilitation; POEM, Perioperative Evaluation & Management (includes internal medicine and the anesthesia assessment clinic); PT, physical therapist; RN, registered nurse.

treatments. Breast cancer is the leading cause of upper-extremity lymphedema in the US and develops in 2% to 40% of patients after surgery, radiation, or both.[116,117] The majority of cases are diagnosed clinically, but the differential diagnosis may include DVT, venous insufficiency, myxedema, lipedema, heart failure, kidney failure, and hypoproteinemia. In cases difficult to diagnose, lymphoscintigraphy is the gold standard imaging modality.

Treatment typically starts with one or more conservative techniques, such as manual lymph drainage, compression garments, and pneumatic compression devices. Patients are taught a home lymphedema care regimen to perform daily over several sessions by lymphedema-certified physical or occupational therapists. Periodic follow-ups with measurements are conducted to ensure adherence to the prescribed regimen and to track any changes in their lymphedema. Progression can be measured by volumetric/circumferential measurements, bioelectric impedance, tonometry, and/or perometry. In severe or refractory cases, surgical options such as microsurgery (eg, lymph node transfer or lymphovenous anastomosis/bypass), liposuction, and debulking may be considered.

Pressure Ulcers

According to the National Pressure Ulcer Advisory Panel (NPUAP), a pressure ulcer is an area of unrelieved pressure over a defined area, usually over a bony prominence, resulting in ischemia, cell death, and tissue necrosis. Incidence of pressure ulcers in the acute care setting is 7% to 9%; long-term care incidence is estimated to be between 3% to 31%; home care estimates incidence at 0% to 17%. Patients with cancer have several risk factors that place them at risk of pressure ulcer development (Table 67–2).

The NPUAP staging system for pressure ulcers includes the following:

- Stage I: intact skin with nonblanchable redness of a localized area, usually over a bony prominence.
- Stage II: partial-thickness loss of dermis presenting as a shallow open ulcer with a red-pink wound bed, without slough.
- Stage III: full-thickness tissue loss, subcutaneous fat may be visible, but bone, tendon, or muscle is not exposed.
- Stage IV: full-thickness tissue loss with exposed bone, tendon, or muscle.
- Unstageable: full-thickness tissue loss with slough or eschar covering the wound bed—may become stageable once slough or eschar diminishes to reveal wound bed.
- Deep tissue injury: localized discolored intact skin or blood-filled blister caused by damage of underlying soft tissue from pressure or shear forces.

Table 67–2 Risk Factors for Pressure Ulcer Development

Impaired proprioception	Decreased activity	Impaired mobility
Decreased nutrition	Friction/shear forces	Advanced age
Male gender	Low body-mass index	Urinary or fecal incontinence
Fever/sepsis	Hypotension	Dehydration
Anemia	Immunosuppression	Renal failure

The mainstay of pressure ulcer treatment is the offloading of pressure. This is accomplished by a turning schedule at least every 2 hours while the patient is in bed and frequent position changes up to every 15 minutes when they are seated in a chair or wheelchair.

Other interventions include the use of appropriate support surfaces for the bed and wheelchair, nutritional consultation, PT and OT for mobility issues, and addressing incontinence. Topical dressings may be used based on wound characteristics (Table 67–3). Surgical treatment can include sharp debridement of devitalized tissue if the patient's immune status allows, and plastic surgery intervention may include flap coverage. If available, wound care nursing specialists can also assess the wound and help guide treatment recommendations.

Pressure ulcer healing will also depend on improvement in the patient's overall health and medical condition. Healed ulcers can have decreased tissue tolerance and are at risk for reinjury without ongoing prevention measures. Patients should be monitored throughout cancer treatment for signs of skin compromise or wound degradation.

Thrombocytopenia

Thrombocytopenia, along with the suppression of other blood cell lines, is commonly seen in patients with cancer. These findings are especially frequent in patients receiving chemotherapy or extensive irradiation, with resulting myelosuppression, bone marrow infiltration, and splenomegaly. Hematologic malignancies introduce a variety of associated complications that previously limited implementation of intensive rehabilitation programs with patients at greatest risk. A rehabilitation or exercise program in a severely thrombocytopenic patient remains somewhat controversial, with the major concern being development of a spontaneous bleeding event (eg, intracranial hemorrhage).

Dimeo et al monitored patients during a 6-week intensive aerobic exercise program after high-dose chemotherapy and autologous stem cell transplantation.

Table 67–3 Examples of Wound Dressings

Wound Characteristic	Type of Topical Dressing
Scant or small amounts of drainage	Foam dressing, hydrocolloid, gel/gauze dressing, composite dressing, transparent film
Moderate drainage	Foam dressing, calcium alginate, or hydrofiber
Deep wounds	"Filler" dressing followed by a cover dressing
High drainage	Negative pressure drainage management system, calcium alginate/foam dressing combination, and increased frequency of dressing changes

The investigators did not exclude for neutropenia, anemia, or thrombocytopenia, but they observed no adverse effects. Based on this initial study, the authors proposed using lower limit thresholds of 20,000/μL for platelet counts and 1500/μL for leukocyte counts for safely engaging in a rehabilitation program.[118] With platelet counts over 5000/μL, another study found fatal intracranial hemorrhage in only 1 of 92 patients receiving chemotherapy.[119]

No clear guidelines exist but one recommendation is to allow nonresistive activities and ambulation at platelet counts above 5000/μL and light resistive exercises with counts above 10,000/μL.[120] In addition, platelet transfusions with counts below 10,000/μL should be performed in patients undergoing comprehensive rehabilitation. Clinicians use these values to guide the therapy intervention but apply clinical judgment about how strictly to adhere.

Durable Medical Equipment

Patients with cancer may have a number of rehabilitation-related DME needs, both as inpatients and outpatients. Many are covered by Medicare and third-party payors when patients demonstrate the appropriate need. These can include but are not limited to orthotic (arm, leg, back, and neck braces) and prosthetic prosthetic limbs canes, commode chairs, continuous passive motion machines, crutches, patient lifts, reachers, tub benches, walkers, wheelchairs, and power mobility devices. Table 67–4 lists several commonly prescribed pieces of equipment with a few of their most common indications. Many variations exist within the categories of orthotics and DMEs mentioned. Thus, consultation between a trained physiatrist, therapist, and orthotist may be required to ensure adequate performance, safe mobility, and optimization of self-care.

Survivorship

As of January 2019, it is estimated that there are 16.9 million Americans who are cancer survivors. That number is expected to increase to 26.1 million by 2040.[121] A cancer survivor is any person diagnosed with cancer, from the time of initial diagnosis until his or her death.[122] This definition includes patients receiving active treatment for malignant disease. The number of long-term cancer survivors without evidence of disease is also growing, and these long-term

Table 67–4 Commonly Prescribed Orthotics and Durable Medical Equipment

Prescribed equipment	Common indications
Ankle foot orthosis (AFO)	Ankle dorsiflexion weakness or "foot drop"
Neutral wrist hand orthosis	Median neuropathy at the wrist or "carpal tunnel syndrome"
Shoulder sling	Hemiparesis with shoulder pain caused by glenohumeral subluxation
Thoracic Lumbar Sacral Orthosis (TLSO)	Mild spinal instability or vertebral compression fractures
Rolling walker	Impaired mobility, balance, or proprioception
Hemi-walker	Hemiparesis with impaired mobility or balance
Manual wheelchair	Unsafe gait, poor endurance
Bedside commode	Impaired transfers to/from toilet
Sliding board	Impaired transfers in/out of bed or chair
Tub transfer chair	Impaired transfers in/out of shower
Shower chair	Poor endurance, impaired ADLs
Reacher	Impaired mobility or ADLs

survivors are left with a multitude of disabilities acquired during their cancer treatment. Rehabilitation can help patients with hemiparesis,[123] neuropathy/plexopathy,[124] myopathy,[125] chronic fatigue,[126] RFS,[127] postmastectomy pain syndrome, cognitive deficits,[128] lymphedema,[129] spasticity,[130] cervical dystonia,[131] trismus,[132] and chronic musculoskeletal pain.[72] Once the focus has shifted from surviving cancer to recovering quality of life, rehabilitation often plays an integral role. The bulk of the growth in the field of cancer rehabilitation over the past several decades has been surrounding the growth in the numbers of long-term cancer survivors. This rehabilitation is predominantly provided in outpatient clinics.

Eliminating Barriers

Physiatrists are optimally trained to facilitate a patient's transition from illness and its associated medical care to home with functional restoration. With the appropriate tools and resources, physiatrists can modify, support, or eliminate impairments. In general, musculoskeletal injuries are among the most common causes of disability and contribute to a great deal of functional impairment. In a population of patients with cancer, these injuries may be overlooked because of the presence of more serious illnesses, but a well-trained physiatrist is equipped to detect, diagnose, and treat them. If resolution of an impairment is feasible and presents relatively low risk, treatment should be pursued to alleviate activity limitations (Table 67–5). If treatment is inappropriate or not feasible, a physiatrist may employ alternative strategies, such as orthotics or DMEs, to reduce the burden of activity limitations and participation restrictions.

Employment-Related Disability Management and Return to Work

It has been reported that 38% of cancer survivors are of working age.[133] Increasing survivorship among patients with cancer has led to an increased focus on a return to work and disability. Survivors frequently wish to return to work for continued insurance benefits, income, and self-esteem. Quality of life assessments also show that employed cancer survivors have a higher quality of life. Employment provides a sense of normalcy and control when cancer takes control away from other aspects of their lives.[134] However, many cancer survivors are unable to work secondary to the effects of chemotherapy or radiation, delayed recovery after surgery, the tumor itself, and symptoms associated with the tumor. Survivors may report an inability to return to work for a variety of reasons including fatigue, physical limitations, emotional problems, changing personal priorities, cognitive deficits, awkward interaction with coworkers, and unsympathetic employers.[135]

Twenty percent of patients with cancer report some cancer-related disability. However, most employed patients with cancer do return to work after treatment. At 1 year, 73% are employed, and 84% are employed at 4 years post-treatment. Patients with CNS, head and neck, and stage IV hematologic cancers had the highest risk of disability. Risk factors for not returning to work include older age, female gender, lower level of education, and more physically demanding work. Of note, 87% reported that their employer was accommodating.[136] Of employed cancer survivors, 54% reported having to adjust their work schedule during their cancer treatment.[137]

The Americans With Disabilities Act of 1990 brought legislative protection to cancer survivors with disabilities by requiring employers to make "reasonable accommodation" for employees with disabilities and preventing discrimination in pay, hiring, firing, fringe benefits, and working conditions. It also requires employers to make accommodations for family members that are not an "undue hardship." Accommodations can include extended leave, flexible work schedules, permitting working from home, changing work environment, and allowing rest periods during the day.

If there is uncertainty about whether a cancer survivor can return to work, several options are available. If the primary concern is energy and endurance, the cancer survivor's hours can be started slowly and gradually increased each week, with the patient reporting any difficulties to the physician. When issues of coordination, strength, or endurance are uncertain, a functional capacity evaluation can be performed by an occupational or physical therapist. The evaluation can be useful for determining tolerance for lifting, bending, squatting, walking, and/or prolonged standing or sitting. Often the therapist is able to replicate the duties of the patient, simulate the work environment, and recommend ergonomic or environmental modifications as necessary.

When a return to work is not feasible, physicians may be asked to play a role in supporting claims for disability. Impairment and disability evaluations can often by complicated by considerable variation between objectively measured impairments and subjectively reported disability. Psychological, social, and behavioral factors must be recognized as significant contributors to the relationship between impairment and disability.

REHABILITATION AT THE END OF LIFE

Mackey described caregiver concerns, which can include fear of hurting the patient physically by moving them, fear of hurting themselves when moving or transferring the patient, and a lack of clarity regarding

Table 67–5 Adjunctive Diagnostic and Therapeutic Interventions That May Be Employed by a Trained Physiatrist[a]

Procedure	Indication	Common sites
Botulinum toxin injection for chemodenervation	Upper motor neuron or mixed motor neuron injury leading to spasticity or dystonia	Shoulder internal rotators Upper and lower extremity flexors Lower extremity adductors
	Migraine headache	Facial and suboccipital musculature Sternocleidomastoid, scalene, trapezius, levator scapularis musculature
	Spasmodic torticollis	Muscles of mastication Shoulder adductors and internal rotators
	Trismus Post-mastectomy syndrome Post-radiation muscle spasms	Location dependent
Phenol injection for chemical neurolysis	Upper motor neuron or mixed motor neuron injury leading to spasticity or dystonia	Terminal motor branch of femoral, obturator, tibial nerves
	Painful neuroma	Morton (intermetatarsal) neuroma Post-amputation neuroma
	Trigeminal neuralgia	Terminal branch of trigeminal nerve
	Spasmodic torticollis	Sternocleidomastoid, scalene, trapezius, levator scapularis musculature
Corticosteroid injection	Arthritis	Shoulder or knee joints
	Rotator cuff tendinopathy	Subacromial or glenohumeral space
	Bursitis	Subacromial, knee, or trochanteric bursae
	Adhesive capsulitis	Shoulder
	Carpal tunnel syndrome	Wrist
Hyaluronic acid injection	Degenerative arthritis	Knee joint
Trigger point injection	Muscle spasm with painful trigger points	Trapezius, levator scapularis, rhomboid musculature
Prolotherapy	Tendinopathy	Achilles or patellar tendons
	Fasciitis	Plantar fascia
	Enthesopathy	Origin of extensor carpi radialis brevis (ECRB) musculature for "tennis elbow"
Electrodiagnostic study	Foot drop Carpal tunnel syndrome Ulnar neuropathy Radiculopathy Brachial plexopathy Guillain-Barre syndrome Peripheral mono- or polyneuropathy of unknown origin	Nerve conductions and needle electromyography of upper and/or lower extremities +/- paraspinal musculature
Diagnostic dynamic ultrasound	Tendinopathy	Rotator cuff, Achilles, gluteus medius, patellar tendons ECRB
	Enthesopathy	Subacromial, greater trochanteric, pes anserine bursae
	Bursitis	Popliteal fossa
	Baker's cyst Carpal tunnel syndrome	Median nerve proximal to and within carpal tunnel

[a]Not intended to serve as an exhaustive list.

how hard to push the patient. Family education in transfer training and positioning can decrease caregiver stress of providing care as well as the patient's concern about being a burden.

In the end-of-life setting, the practices of cancer rehabilitation and palliative care share several similarities. Both support quality of life and strive to relieve discomfort. The framework for intervention can be similar with a multidisciplinary team to comprehensively assess and treat the patient. Both have an emphasis not only on the disease process, but also on physical symptoms, limitations of the patient, and how to improve or relieve them. Both also emphasize the family in patient care and education. Rehabilitation interventions at the end of life can include mobility and ADL training, positioning and pressure relief techniques, chest physiotherapy, swallow therapy, edema management, physical modalities to treat pain, and bracing and splinting to relieve pain and assist with mobility.

FUTURE OF CANCER REHABILITATION

Cancer rehabilitation has suffered from under-referrals by oncologists and lack of availability at many cancer centers.[138] Cancer rehabilitation education is still lacking in PM&R departments.[139] However, the field has experienced tremendous growth and increasing acceptance over the past decade. Cancer rehabilitation has become increasingly viewed as important by physiatry academic departments across the United States.[138] Furthermore, cancer rehabilitation research publications have grown at a significantly faster rate than the whole field of rehabilitation.[140] However, more research is needed, and discussions among cancer physiatrists are ongoing to establish core services offered by cancer rehabilitation professionals, because this is still widely variable across healthcare systems.

MD ANDERSON PRACTICE TIPS

- Physiatrist-led rehabilitation programs should be included at comprehensive cancer centers. Rehabilitation services include PT, OT, and speech-language pathology. Referrals to these specialists may be considered at any point in the continuum of care.
- Prehabilitation has emerged as an important step in improving outcomes in surgical oncology patients and most often include physical-activity recommendations, nutrition optimization, and/or psychosocial interventions.
- The Boston University Activity Measure for Post-Acute Care (AM-PAC) is widely used in rehabilitation for monitoring physical function, including mobility and ADLs. The Six-Clicks Basic Mobility and Daily Activity assessments are quick to administer and may be helpful tools to monitor for changes in function in hospitalized patients, and signal the need for closer intervention.
- Neurorehabilitation for patients with malignancy involving the brain or spinal cord is key in facilitating recovery. Functional outcomes in this patient population are similar to what is seen in noncancer neurorehabilitation patients.
- If a patient has painful or function-limiting radiation-induced muscle fibrosis, a consultation to a physiatrist experienced in cancer rehabilitation is warranted. Treatment options include PT, OT, topical medications, optimization of oral pain medications and muscle relaxants, and procedures such as trigger point injections or chemodenervation with botulinum toxin.
- As per the American College of Sports Medicine's 2019 update, cancer survivors should engage in at least 30 minutes of moderate-intensity aerobic exercise at least three times per week, for at least 8 to 12 weeks. In addition, cancer survivors should engage in strengthening exercises at least two times per week, using at least two sets of 8 to 15 repetitions of weights at 60% or more of their one-repetition maximum. Referral to a rehabilitation or oncology exercise specialist is recommended if there are safety concerns.

REFERENCES

1. Lehmann JF, DeLisa JA, Warren CG, et al. Cancer rehabilitation: assessment of need, development, and evaluation of a model of care. *Arch Phys Med Rehabil.* 1978;59(9):410-419.
2. Delisa JA. *Physical Medicine and Rehabilitation: Principles and Practice.* 6th ed. Lippincott; 1993.
3. Dietz JH, Jr. Adaptive rehabilitation of the cancer patient. *Curr Probl Cancer.* 1980;5(5):1-56.
4. Courneya KS, Friedenreich CM. Framework PEACE: an organizational model for examining physical exercise across the cancer experience. *Ann Behav Med.* 2001;23(4):263-272.
5. Santa Mina D, Clarke H, Ritvo P, et al. Effect of total-body prehabilitation on postoperative outcomes: a systematic review and meta-analysis. *Physiotherapy.* 2014;100(3):196-207.
6. Gillis C, Li C, Lee L, et al. Prehabilitation versus rehabilitation: a randomized control trial in patients undergoing colorectal resection for cancer. *Anesthesiology.* 2014;121(5):937-947.
7. West MA, Loughney L, Lythgoe D, et al. Effect of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in preoperative rectal cancer patients: a blinded interventional pilot study. *Br J Anaesth.* 2015;114(2):244-251.
8. Jensen BT, Petersen AK, Jensen JB, et al. Efficacy of a multiprofessional rehabilitation programme in radical cystectomy pathways: a prospective randomized controlled trial. *Scand J Urol.* 2015;49(2):133-141.
9. Santa Mina D, Matthew AG, Hilton WJ, et al. Prehabilitation for men undergoing radical prostatectomy: a multi-centre, pilot randomized controlled trial. *BMC Surg.* 2014;14:89.
10. Fu J. Palliative Rehabilitation: Optimizing Function at End of Life. Austin, Texas: American Academy of Physical Medicine & Rehabilitation Medicine Annual Assembly; 2009.
11. Houts PS, Yasko JM, Harvey HA, et al. Unmet needs of persons with cancer in Pennsylvania during the period of terminal care. *Cancer.* 1988;62(3):627-634.
12. Morasso G, Capelli M, Viterbori P, et al. Psychological and symptom distress in terminal cancer patients with met and unmet needs. *J Pain Symptom Manage.* 1999;17(6):402-409.
13. Marciniak CM, Sliwa JA, Spill G, et al. Functional outcome following rehabilitation of the cancer patient. *Arch Phys Med Rehabil.* 1996;77(1):54-57.
14. Sliwa JA, Marciniak C. Physical rehabilitation of the cancer patient. *Cancer Treat Res.* 1999;100:75-89.
15. Cole RP, Scialla SJ, Bednarz L. Functional recovery in cancer rehabilitation. *Arch Phys Med Rehabil.* 2000;81(5):623-627.
16. McKinley WO, Conti-Wyneken AR, Vokac CW, et al. Rehabilitative functional outcome of patients with neoplastic spinal cord compressions. *Arch Phys Med Rehabil.* 1996;77(9):892-895.
17. Scialla S, Cole R, Scialla T, et al. Rehabilitation for elderly patients with cancer asthenia: making a transition to palliative care. *Palliat Med.* 2000;14(2):121-127.
18. Oldervoll LM, Loge JH, Paltiel H, et al. The effect of a physical exercise program in palliative care: a phase II study. *J Pain Symptom Manage.* 2006;31(5):421-430.
19. Sabers SR, Kokal JE, Girardi JC, et al. Evaluation of consultation-based rehabilitation for hospitalized cancer patients with functional impairment. *Mayo Clin Proc.* 1999;74(9):855-861.
20. Yoshioka H. Rehabilitation for the terminal cancer patient. *Am J Phys Med Rehabil.* 1994;73(3):199-206.
21. Cheville A. Rehabilitation of patients with advanced cancer. *Cancer.* 2001;92(suppl 4):1039-1048.
22. Porock D, Kristjanson LJ, Tinnelly K, et al. An exercise intervention for advanced cancer patients experiencing fatigue: a pilot study. *J Palliat Care.* 2000;16(3):30-36.
23. Newton RU, Galvao DA. Exercise in prevention and management of cancer. *Curr Treat Options Oncol.* 2008;9(2-3):135-146.
24. Friedenreich CM, Gregory J, Kopciuk KA, et al. Prospective cohort study of lifetime physical activity and breast cancer survival. *Int J Cancer.* 2009;124(8):1954-1962.
25. Guo Y, Persyn L, Palmer JL, et al. Incidence of and risk factors for transferring cancer patients from rehabilitation to acute care units. *Am J Phys Med Rehabil.* 2008;87(8):647-653.
26. Karnofsky D, Burchenal JH. Clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod CM, editor. *Evaluation of Chemotherapy Agents*. Columbia University Press; 1949:191-205.
27. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5(6):649-655.
28. Meyers CA, Weitzner MA. Neurobehavioral functioning and quality of life in patients treated for cancer of the central nervous system. *Curr Opin Oncol.* 1995;7(3):197-200.
29. Taylor AE, Olver IN, Sivanthan T, et al. Observer error in grading performance status in cancer patients. *Support Care Cancer.* 1999;7(5):332-335.
30. Meyers CA. Neuropsychological aspects of cancer and cancer treatment. In: Garden FH, Grabois M, eds. *Physical Medicine and Rehabilitation: State of the Art Reviews*. Hanley & Belfus; 1994:229-241.
31. Haley SM, Coster WJ, Andres PL, et al. Activity outcome measurement for postacute care. *Med Care.* 2004;42(suppl 1):I49-I61.
32. Haley SM, Siebens H, Coster WJ, et al. Computerized adaptive testing for follow-up after discharge from inpatient rehabilitation: I. Activity outcomes. *Arch Phys Med Rehabil.* 2006;87(8):1033-1042.
33. Radhakrishnan K, Bohnen NI, Kurland L. Epidemiology of brain tumors. In: Morantz RA, Walsh JW, eds. *Brain Tumors: A Comprehensive Text*. Marcel Dekker; 1994:1-18.
34. Osborn A. *Diagnostic Neuroradiology.* Mosby; 1994.
35. Nugent JL, Bunn PA, Jr., Matthews MJ, et al. CNS metastases in small cell bronchogenic carcinoma: increasing frequency and changing pattern with lengthening survival. *Cancer.* 1979;44(5):1885-1893.
36. Bell KR, O'Dell MW, Barr K, et al. Rehabilitation of the patient with brain tumor. *Arch Phys Med Rehabil.* 1998;79(3):S37-S46.
37. Greenberg MS. *Handbook of neurosurgery, Volume 1*. Greenberg Graphics; 1997.
38. Ulmer S, Braga TA, Barker FG 2nd, et al. Clinical and radiographic features of peritumoral infarction following resection of glioblastoma. *Neurology.* 2006;67(9):1668-1670.
39. Dropcho EJ. Central nervous system injury by therapeutic irradiation. *Neurol Clin.* 1991;9(4):969-988.
40. DeAngelis LM, Delattre JY, Posner JB. Radiation-induced dementia in patients cured of brain metastases. *Neurology.* 1989;39(6):789-796.
41. Fu JB, Molinares DM, Morishita S, et al. Retrospective analysis of acute rehabilitation outcomes of cancer inpatients with leptomeningeal disease. *PM R.* 2020;12(3):263-270.
42. Mukand JA, Blackinton DD, Crincoli MG, et al. Incidence of neurologic deficits and rehabilitation of patients with brain tumors. *Am J Phys Med Rehabil.* 2001;80(5):346-350.
43. Marciniak CM, Sliwa JA, Heinemann AW, et al. Functional outcomes of persons with brain tumors after inpatient rehabilitation. *Arch Phys Med Rehabil.* 2001;82(4):457-463.
44. Huang ME, Cifu DX, Keyser-Marcus L. Functional outcome after brain tumor and acute stroke: a comparative analysis. *Arch Phys Med Rehabil.* 1998;79(11):1386-1390.
45. Huang ME, Cifu DX, Keyser-Marcus L. Functional outcomes in patients with brain tumor after inpatient rehabilitation: comparison with traumatic brain injury. *Am J Phys Med Rehabil.* 2000;79(4):327-335.

46. Huang ME, Wartella J, Kreutzer J, et al. Functional outcomes and quality of life in patients with brain tumours: a review of the literature. *Brain Inj.* 2001;15(10):843-856.
47. O'Dell MW, Barr K, Spanier D, et al. Functional outcome of inpatient rehabilitation in persons with brain tumors. *Arch Phys Med Rehabil.* 1998;79(12):1530-1534.
48. Gilbert RW, Kim JH, Posner JB. Epidural spinal cord compression from metastatic tumor: diagnosis and treatment. *Ann Neurol.* 1978;3(1):40-51.
49. Garden FH, Gillis TA. Principles of cancer rehabilitation. In: Braddom RL, editor. *Physical Medicine and Rehabilitation*. Saunders; 1996:1199-1214.
50. Twitchell TE. The restoration of motor function following hemiplegia in man. *Brain.* 1951;74(4):443-480.
51. Sawner KA, Brunnstrom S, La Vigne JM. *Brunnstrom's Movement Therapy in Hemiplegia: A Neurophysiological Approach.* 2nd ed. Lippincott; 1992.
52. Kraft GH. New methods for the assessment and treatment of the hemiplegic arm and hand. *Phys Med Rehabil Clin N Am.* 1991;2(3):579-597.
53. Garrison SJ. Rehabilitation of the stroke patient. *Rehabilitation medicine: Principles and practice.* 1993.
54. Chaco J, Wolf E. Subluxation of the glenohumeral joint in hemiplegia. *Am J Phys Med.* 1971;50(3):139-143.
55. Macdonald DR. Neurologic complications of chemotherapy. *Neurol Clin.* 1991;9(4):955-967.
56. Posner JB. Paraneoplastic syndromes. *Neurol Clin.* 1991;9(4):919-936.
57. Diener HC, Dichgans J. Pathophysiology of cerebellar ataxia. *Mov Disord.* 1992;7(2):95-109.
58. Silver KH, Fishman P, Speed J. Movement disorders. In: O'Young BJ, Young MA, Steins SA, eds. *Physical Medicine & Rehabilitation Secrets*. 2nd ed. Hanley & Belfus; 2002:182-193.
59. Rao PR. Adult communication disorders. In: Braddom RL, Buschbacher RM, eds. *Physical Medicine & Rehabilitation*. WB Saunders; 1996:43-65.
60. Gillis TA, Yadav R, Guo Y. Rehabilitation of patients with neurologic tumors and cancer-related central nervous system disabilities. In: Jellinger KA, editor. *Cancer in the Nervous System*. 2nd ed. Wiley; 2002:470-492.
61. Noll SF, Bender CE. Rehabilitation of patients with swallowing disorders. In: Braddom RL, ed. *Physical Medicine & Rehabilitation*. 2nd ed. Philadelphia: WB Saunders; 2000:553-555.
62. Kaplan M. Upper motor neuron syndrome and spasticity. In: Woo BH, Nesathurai S, eds. *The Rehabilitation of People with Traumatic Brain Injury*. Blackwell Science; 2000:85-99.
63. Cardenas DD, Mayo ME, King JC. Urinary tract and bowel management in the rehabilitation setting. In: Braddom RL, Buschbacher RM, eds. *Physical Medicine & Rehabilitation*. WB Saunders; 1996:555-579.
64. Bergman SB. Bowel management. In: Nesathura S, ed. *The Rehabilitation of People with Spinal Cord Injury*. 2nd ed. Blackwell Science; 2000:53-58.
65. Osasan S, Zhang M, Shen F, et al. Osteogenic sarcoma: a 21st century review. *Anticancer Res.* 2016;36(9):4391-4398.
66. Stubblefield MD. *Cancer Rehabilitation: Principles and Practice.* 2nd ed. Springer; 2018.
67. Salunke AA, Shah J, Warikoo V, et al. Surgical management of pelvic bone sarcoma with internal hemipelvectomy: oncologic and Functional outcomes. *J Clin Orthop Trauma.* 2017;8(3):249-253.
68. Guo Y, Palmer JL, Shen L, et al. Bowel and bladder continence, wound healing, and functional outcomes in patients who underwent sacrectomy. *J Neurosurg Spine.* 2005;3(2):106-110.
69. Zoccali C, Skoch J, Patel AS, et al. Residual neurological function after sacral root resection during en-bloc sacrectomy: a systematic review. *Eur Spine J.* 2016;25(12):3925-3931.
70. Yu H, Hoffe S. Epidemiology, clinical presentation, and diagnosis of bone metastasis in adults. *UpToDate*. Accessed July 25, 2019. https://www.uptodate.com/contents/epidemiology-clinical-presentation-and-diagnosis-of-bone-metastasis-in-adults
71. DiFrancesco T, Khanna A, Stubblefield MD. Clinical evaluation and management of cancer survivors with radiation fibrosis syndrome. *Semin Oncol Nurs.* 2020;36(1):150982.
72. Stubblefield MD. Radiation fibrosis syndrome: neuromuscular and musculoskeletal complications in cancer survivors. *PM R.* 2011;3(11):1041-1054.
73. Cross NE, Glantz MJ. Neurologic complications of radiation therapy. *Neurol Clin.* 2003;21(1):249-277.
74. Straub JM, New J, Hamilton CD, et al. Radiation-induced fibrosis: mechanisms and implications for therapy. *J Cancer Res Clin Oncol.* 2015;141(11):1985-1994.
75. Jacobson G, Bhatia S, Smith BJ, et al. Randomized trial of pentoxifylline and vitamin E vs standard follow-up after breast irradiation to prevent breast fibrosis, evaluated by tissue compliance meter. *Int J Radiat Oncol Biol Phys.* 2013;85(3):604-608.
76. Muller EA. Influence of training and of inactivity on muscle strength. *Arch Phys Med Rehabil.* 1970;51(8):449-462.
77. Deitrick JE, Whedon GD, Shorr E. Effects of immobilization upon various metabolic and physiologic functions of normal men. *Am J Med.* 1948;4(1):3-36.
78. Greenleaf JE, Van Beaumont W, Convertino VA, et al. Handgrip and general muscular strength and endurance during prolonged bedrest with isometric and isotonic leg exercise training. *Aviat Space Environ Med.* 1983;54(8):696-700.
79. Appell HJ. Muscular atrophy following immobilisation. A review. *Sports Med.* 1990;10(1):42-58.
80. Baker JH, Matsumoto DE. Adaptation of skeletal muscle to immobilization in a shortened position. *Muscle Nerve.* 1988;11(3):231-244.
81. Houston ME, Bentzen H, Larsen H. Interrelationships between skeletal-muscle adaptations and performance as studied by detraining and retraining. *Acta Physiol Scand.* 1979;105(2):163-170.
82. Taylor HL, Henschel A, Brozek J, et al. Effects of bed rest on cardiovascular function and work performance. *J Appl Physiol.* 1949;2(5):223-239.
83. Stremel RW, Convertino VA, Bernauer EM, et al. Cardiorespiratory deconditioning with static and dynamic leg exercise during bed rest. *J Appl Physiol.* 1976;41(6):905-909.
84. Buschbacher RM. Deconditioning, conditioning, and the benefits of exercise. In: Braddom RL, Buschbacher RM, eds. *Physical Medicine & Rehabilitation*. Saunders; 1996:687-707.
85. Alam E, Wilson RD, Vargo MM. Inpatient cancer rehabilitation: a retrospective comparison of transfer back to acute care between patients with neoplasm and other rehabilitation patients. *Arch Phys Med Rehabil.* 2008;89(7):1284-1289.
86. Asher A, Roberts PS, Bresee C, et al. Transferring inpatient rehabilitation facility cancer patients back to acute care (TRIP-BAC). *PM R.* 2014;6(9):808-813.
87. Fu JB, Lee J, Smith DW, et al. Frequency and reasons for return to the primary acute care service among patients with lymphoma undergoing inpatient rehabilitation. *PM R.* 2014;6(7):629-634.
88. Fu JB, Lee J, Smith DW, et al. Frequency and reasons for return to acute care in patients with leukemia undergoing inpatient rehabilitation: a preliminary report. *Am J Phys Med Rehabil.* 2013;92(3):215-222.
89. Fu JB, Lee J, Smith DW, et al. Return to primary service among bone marrow transplant rehabilitation inpatients: an index for predicting outcomes. *Arch Phys Med Rehabil.* 2013;94(2):356-361.
90. Arnold M, Pandeya N, Byrnes G, et al. Global burden of cancer attributable to high body-mass index in 2012: a population-based study. *Lancet Oncol.* 2015;16(1):36-46.

91. Rajarajeswaran P, Vishnupriya R. Exercise in cancer. *Indian J Med Paediatr Oncol.* 2009;30(2):61-70.
92. Wolin KY, Yan Y, Colditz GA, et al. Physical activity and colon cancer prevention: a meta-analysis. *Br J Cancer.* 2009;100(4):611-616.
93. Boyle T, Keegel T, Bull F, et al. Physical activity and risks of proximal and distal colon cancers: a systematic review and meta-analysis. *J Natl Cancer Inst.* 2012;104(20):1548-1561.
94. US Department of Health and Human Services. 2018 Physical Activity Guidelines Advisory Committee Scientific Report. Accessed May 16, 2021. https://health.gov/our-work/physical-activity/current-guidelines/scientific-report
95. McTiernan A, Friedenreich CM, Katzmarzyk PT, et al. Physical activity in cancer prevention and survival: a systematic review. *Med Sci Sports Exerc.* 2019;51(6):1252-1261.
96. World Cancer Research Fund/American Institute for Cancer Research. Diet, Nutrition, Physical Activity and Cancer: A Global Perspective. Continuous Update Project. The Third Expert Report. American Institute for Cancer Research; 2018. Accessed July 21, 2019. https://www.wcrf.org/diet-and-cancer/
97. Rock CL, Thomson C, Gansler T, et al. American Cancer Society guideline for diet and physical activity for cancer prevention. *CA Cancer J Clin.* 2020.
98. Thomas GA, Cartmel B, Harrigan M, et al. The effect of exercise on body composition and bone mineral density in breast cancer survivors taking aromatase inhibitors. *Obesity (Silver Spring).* 2017;25(2):346-351.
99. Brown JC, Zemel BS, Troxel AB, et al. Dose-response effects of aerobic exercise on body composition among colon cancer survivors: a randomised controlled trial. *Br J Cancer.* 2017;117(11):1614-1620.
100. Cormie P, Galvao DA, Spry N, et al. Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: a randomised controlled trial. *BJU Int.* 2015;115(2):256-266.
101. Campbell KL, Winters-Stone KM, Wiskemann J, et al. Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. *Med Sci Sports Exerc.* 2019;51(11):2375-2390.
102. Mishra SI, Scherer RW, Snyder C, et al. Exercise interventions on health-related quality of life for people with cancer during active treatment. *Cochrane Database Syst Rev.* 2012(8):CD008465.
103. Guercio BJ, Zhang S, Ou FS, et al. Associations of physical activity with survival and progression in metastatic colorectal cancer: results from Cancer and Leukemia Group B (Alliance)/SWOG 80405. *J Clin Oncol.* 2019;37(29):2620-2631.
104. Cannioto RA, Dighe S, Mahoney MC, et al. Habitual recreational physical activity is associated with significantly improved survival in cancer patients: evidence from the Roswell Park Data Bank and BioRepository. *Cancer Causes Control.* 2019;30(1):1-12.
105. Friedenreich CM, Wang Q, Neilson HK, et al. Physical activity and survival after prostate cancer. *Eur Urol.* 2016;70(4):576-585.
106. Cheville AL, Dose AM, Basford JR, et al. Insights into the reluctance of patients with late-stage cancer to adopt exercise as a means to reduce their symptoms and improve their function. *J Pain Symptom Manage.* 2012;44(1):84-94.
107. Schmitz KH, Ahmed RL, Troxel A, et al. Weight lifting in women with breast-cancer-related lymphedema. *N Engl J Med.* 2009;361(7):664-673.
108. Winters-Stone KM, Dobek J, Nail L, et al. Strength training stops bone loss and builds muscle in postmenopausal breast cancer survivors: a randomized, controlled trial. *Breast Cancer Res Treat.* 2011;127(2):447-456.
109. Winters-Stone KM, Dobek J, Nail LM, et al. Impact + resistance training improves bone health and body composition in prematurely menopausal breast cancer survivors: a randomized controlled trial. *Osteoporos Int.* 2013;24(5):1637-1646.
110. Schmitz KH, Campbell AM, Stuiver MM, et al. Exercise is medicine in oncology: engaging clinicians to help patients move through cancer. *CA Cancer J Clin.* 2019;69(6):468-484.
111. Silver JK, Baima J. Cancer prehabilitation: an opportunity to decrease treatment-related morbidity, increase cancer treatment options, and improve physical and psychological health outcomes. *Am J Phys Med Rehabil.* 2013;92(8):715-727.
112. Ngo-Huang A, Parker NH, Bruera E, et al. Home-based exercise prehabilitation during preoperative treatment for pancreatic cancer is associated with improvement in physical function and quality of life. *Integr Cancer Ther.* 2019;18:1534735419894061.
113. Lai Y, Su J, Qiu P, et al. Systematic short-term pulmonary rehabilitation before lung cancer lobectomy: a randomized trial. *Interact Cardiovasc Thorac Surg.* 2017;25(3):476-483.
114. Souwer ETD, Bastiaannet E, de Bruijn S, et al. Comprehensive multidisciplinary care program for elderly colorectal cancer patients: "From prehabilitation to independence." *Eur J Surg Oncol.* 2018;44(12):1894-1900.
115. Dewberry LC, Wingrove LJ, Marsh MD, et al. Pilot prehabilitation program for patients with esophageal cancer during neoadjuvant therapy and surgery. *J Surg Res.* 2019;235:66-72.
116. Logan V. Incidence and prevalence of lymphoedema: a literature review. *J Clin Nurs.* 1995;4(4):213-219.
117. Ozaslan C, Kuru B. Lymphedema after treatment of breast cancer. *Am J Surg.* 2004;187(1):69-72.
118. Dimeo FC, Tilmann MH, Bertz H, et al. Aerobic exercise in the rehabilitation of cancer patients after high dose chemotherapy and autologous peripheral stem cell transplantation. *Cancer.* 1997;79(9):1717-1722.
119. Gaydos LA, Freireich EJ, Mantel N. The quantitative relation between platelet count and hemorrhage in patients with acute leukemia. *N Engl J Med.* 1962;266:905-909.
120. Sayre R, Marcoux B. Exercise and autologous bone marrow transplants. *Clin Manage Phys Ther.* 1992;12:78-82.
121. Bluethmann SM, Mariotto AB, Rowland JH. Anticipating the "silver tsunami": prevalence trajectories and comorbidity burden among older cancer survivors in the United States. *Cancer Epidemiol Biomarkers Prev.* 2016;25(7):1029-1036.
122. Centers for Disease Control and Prevention. What CDC is doing to help cancer survivors. 2021. https://www.cdc.gov/cancer/ncccp/priorities/cancer-survivor-caregiver.htm
123. Fu JB, Parsons HA, Shin KY, et al. Comparison of functional outcomes in low- and high-grade astrocytoma rehabilitation inpatients. *Am J Phys Med Rehabil.* 2010;89(3):205-212.
124. Stubblefield MD, McNeely ML, Alfano CM, et al. A prospective surveillance model for physical rehabilitation of women with breast cancer: chemotherapy-induced peripheral neuropathy. *Cancer.* 2012;118(8 Suppl):2250-2260.
125. Morishita S, Kaida K, Yamauchi S, et al. Relationship between corticosteroid dose and declines in physical function among allogeneic hematopoietic stem cell transplantation patients. *Support Care Cancer.* 2013;21(8):2161-2169.
126. Meneses-Echávez JF, González-Jiménez E, Ramírez-Vélez R. Supervised exercise reduces cancer-related fatigue: a systematic review. *J Physiother.* 2015;61(1):3-9.
127. Stubblefield MD, Levine A, Custodio CM, et al. The role of botulinum toxin type A in the radiation fibrosis syndrome: a preliminary report. *Arch Phys Med Rehabil.* 2008;89(3):417-421.
128. Gehring K, Roukema JA, Sitskoorn MM. Review of recent studies on interventions for cognitive deficits in patients with cancer. *Expert Rev Anticancer Ther.* 2012;12(2):255-269.
129. Ochalek K, Gradalski T, Szygula Z. Five-year assessment of maintenance combined physical therapy in postmastectomy lymphedema. *Lymphat Res Biol.* 2015;13(1):54-58.

130. Fu J, Gutierrez C, Bruera E, et al. Use of injectable spasticity management agents in a cancer center. *Support Care Cancer.* 2013;21(5):1227-1232.
131. Jinnah HA, Factor SA. Diagnosis and treatment of dystonia. *Neurol Clin.* 2015;33(1):77-100.
132. Hartl DM, Cohen M, Julieron M, et al. Botulinum toxin for radiation-induced facial pain and trismus. *Otolaryngol Head Neck Surg.* 2008;138(4):459-463.
133. Hoffman B. The employment and insurance concerns of cancer survivors. In: Ganz PA, editor. *Cancer Survivorship: Today and Tomorrow*. Springer New York; 2007:272-282.
134. Frazier LM, Miller VA, Horbelt DV, et al. Employment and quality of survivorship among women with cancer: domains not captured by quality of life instruments. *Cancer Control.* 2009;16(1):57-65.
135. Chapman SA. The experience of returning to work for employed women with breast cancer. Academy of Health Services Research and Health Policy Annual Meeting. 2000; Los Angeles, CA.
136. Short PF, Vasey JJ, Tunceli K. Employment pathways in a large cohort of adult cancer survivors. *Cancer.* 2005;103(6): 1292-1301.
137. Bradley CJ, Bednarek HL. Employment patterns of long-term cancer survivors. *Psychooncology.* 2002;11(3):188-198.
138. Cheville AL. Cancer rehabilitation. *Semin Oncol.* 2005;32(2): 219-224.
139. Raj VS, Balouch J, Norton JH. Cancer rehabilitation education during physical medicine and rehabilitation residency: preliminary data regarding the quality and quantity of experiences. *Am J Phys Med Rehabil.* 2014;93(5):445-452.
140. Ugolini D, Neri M, Cesario A, et al. Scientific production in cancer rehabilitation grows higher: a bibliometric analysis. *Support Care Cancer.* 2012;20(8):1629-1638.

68 Pain Management and Symptom Control

Kaoswi K. Shih
Rony Dev
Shalini Dalal

KEY CONCEPTS

- Patients with cancer experience multiple symptoms that are often under-reported and not alleviated. Symptoms are often interrelated and can be both physical and/or psychological.
- Pain expression can be modified by cognitive and psychological factors associated with advanced disease or the dying process.
- A thorough psychosocial history, assessment of mental status, and screening with risk assessment tools for nonmedical opioid use is critical before prescribing opioid analgesics.
- Fatigue is the most common symptom in patients with advanced cancer and its treatment is challenging in later stages of disease. Patients and families benefit from education about the burdens of both physical and emotional fatigue. It can be helpful to modify daily activities and rest to accommodate for symptoms of fatigue as well as optimizing nutrition and hydration.
- Dyspnea is often an indicator of poor prognosis in advanced cancer. Initial management includes treating underlying causes medically when able. Palliative measures to reduce the sensation of air hunger include low flow supplemental oxygen for those with hypoxemia, opioids, or corticosteroids.
- Anorexia and weight loss are a result of systemic inflammation and inadequate caloric intake because of cancer and are often difficult to reverse. Psychosocial support for cachectic patients and their family caregivers can help diminish patient-family distress.
- Advanced care planning can decrease anxiety and suffering of patients and families as well as ensure autonomy for patients, especially if they become unable to express informed consent. However, it is an ongoing process that is best started early, revisited periodically, and incorporates room for change owing to unforeseen changes in the patient's clinical condition.

Cancer is frequently associated with a multitude of distressing physical and psychosocial symptoms that can occur throughout the disease trajectory.[1] Access to a multidisciplinary supportive care team is imperative for patients with cancer experiencing multidimensional symptoms including pain, lack of energy, fatigue or drowsiness, dry mouth, dyspnea, anorexia and weight loss, insomnia, changes in mood, constipation, and delirium.[2] Without optimal symptom control in patients, administration of anticancer therapies may be delayed or discontinued, quality of life will be diminished, and unnecessary suffering will increase (Fig. 68–1).

CANCER PAIN

Forty-two percent of patients seen in the outpatient cancer center[1] and 50% of hospitalized patients with cancer have been reported to have uncontrolled pain.[3] In patients with cancer, pain may be the only symptom present before diagnosis and can indicate the recurrence and/or spread of disease.

As many as 30% to 50% of patients receiving active anticancer therapy experience pain.[1] Pain resulting from the tumor burden occurs in approximately 65% to 85% of patients with advanced cancer.[4] In addition, cancer treatment with chemotherapy, radiation, or surgery accounts for the remaining etiology of pain in approximately 15% to 25 % of patients. Three percent to 10% of patients with cancer have chronic nonmalignant pain syndromes similar to the general population (eg, low back pain associated with degenerative disc disease).[5]

Cancer pain can be described by its timing including acute versus chronic, intermittent versus continuous, as well as by its intensity or severity. Pain can be further

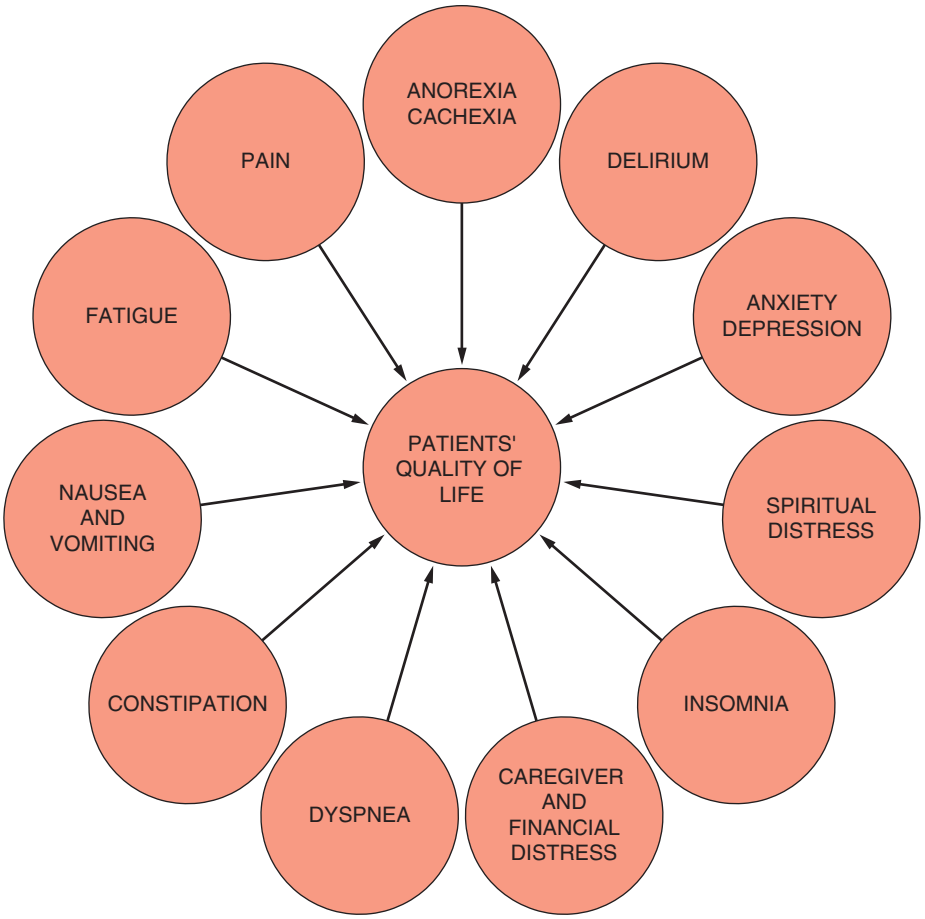


FIGURE 68–1 **Multidimensional Symptoms Impacting Quality of Life.**

categorized based on pathophysiology such as tumor related, complication of chemotherapy, radiation or surgery, or noncancer pain syndrome.

Pathophysiology

The pathophysiologic classification of pain forms the basis for therapeutic choices. Pain may be broadly divided into pain associated with ongoing tissue damage resulting in stimulation of pain receptors (nociceptive) and pain resulting from nervous system dysfunction (neuropathic) (Fig. 68–2).[6] Nociceptive pain can be classified as either somatic or visceral and results from the activation of nociceptors in cutaneous or deep tissues. Multinational data recently revealed that 72% of cancer pain is somatic, whereas 35% is described as visceral, and 40% is characterized as neuropathic.[7] Nociceptive somatic pain can be experienced as localized aching or throbbing and gnawing discomfort (eg, pain related to bony metastases). Visceral pain is the result of activation of nociceptors resulting from distention, stretching, and inflammation of internal organs, such as right upper quadrant abdominal pain due to the stretching of the liver capsule. Visceral pain is often poorly localized discomfort, described as a deep aching, cramping, and/or pressure-like sensation.

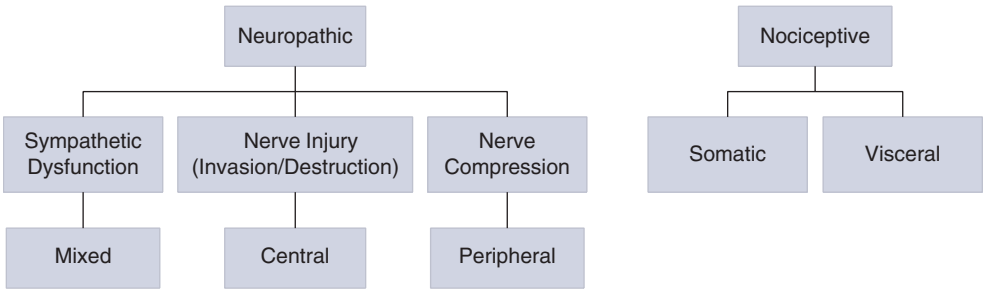


FIGURE 68–2 **Pathophysiologic Classification of Pain.**

Classification of pain can help guide selection of appropriate interventions to improve pain control. Pain mechanism, incidental occurrences, psychological distress, history of substance or opioid use disorder, and cognitive dysfunction have been indicated to be factors associated with higher ratings of pain intensity.[8] The revised Edmonton Classification System for Cancer Pain characterizing these factors has been used at our institution to guide pain management (Fig. 68–3).

1. Mechanism of pain	
No	No pain syndrome
Nc	Nociceptive pain
Ne	Neuropathic pain with or without nociceptive pain
Nx	Insufficient information to classify
2. Incident pain	
Io	No incident pain
Ii	Incident pain Present
Ix	Insufficient information to classify
3. Psychological distress	
Po	No psychological distress
Pp	Psychological distress present
Px	Insufficient information to classify
4. Addictive behavior	
Ao	No addictive behavior
Aa	Addictive behavior present
Ax	Insufficient information to classify
5. Cognitive function	
Co	No cognitive impairment
Ci	Partial cognitive impairment[1]
Cu	Total cognitive impairment[2]
Cx	Insufficient information to classify

[1]Sufficient impairment to affect patient's ability to provide accurate present and/or past pain history.
[2]Patient unresponsive, delirious, or demented to the stage of being unable to provide and present and past pain history.

FIGURE 68–3 Edmonton System of Classification of Cancer Pain. (Reproduced with permission from Elsayem A, Driver LC, Bruera E. *The MD Anderson Palliative Care Handbook*. MD Anderson Cancer Center; 2002.)

Breakthrough pain is defined as a transitory exacerbation of discomfort that occurs on a background of stable persistent chronic pain. Causes of breakthrough pain include end-of-dose failure of an opioid or pain exacerbated by activity or spontaneous occurrence. Breakthrough pain is also characterized by a short duration, often less than 3 minutes in 43% of cases according to previous prospective surveys.[9]

Pain Assessment

Pain can be measured by using visual, analog, verbal, or numerical scales and, in the research setting, complex pain questionnaires.[10] The Edmonton Symptom Assessment Scale is a useful assessment tool that allows patients to rate average pain intensity from 0 to 10 over the past 24 hours, where 0 signifies no pain and 10 is the worst pain imaginable (Fig. 68–4). However, pain assessment needs to take into account other symptoms experienced by patients with cancer because they are often interconnected and can affect symptom expression. For example, pain expression can be influenced by psychological distress or delirium which can be misinterpreted as worsening physical pain.[11,12]

In 1984, the World Health Organization (WHO) proposed an analgesic ladder for the pharmacologic management of cancer pain[13] and recommended the simple principle of escalating from nonopioid to strong opioid analgesics (Fig. 68–5). Other guidelines have been published such as the Analgesic Quantification Algorithm and National Comprehensive Cancer Network guidelines for treating cancer pain.[14]

Principles of Management

- Assess pain syndromes and other symptoms accurately.
- Respect and accept the complaint of pain as real.
- Treat pain appropriately.
- Treat underlying disorders.
- Address psychosocial concerns.
- Multidisciplinary approach is essential.

Principles of Pharmacotherapy

- Match drug to pain syndrome.
- Low threshold to prescribe opioids.
- Sustained-release formulations for constant, chronic pain and short acting for breakthrough discomfort for pain from cancer.
- Adjunct medications for certain pain syndromes.
- Oral analgesics where possible.
- Intravenous route for acute titration.

No Pain	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Pain
No Fatigue	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Fatigue
No Nausea	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Nausea
No Depression	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Depression
No Anxiety	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Anxiety
No Drowsiness	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Drowsiness
No Shortness of Breath	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Shortness of Breath
Best Appetite	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Appetite
Best Sleep	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Sleep
Best Feeling of Well-Being	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Feeling or Well-being
No Financial Distress	0	1	2	3	4	5	6	7	8	9	10	Worst Financial Distress
No Spiritual Pain	0	1	2	3	4	5	6	7	8	9	10	Worst Spiritual Pain

Completed By: Patient Family

0 = No Symptom; Best 10 = Worst Imaginable on average in the past 24 hours

FIGURE 68–4 Edmonton Symptom Assessment Scale.

- Treat side effects before switching opioids (unless causes for rotation, see below "Opioid Rotation").
- Sequential opioid trials are often beneficial.
- Familiarize with equianalgesic dosing.
- Familiarize with the pharmacokinetics of opioids.
- Differentiate between tolerance, physical dependence, chemical coping, and opioid use disorder.
- Caution with opioid titration in the setting of renal impairment.

Constipation Prevention and Treatment

A bowel regimen should always be prescribed with an opioid prescription.

- Always include stool softeners and laxatives to prevent opioid-induced constipation.
- Preferred choices include sennosides and polyethylene glycol.
- Decreased motility (gastroparesis) is a common side effect of opioids and can be treated with metoclopramide.
- Activity and adequate hydration are important.
- Bulking agents without a pro-kinetic may worsen constipation.
- Refractory constipation may be managed with lactulose 30 mL by mouth every 6 hours until a large bowel movement occurs.
- Intractable cases may require a suppository or enema.

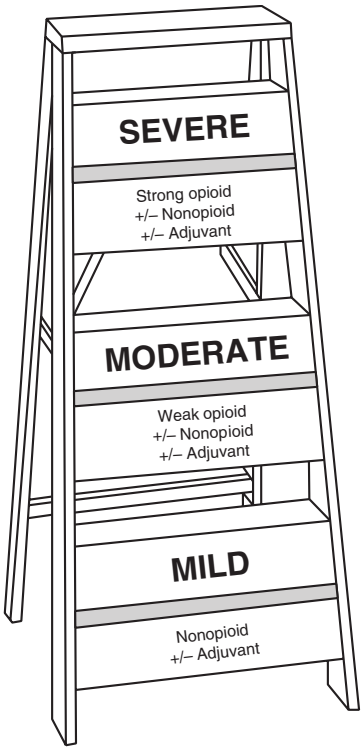
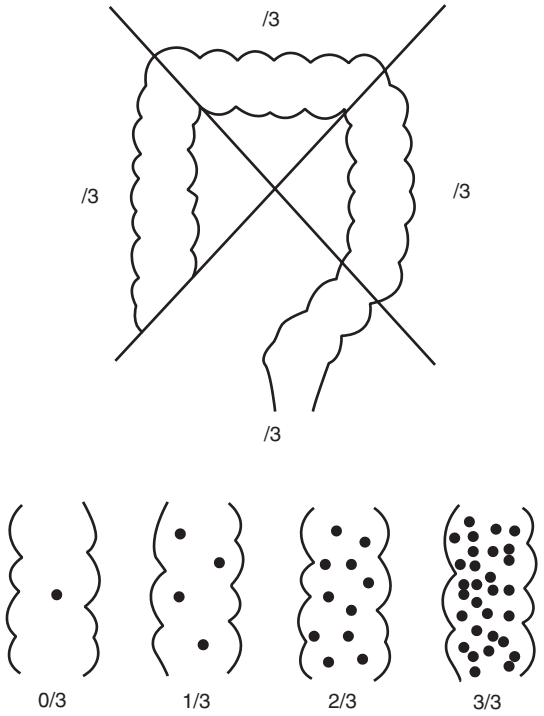


FIGURE 68–5 WHO (World Health Organization) 3-Step ladder for oral analgesic management of pain. (Reproduced with permission from World Health Organization. Cancer Pain Relief. Geneva, Switzerland: World Health Organization, 1986.)



On a flat abdominal x-ray, draw two diagonal lines intersecting at the umbilicus as shown here. This transects the abdomen into four quadrants corresponding to the ascending, transverse, descending, and rectosigmoid colons. Then, assess the amount of stool in each of the four quadrants using the following scoring system: 0 = no stool; 1 = stool occupying <50% of the lumen of colon; 2 = stool occupying >50% of the lumen; 3 = stool completely occupying the lumen. The total score will therefore range from 0 to 12. A score of 7 indicates severe constipation and requires immediate intervention.

FIGURE 68–6 Constipation score via objective assessment of fecal load on an abdominal radiograph. (Reproduced with permission from Elsayem A, Driver LC, Bruera E. *The MD Anderson Palliative Care Handbook*. Houston, TX: MD Anderson Cancer Center; 2002.)

- Proximal impaction may require oral laxatives.
- Cases where hard stools are present in the vault may necessitate manual dis-impaction.
- The degree of constipation may be evaluated with imaging (Fig. 68–6).

Opioid Rotation

Defined as switching from one type of opioid to another, often in the setting of opioid neurotoxicity.

Reasons to rotate opioids:

- Uncontrolled pain despite escalating opioid doses.
- Development of tolerance or dose-limiting side effects of opioid neurotoxicity (sedation, hallucinations, confusion, myoclonus).
- Hyperalgesia as a result of the production of excitatory amino acids from the opioid itself.
- Cost necessitating alternate opioid.

Opioid rotation has been reported to not only improve pain control, resolve delirium, and alleviate myoclonus, but it may also improve other symptoms including depression and insomnia (Table 68–1).[15]

In a recent study of an outpatient population of 114 cancer patients at MDACC with a mean Eastern Cooperative Oncology Group performance status of 1, opioid rotation for side effects or uncontrolled pain achieved improved symptom control successfully in 65% of the patient population.[16]

Individual variability of opioid activation of multiple subtypes of opioid receptors accounts for the benefits of opioid rotation, which should be considered when managing uncontrolled pain.[17,18] In difficult cases, this may include rotation on two to three occasions to reduce opioid neurotoxicity and improve pain control.

General guidelines for opioid rotation:

1. Calculate total daily dose.
2. Calculate dose of new opioid using opioid conversion table (Table 68–2).
3. Reduce dose of new opioid to account for incomplete cross-tolerance.

Table 68–1 Commonly Used Opioids

Drug Usual Starting Dosages
Full opioid agonists
Morphine[a] 15–30 mg PO every 3–4 h
Morphine extended release (MScontin) 15–30 mg PO every 8–12 h
Hydromorphone (Dilaudid) 2–4 mg PO every 4–6 h
Hydromorphone extended release (Exalgo) 8–16 mg PO every 12–24 h
Fentanyl (Duragesic) 12–25 µg/h TD changed every 48–72 h
Codeine 15–30 mg PO every 3–4 h
Oxycodone (Percodan and others) 5–10 mg PO every 3–4 h
Oxycodone extended release (OxyContin) 10–20 mg PO every 3–4 h
Meperidine (Demerol hydrochloride) 75–100 mg IM q 3–4 h
Methadone hydrochloride (Dolophine)[b] 5–10 mg PO every 3–4 h
Partial agonists and mixed agonists/antagonistsc
Nalbuphine (Nubain) 10 mg IV q 3–4 h
Butorphanol (Stadol) 0.5–2 mg IV q 3–4 h
Buprenorphine 5µh/h topical patch every week or 1–2 mg SL 3×/d

[a]Morphine can be given as an immediate-release or sustained-release preparation. It is recommended that a relatively rapid onset, short-acting opioid preparation (such as immediate-release morphine) be given to patients who take sustained-release morphine to provide rescue medication for breakthrough pain.
[b]Methadone is 10 to 15 times more potent than morphine. Expertise is needed to prescribe and administer it.
[c]This class of drugs is *not* recommended for the management of chronic cancer pain because it will reverse analgesia when coadministered with full opioid agonists and precipitate withdrawal in physically-dependent individuals.
IM, intramuscular; IV, intravenous; PO, by mouth.

Table 68–2 Opioid Conversion Table

IV MO	PO MO	1:2.5
IV HM	PO HM	1:2.5
PO HM	PO MO	1:5
IV HM	IV MO	1:5
PO Oxymorphone	PO MO	1:3
PO Oxycodone	PO MO	1:1.5
PO HCD	PO MO	1:1 at ≥ 40 mg HCD/day
PO HCD	PO MO	1:1.5 at <40 mg HCD/day
Fentanyl patch	PO MO	Fentanyl Patch × 2.5 = PO MO
IV FENT	IV MO	15 µg: 1 mg

Steps for conversion: (1) take the total amount of opioid that effectively controls pain in 24 hours; (2) multiply by conversion factor in table; give 30% less of the new opioid to avoid partial cross-tolerance; (3) divide by the number of doses per day.
HCD, hydrocodone; HM, hydromorphone; MO, morphine.
Reproduced with permission from Elsayem A, Driver LC, Bruera E. *The MD Anderson Palliative Care Handbook*. Houston, TX: MD Anderson Cancer Center; 2002.

Opioids

Codeine

Codeine is a prodrug used to treat mild to moderate pain, diarrhea, and intractable coughing spells. It is the second most common alkaloid in opium and is hypothesized to be 200 times less potent than morphine. Metabolism by the liver converts 90% of the drug to inactive metabolites and 10% as morphine. The cytochrome oxidase 2D6 (*CYP2D6*) gene is responsible for the conversion to morphine and, in some groups, may not be fully active, whereas others may express multiple copies of the gene and are considered ultrarapid metabolizers.[14] These ultrarapid metabolizers pose a greater risk of opioid neurotoxicity because of the codeine rapidly metabolizing into morphine, especially in the pediatric population. On the other hand, patients who have decreased metabolization may experience ineffective analgesia with the drug.

In addition, some medications are CYP2D6 inhibitors and block conversion of codeine to morphine when coadministered. These include antidepressants paroxetine, fluoxetine, bupropion, and diphenhydramine. Medications known to increase *CYP2D6*, such as dexamethasone, should also be used with caution with codeine (Fig. 68–7).

Hydrocodone

Hydrocodone has historically been considered a weak opioid on the WHO ladder. It is manufactured commonly in combination with acetaminophen or

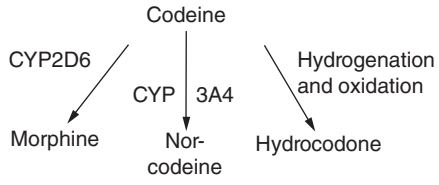


FIGURE 68–7 Codeine metabolism diagram.

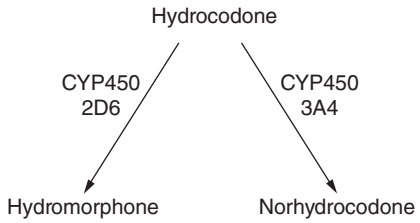


FIGURE 68–8 Hydrocodone metabolism diagram.

ibuprofen. It is a semisynthetic opioid derived from codeine and is metabolized by the liver and excreted in the urine. Hydrocodone is metabolized by cytochrome P450 2D6 to hydromorphone (Fig. 68–8). Recent studies have shown that hydrocodone, when taken at doses of less than 40 mg per day, is equivalent to twice the strength of morphine; however, the ratio of morphine to hydrocodone at doses greater than or equal to 40 mg per day have been shown to be closer to 1:1.[15]

Morphine

Morphine is commonly used as a standard prototype drug for opioid pain management. It is a naturally occurring opioid purified from opium poppy seeds and is available in short- and long-acting preparations. In the liver, it is converted to morhine-3-glucoronide and morphine-6-glucoronide (M3G and M6G, respectively) by glucuronyl transferase (Fig. 68–9). M3G is responsible for excitatory neurotoxic side effects including myoclonus, hallucinations, seizures, and confusion, and accumulates with renal insufficiency. Morphine is available as oral, rectal, intramuscular, intravenous, and sublingual preparations.

Hydromorphone

Hydromorphone is a semisynthetic opioid derived from morphine and is 6 to 7 times more potent. It is available for administration via all routes including neuroaxial. It may be an alternative to morphine when dose-limiting side effects require rotation to a more potent opioid. Long-acting formulations are available (trade name Exalgo) but are expensive.

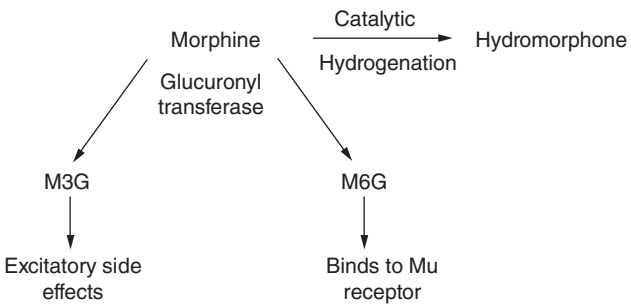


FIGURE 68–9 Morphine metabolism diagram.

Oxycodone

Oxycodone is another semisynthetic opioid derived from thebaine, a minor natural component of opium similar to morphine and codeine. Oxycodone has been known to be 1.5 times more potent than morphine. Previously its dosage was limited by its combination with acetaminophen or aspirin, but it is now commonly available in the US as oxycodone by itself as a pill. It has a higher bioavailability than morphine and exists both as extended-release and short-acting formulations.

Oxymorphone

Oxymorphone is produced after the *CYP2D6* metabolism of oxycodone. It is a semisynthetic opioid and, like oxycodone, is derived from thebaine. It has low bioavailability orally and is three times more potent than morphine. Its maximum serum concentration is reached in 30 minutes, and immediate-release tablets may last up to 6 to 8 hours. Extended-release oxymorphone lasts 12 hours and should be dosed as such because of its long half-life of 14 hours. Advantages of oxymorphone include its compatibility with either a venting gastrostomy-tube (administer by mouth and clamp tube for 30 minutes) or with a feeding tube (crush and administer immediate-release form via the tube every 8 hours as scheduled) as an option for a scheduled analgesic regimen. It should be noted that extended-release morphine, oxymorphone, and hydromorphone are all contraindicated in patients with partial or complete bowel obstruction and should be avoided in those at risk as well.

Meperidine

Meperidine (Demerol) is a weaker opioid with potency one-tenth that of morphine. Dose escalation is limited by the risk of accumulation of the metabolite normeperidine, metabolized by the liver. Both meperidine and nor-meperidine cause central nervous system toxicity including convulsions, especially in renal impairment and in the geriatric population. Because of these risks, it is becoming used less commonly.

Fentanyl

Fentanyl is a synthetic opioid that is 80 to 100 times more potent than morphine and has a rapid onset and short duration of analgesia. It is often used in the setting of acute or incidental breakthrough pain. Transdermal sustained-release formulations (fentanyl patches) are a good choice for stable pain and are changed every 72 hours. Fentanyl patches are convenient in patients

in whom oral routes are limited or unavailable. Oral transmucosal fentanyl has been used for breakthrough pain; however, fentanyl has a very rapid onset of action, which makes it difficult to calculate total dose delivered, and erratic equianalgesic dosing often raises safety concerns.

Methadone

Methadone is a synthetic opioid. Recent research[16] has characterized appropriate equianalgesic dosing,[17,18] and advantages include low cost, less active metabolites, good bioavailability, and *N*-methyl-d-aspartate antagonism, which may account for the absence of the development of tolerance associated with chronic use. Methadone potency can be 10 to 15 times that of morphine, so caution should be exercised when rotating to methadone. Close monitoring after its initiation is necessary because of its tendency to accumulate as time advances before reaching a steady state. The half-life varies with individuals between 15 to 190 hours. Clinicians prescribing methadone should be aware of potential drug interactions, because of metabolism via the cytochrome P-450 system, which include antifungals, antiretroviral medications, and selective serotonin reuptake inhibitors (SSRIs).[19] Methadone has also been associated with QTc interval prolongation,[20,21] so proper cardiac monitoring is indicated. Prospective studies at MDACC found it to be safe for use in advanced cancer.[11] It is being researched as a viable first-line treatment option for pain management[22] and is especially useful for patients with refractory cancer pain.[23]

Opioid Safety

Opioids can be a safe and effective analgesic for cancer pain treatment; however, adverse effects and unintended outcomes can still occur. It is important to conduct a thorough history that considers patient-related factors including age, renal and liver function, and drug interactions with concurrent medications that can cause altered opioid absorption, metabolism, or clearance that could potentially increase the risk of side effects.

Side effects of opioid analgesics include nausea, gastroparesis, constipation, drowsiness, cognitive impairment, hallucinations, myoclonus, allodynia, hyperalgesia, seizure disorder, QT prolongation with the use of methadone, bradycardia, hypotension, respiratory depression, urinary retention, xerostomia, sweating, pruritus, hormonal changes, and immunosuppression. Concurrent use of some medications can exacerbate these side effects, for example benzodiazepines which can increase sedation, alter mental status, or precipitate respiratory suppression.[24]

Other unintended outcomes include opioid use disorder or chemical coping. Opioid use disorder is defined as intentional use of a medication for nonmedical purposes that causes significant functional impairment or distress.[25,26] Symptoms of opioid use disorder include strong desire to use opioids, difficulty fulfilling obligations, and difficulty reducing use. Chemical coping is defined as inappropriate excessive use of opioids to cope with various stressful events including the disclosure of a cancer diagnosis and during treatment.[27–29]

Before starting prescribed opioids, it is important to screen patients with a comprehensive history covering psychosocial history and personal or family history of substance or opioid use disorder, as well as utilizing risk assessment tools. Examples include the Cut down, Annoyed, Guilty, and Eye-opener (CAGE) questionnaire; Screener and Opioid Assessment for Patients with Pain form; the Opioid Risk Tool; and Diagnosis, Intractability, Risks, and Efficacy (DIRE) inventory.

The CAGE questionnaire is clinician administered and asks about the patient's perceived:

1. Need to cut down on alcohol use.
2. Annoyance with questions about alcohol use.
3. Guilt over drinking habits.
4. Use of eye-opener drinks.[30]

For every "yes" answered, patients score 1 point with a cutoff score of 2 or greater being considered positive and with a sensitivity of 0.93 and specificity of 0.76 for identifying excessive alcohol use.[31] The CAGE-AID (adapted to include drugs) substitutes "drink" with "drink or drugs" to evaluate for the detection of substance use disorder and has a sensitivity of 0.88 and specificity of 0.55 with cut off score of 2.[32] A positive CAGE score may indicate increased risk for chemical coping and opioid use disorder. Other risk factors include being younger, male, having mental health or substance use disorders, and tobacco use. High-risk patients should have close follow-up and monitoring. Prescription drug monitoring programs that collect data from pharmacies that dispense controlled substances can also provide important information about patients' prescription history and past prescribers.

Urine drug screens (UDSs) may also provide additional means of monitoring (Table 68–3). Two main types are immunoassays and confirmatory testing. Immunoassays use antibodies to detect the presence of a specific drug or its metabolite. These are economical and have quick turnaround times but are unable to distinguish different drugs in the same class or detect synthetic opioids. Confirmatory tests use gas or liquid chromatography or mass spectrometry. These are able to detect specific drugs but are more expensive

Table 68–3 Abnormal Urine Drug Screen Results[a]

Results	Possible Indications
Absence of prescribed opioids	Diversion
Presence of unprescribed opioids	Multiple prescribers, opioids from unapproved sources
Presence of illicit drugs	Substance use disorder

[a]Data from Magnani B, Kwong T. Urine drug testing for pain management, *Clin Lab Med* 2012 Sep;32(3):379-390.

and have a slower turnaround time.[33] UDSs may still be underutilized in patients with cancer as opposed to persons with chronic pain.[24]

All patients should be given informed consent that communicates the potential risks and benefits of opioids and other controlled substances, as well as education on storage and proper disposal of opioid medications. Opioid management plans, contracts, or agreements can help outline goals, expectations, responsibilities of the clinician and patient regarding prescription, and monitoring at subsequent follow-up appointments. Safe practices include receiving opioids from one prescriber and designating one pharmacy for dispensing medication. Regular consistently scheduled appointments and random UDSs and prescription monitoring programs can assist with monitoring for adherence. Procedures if adherence is not maintained are also important to outline and convey to patients.[34]

Adjuvant Medications

Although opioids are often first-line analgesics, adjuvant medications are useful for pain control in some settings such as neuropathic pain. Because of the delay in onset and potential side effects with some drug groups, adjuvant drugs may be best reserved after optimal trials of opioids. Of the tricyclic antidepressants drug class, amitriptyline and nortriptyline are felt to be the most efficacious and have lower cardiovascular side effects. Tricyclic antidepressants are limited by anticholinergic and sedative side effects. Anticonvulsants are helpful in treating brachial and lumbosacral plexopathies, but side effects and safety limit their wide use. For the adjuvant treatment of neuropathic pain, gabapentin has been shown to be effective but does require dose adjustment in renal failure and can be associated with increased risk for sedation, altered mental status, and respiratory suppression. Pregabalin has been used as an alternative to gabapentin but is costly and has not shown greater efficacy (Table 68–4).

Table 68–4 Adjuvant Analgesics

Nonsteroidal Antiinflammatory Drugs
Acetaminophen
Aspirin
Ibuprofen
Naproxen
Celecoxib
Ketorolac
Tricyclic antidepressants
Amitriptyline
Nortriptyline
Doxepin
Doxeparin
Antiepileptic drugs
Gabapentin
Topiramate
Levetiracetam
Tiagabine
Oxcarbazepine
Lamotrigine
Felbamate
Local anesthetics
Lidocaine
N-methyl-d-aspartate receptor antagonists
Ketamine
Methadone
Dextromethorphan
Haldol
Topical analgesics
Capsaicin
Lidocaine patches

Reproduced with permission from Elsayem A, Driver LC, Bruera E. *The MD Anderson Palliative Care Handbook*. Houston, TX: MD Anderson Cancer Center; 2002.

Nonpharmacologic Treatment

Adjuvant nonpharmacologic treatments include nerve blocks, neurosurgical procedures, and radiation therapy. Physical and psychological interventions to treat pain include counseling, psychotherapy, relaxation techniques, massage therapy, music therapy, and acupuncture. Addressing psychosocial and spiritual distress for both patients and family may be needed for patients experiencing complex, total pain at the end of life.

Anesthetic Procedures

- Celiac plexus/splanchnic block for abdominal visceral pain
- Subarachnoid neurolytic block for extremity and thoracic wall
- Epidural/intrathecal opioids with or without local anesthetic (eg, for neuropathic or plexopathy pain)
- Cordotomy for intractable lower extremity pain
- Vertebroplasty (injection of cement into a vertebral body) for metastatic spinal pain involving one or two vertebrae

CANCER-RELATED FATIGUE

Fatigue is among the most common and distressing symptoms encountered in approximately 60% to 90% of patients with cancer.[35] The National Comprehensive Cancer Network defines cancer-related fatigue as a persistent subjective sense of physical, emotional, and cognitive tiredness or exhaustion related to cancer or cancer treatment, that is not proportional to recent activity and is both distressing and interferes with usual function.[36] Fatigue may include a lack of interest and difficulty maintaining attention, concentration, or motivation in objects or activities. Patients may present with depressed mood, have a flat affect, and appear lethargic or somnolent. Rest or sleep does not eliminate or alleviate symptoms of cancer-related fatigue.

Fatigue may be experienced at any point in the cancer trajectory and often worsens at the end of life. Cancer-related fatigue may render patients unable to tolerate physical or mental activity, resulting in an inability to complete activities of daily living, impairment of social and occupational function, and diminishment in overall quality of life. Fatigue may also heighten other symptoms associated with cancer.

Etiologies of cancer-related fatigue are often multifactorial (Fig. 68–10) including not only the underlying cancer itself but also treatments such as chemotherapy or radiation therapy. Fatigue may be exacerbated by other underlying metabolic abnormalities such as hypothyroidism or hypogonadism and can be amplified by psychosocial distress.

Fatigue Assessment

Assessment of fatigue requires a multidimensional approach. Fatigue severity is included on the Edmonton Symptom Assessment Scale, where 0 equals no fatigue and 10 equals the worst fatigue imaginable (Fig. 68–4). Other numeric and verbal rating scales have been validated for fatigue including the Functional Assessment of Cancer Therapy-Fatigue, the Piper Fatigue Scale, Schwartz Cancer Fatigue Scale, Fatigue Symptom Inventory, and the Functional Assessment of Chronic Illness-Fatigue (FACIT-F) (Table 68–5).

Cancer-related fatigue should not be primarily a consequence of comorbid psychiatric disorders, which must be excluded, including major depression, somatization disorder, somatoform disorder, or delirium.

Table 68–5 ICD-10 Criteria for Cancer Fatigue

Symptoms present daily	Yes	No
Fatigue, decreased energy, increased need to rest[a]		
Generalized weakness/limb heaviness		
Diminished concentration or attention		
Decreased motivation/interest to engage in usual activities		
Insomnia/Hypersomnia		
Sleep unrefreshing or nonrestorative		
Struggle to overcome inactivity		
Emotional reactivity to feeling fatigue—sadness/frustration/irritability		
Difficulty completing daily tasks		
Problems with short term memory		
Postexertional fatigue lasting several hours		

[a]Significant fatigue, diminished energy, or increased need to rest, disproportionate to any recent change in activity level must be present in addition to five or more of the other symptoms present daily or nearly every day during the same two-week period in the past month (Data from National Cancer Institute).

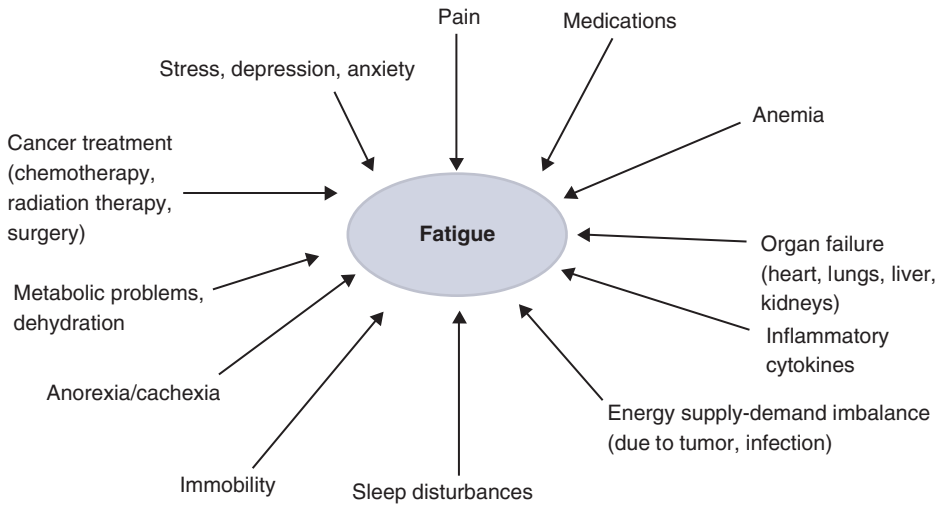


FIGURE 68–10 Multidimensional Assessment of Fatigue.

Fatigue Management

The initial assessment of fatigue should focus on contributing factors that can be corrected such as hypothyroidism, anemia, vitamin B12 deficiency, and renal insufficiency. Treatment of cancer-related fatigue should be considered only after correction of underlying etiologies.[37,38] Treatment of pain, depression, anxiety, sleep disturbances, dehydration, and cancer anorexia–cachexia syndrome are critical to improving symptoms of fatigue. Medications that exacerbate fatigue should be reviewed and discontinued if indicated, underlying infections should be aggressively treated, and patients with symptomatic anemia should receive blood transfusions when appropriate.[39]

Corticosteroids

Low-dose steroids may alleviate some symptoms of fatigue. Recent studies have confirmed their short-term benefit; however, more studies are required to determine the optimal dose.[40]

Methylphenidate

Psychostimulants such as methylphenidate may be useful if the patient is experiencing concomitant problems such as depression or drowsiness related to opioids. However, a recent randomized trial examining methylphenidate reported no significant difference in median FACIT-F scores in cancer-related fatigue when compared with a placebo.[41–44]

Antidepressants

SSRIs may improve fatigue; however, their benefit has not been proven and may be indirectly related to the treatment of underlying mood disorder. A Cochrane review that included two double-blind, placebo-controlled studies (n = 645) using paroxetine in a meta-analysis, did not show any significant improvement in fatigue in patients with cancer.[45]

Testosterone Replacement

Recently there has been evidence that cancer patients with hypogonadism on chronic opioid therapy may benefit from replacement with testosterone.[46] A pilot study of testosterone replacement at 4 weeks in hypogonadal males with advanced cancer did not have significant improvement of fatigue as measured with FACIT-F, although there was a trend for improvement with longer duration of treatment.[47]

Homeopathic Dietary Supplements

Studies have evaluated dietary supplements for treatment of fatigue. Ginseng has been used medicinally in the Far East for several millennia and is a widely used supplement to treat fatigue in the US. The composition of the active ingredients of ginseng root (ginsenosides and saponins) varies and standardization can be problematic. Moreover, a recent randomized, double-bind, placebo-controlled trial of Panax ginseng extract given twice daily versus matched placebo for 28 days did not produce significantly different fatigue scores.[48] Other potentially possible homeopathic supplements include guarana extract and l-carnitine.

Integrative Nonpharmacologic Interventions

Exercise therapy such as brisk walking, may help with fatigue. A recent meta-analysis of randomized trials examining supervised exercise therapy supports exercise improving cancer-related fatigue. These findings suggest that combined aerobic and resistance exercise regimens, with or without stretching, should be included as part of rehabilitation programs for patients with cancer.[49] Yoga has also been studied for the treatment of cancer-related fatigue with some positive results, although level of bias and inconsistent methods in previous randomized studies may have influenced the results.[50] Indirect natural light[51] and massage therapy may also help to reduce fatigue.

In addition, treatment of fatigue should also address underlying psychosocial factors such as depression, anxiety, and other symptoms including pain, cachexia, or dyspnea to be effective. Cognitive behavioral therapy in treating psychosocial distress or insomnia may indirectly improve symptoms of fatigue. In the future, multimodality treatment of cancer-related fatigue should be personalized for each individual patient, and more research is needed to develop successful interventions.

NAUSEA

Physiology

Neuronal impulses from the chemoreceptor trigger zone (CTZ), gastrointestinal tract, higher cortical areas, and vestibular apparatus are responsible for sensations of nausea and emesis when neurons in the vomiting center of the medulla oblongata are activated (Fig. 68–11). This can be either through direct activation from the gastrointestinal tract, or indirectly from visceral vagal afferent signals to the CTZ. The CTZ is located in the fourth ventricle floor outside the blood-brain barrier, which is accessible to emetogenic substances. Neurotransmitters involved in impulses to the CTZ and vomiting center include serotonin, dopamine, and substance P, which acts on natural killer–1 receptors. In addition, histamine and acetylcholine, which act on histaminic and muscarinic receptors, respectively, are involved in motion sickness–related vomiting.

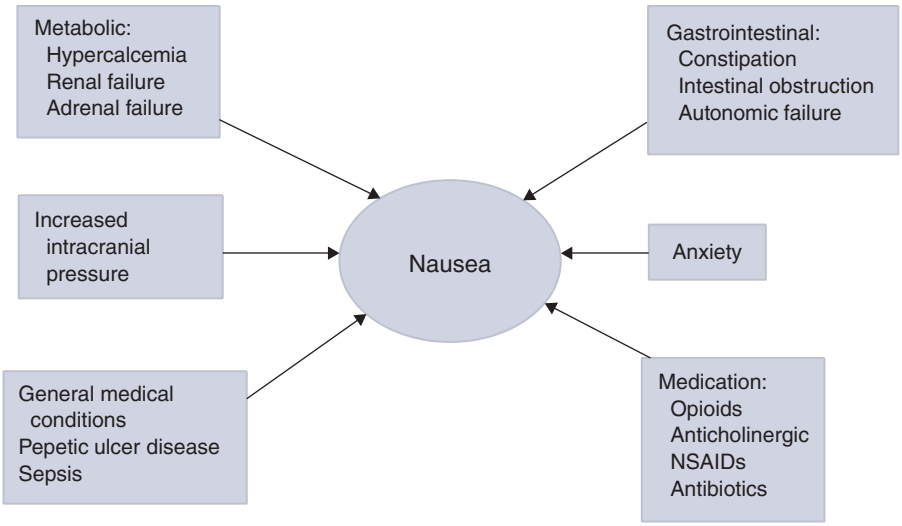


FIGURE 68–11 **Multidimensional Assessment of Nausea. (Reproduced with permission from Elsayem A, Driver LC, Bruera E. *The MD Anderson Palliative Care Handbook*. Houston, TX: MD Anderson Cancer Center; 2002.)**

Assessment

Evaluation of nausea can be approached in a stepwise fashion beginning with determining the intensity, onset, duration, frequency, and temporal factors of episodes of nausea and emesis. It is important to review a patient's history with regards to tumor site and involvement, history of past and current therapies such as chemotherapy and radiation, and a thorough review of medications that can potentially exacerbate nausea such as the use of opioids. Additional examination of the patient should assess hydration status, assessment of bowel function to rule out constipation, and other etiologies that could potential contribute to sensations of nausea and emesis including central nervous system involvement, autonomic failure, and other mechanisms (Fig. 68–11, Table 68–6).

Anorexia-Cachexia

The anorexia-cachexia syndrome is characterized by a loss of appetite coinciding with significant weight loss, loss in lean body mass including muscle wasting, loss of fat, fatigue, immune dysfunction, and metabolic derangements. Cancer cachexia has been defined as a multifactorial syndrome of ongoing skeletal muscle mass atrophy with or without the loss of fat mass that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. Diagnosis of cachexia has been agreed upon by a panel of experts as a weight loss greater than 5%, or weight loss greater than 2% in individuals already with body-mass index less than 20.[52] Studies have shown that even a loss of 5% or more of premorbid weight before chemotherapy is associated with a shorter survival.[53]

Cachexia is found in the majority of patients with advanced cancer and is a major contributing factor to death in about 50% of these patients.[52] Complex interactions between tumor and host lead to an aberrant immune response, neuro-hormonal dysfunction, and endocrine dysregulation (Fig. 68–12). Both cachexia and fatigue are associated with increased pro-inflammatory cytokines (IL-1, IL-6, tumor necrosis factor–α), low testosterone levels, abnormal cortisol secretion, and resistance to insulin and ghrelin.[54] These cellular derangements are associated with increased production of acute-phase proteins in the liver and loss of muscle protein caused by proteolysis and lipolysis and results in elevated triglycerides and decreased high-density lipoproteins.

Unfortunately, neither nutritional supplementation nor artificial feeding reverses cancer anorexia-cachexia syndrome.[54] Multiple studies have examined the role of total parenteral and enteral nutrition in patients with cancer and have reported limited benefits. Artificial feeding of cancer patients with cachexia was found to increase acute-phase protein production without influencing the rate of albumin synthesis.[55] Other contributory factors resulting in weight loss, including depression, nausea, dysphagia, bowel obstruction, or constipation, should be treated aggressively.

Treating patients in the early stages of weight loss may be important to maintain or increase lean body mass because it is difficult to reverse cachexia in late stages.[54] A comprehensive history including recent changes in weight and diet patterns is important. Simple and inexpensive tests are available to assess body composition, such as anthropometric measurements, skinfold thickness, arm muscle circumference

Table 68–6 Common Nausea Treatments

Druga	Main Receptor	Main Indication	Starling PO Dose/Route	Equivalent Priceb	Side Effects
Metoclopramide	D2	Opioid-induced, gastric stasis	10 mg q4h PO, SC, IV	1	EPS (akathisia, dystonia, dyskinesia)
Prochlorperazine	D2	Opioid-induced	10 mg qbh PO, IV	3	Sedation, hypotension
Cyclizine	HI	Vestibular causes, intestinal obstruction	25–50 mg q8h PO, SC, PR		Sedation, dry mouth, blurred vision
Promethazine	HI	Vestibular, motion sickness, obstruction	12.5 mg q4h PO, PR, IV	2	Sedation
Haloperidol	D2	Opioid, chemical, metabolic	1–2 mg bid PO, IV, SC	1	Rarely EPS
Ondansetron	5 HT^3	Chemotherapy	4–8 mg q8h PO, IV	84	Headache, constipation
Diphenhydramine	HI, Ach	Intestinal obstruction, vestibular ICP	15 mg q4h PO, IV, SC	0.2	Sedation, dry mouth, blurred vision
Hyoscine	Ach	Intestinal obstruction, colic, secretions	0.2–0.4 mg q4h SL, SC, TD	0.4	Dry mouth, blurred vision, urine retention, agitation

[a]Corticosteroids are not included because they vary in dosage and have limited indications (see text).
[b]Prices are compared with metoclopramide 10-mg tablets orally for 10 days based on the formulary prices at MD Anderson Cancer Center. November 2001.
Ach, acetylcholine; D2, dopamine; EPS, extrapyramidal symptoms; HI, histamine; ICP, intracranial pressure; PR, per rectum; SL, sublingual; TD, transdermal.

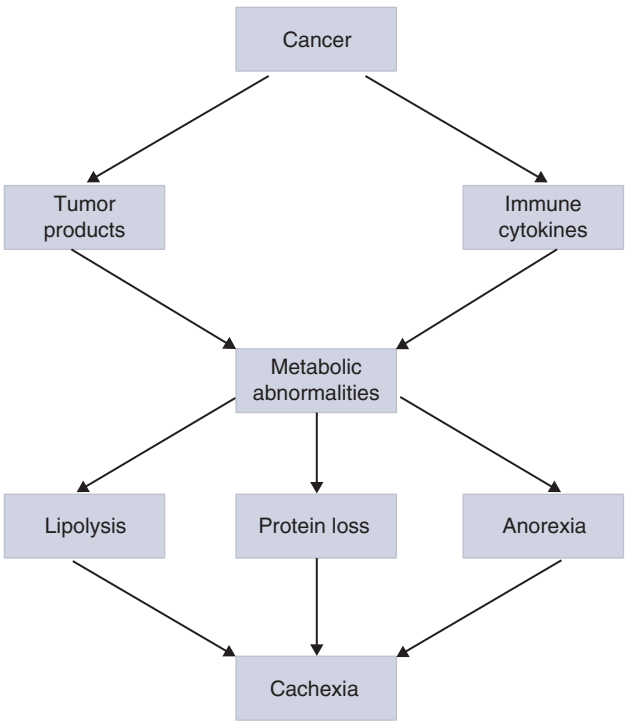


FIGURE 68–12 Etiologies of cancer cachexia. (Reproduced with permission from Elsayem A, Driver LC, Bruera E. *The MD Anderson Palliative Care Handbook*. Houston, TX: MD Anderson Cancer Center; 2002.)

and area, and weight and body mass index. Laboratory markers such as electrolytes, serum albumin, transferrin, and pre-albumin may also be useful.

Management

Identify etiology and treat the underlying cause.

- Treat nausea/early satiety: metoclopramide 5–10 mg every 4 to 6 hours (renal adjustment required) (Table 68–6)
- Progestational agents
- Megestrol acetate: 40–120 mg orally four times daily (risk of thromboembolism, hypogonadism, and adrenal suppression)
- Corticosteroids
- Dexamethasone: 4 mg orally twice daily (lower mineralocorticoid effect than other steroids[54])
- For cancer patients with depression: antidepressants (tricyclic and SSRI, eg, mirtazapine 15 mg orally nightly)
- Nutritionist consultation

Counseling and psychosocial support for cachectic patients and their family/caregivers is critical at the end of life and will decrease patient-family conflict. Counseling should emphasize the pleasure of eating as well as promote social participation of patients in family

meals as opposed to monitoring caloric intake. Emphasis should highlight the normal loss of appetite as patients approach end of life (and are often not hungry), and family/caregivers should not pressure patients to eat, which could result in nausea and psychological distress.

DYSPNEA

Dyspnea is a subjective symptom defined as an "uncomfortable awareness of breathing."[56] It is often described as a sensation of air hunger, suffocation, choking, or heavy breathing. Dyspnea may be related to underlying tumor progression, altered by psychosocial factors including anxiety, and exacerbated by preexisting pulmonary comorbidities. Shortness of breath can develop in response to pain or a mismatch between perceived ventilation rate and respiratory drive. Dyspnea is considered refractory when it persists at rest or with minimal activity and is distressful despite optimal medical therapy.[57]

Dyspnea in patients with advanced cancer is an indicator of poor prognosis.[58,59] The etiology of dyspnea is often multifactorial. It is postulated that in the brain, the cortical-limbic network is responsible for dyspnea perception. Recent research reports that the anterior cingulate cortex and the dorsolateral prefrontal cortex are involved in sensing dyspnea.[60] In addition, the insular cortex is modulated by sensations of dyspnea, and studies of asthmatic patients have shown that it is downregulated in patients experiencing dyspnea and pain.[61]

Treatment of Dyspnea

The aim of treatment for dyspnea is to improve the patient's perception of shortness of breath and involves not only treating the underlying cause but also palliating symptoms of air hunger. Treating the underlying etiologies can vary from thoracentesis for a pleural effusion, blood transfusions for anemic patients, corticosteroids for systemic inflammation or lymphangitic carcinomatosis, or antibiotics for pneumonia.

Symptomatic relief may include oxygen therapy, bilevel positive airway pressure or high-flow oxygen therapy.[62] In patients with chronic obstructive pulmonary disease, long-term oxygen therapy has shown mortality reduction but does not necessarily improve dyspnea. Palliative oxygenation is often prescribed irrespective of oxygen saturation levels. Oxygen delivery by nasal cannula compared with room air does not always equate to relief of dyspnea in nonhypoxemic patients with advanced illness.

Pharmacologic interventions for dyspnea include opioids, benzodiazepines, and corticosteroids and are often utilized when medical therapy fails to improve the perception of dyspnea. Opioids, when titrated carefully, will often improve dyspnea without reducing oxygenation or causing respiratory depression.[60] Immediate-release, short-acting, and sustained-release morphine have been used in clinical trials of dyspnea management. The American Thoracic Society and the Canadian Thoracic Society advocate opioid dose titration to achieve the lowest effective dose based on patient ratings of shortness of breath.[60]

Corticosteroids are most useful in situations of lymphangitic spread or inflammation causing obstruction of airways.[63] Bronchodilators may also play a role when dyspnea is related to bronchospasm and reduce airway smooth muscle tone, thereby improving airflow and deflating an overinflated lung.[60] Tachycardia is a common side effect of bronchodilators.

Integrative approaches may also be effective such as relaxation techniques or guided imagery for patients with anticipatory or anxiety-driven dyspnea. Low-dose benzodiazepines in conjunction with opioids may have a role in the treatment of dyspnea complicated by severe anxiety, but they have the potential to cause delirium and decrease respiratory drive.[64] Acupuncture has also been researched for the treatment of dyspnea. In a study by Jones and colleagues,[65] one 45-minute session of transcutaneous electrical nerve stimulation at acupuncture sites resulted in improvement of dyspnea, increased forced expiratory volume in 1 second, and blood levels of β-endorphin compared with placebo. Suzuki and colleagues reported exertional dyspnea was reduced in patients with chronic obstructive pulmonary disease after receiving acupuncture once per week for 12 weeks compared with placebo.[66] Assistive devices can be used to minimize muscular effort, and postural drainage, a fan with airflow directed to the face,[67] and incentive spirometry can help in certain settings.

DELIRIUM

Delirium, an acute state of encephalopathy, results from diffuse organic brain dysfunction. The prevalence of delirium is approximately 10% in hospitalized medical and surgical patients and is noted in 26% to 44% of patients with advanced cancer at the time of hospital admission. Roughly half of these cases may be reversible. In advanced cancer, delirium will develop in more than 80% of patients at the end of life.[68] Delirium is often misdiagnosed and associated with increased morbidity and mortality.[69] It complicates assessment of pain and other symptoms and results in distress for patients, family/caregivers, and health care providers.

Clinical Presentation

Delirium is characterized by a waxing and waning mentation. The main diagnostic criteria, according to

the *Diagnostic and Statistical Manual of Mental Disorders Fourth Edition-Text Revision* (DSM-IV-TR), includes a disturbance of consciousness with a reduced ability to focus, sustain, or shift attention; a change in cognition (disorientation/language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting dementia; and the disturbance develops over a short period of time (hours to days) and fluctuates during the course of the day. Three clinical variants of delirium have been designated based on type of arousal disorder: hypoactive, hyperactive, and mixed.

Assessment

Delirium is often misdiagnosed as anxiety, insomnia, worsening pain, or mood disturbance, resulting in inappropriate treatment with anxiolytics, hypnotics, inappropriate increase in opioids, or antidepressants, which can worsen symptoms. Maintaining a high index of suspicion can help to avoid misdiagnosis of delirium and routine use of screening tools such as the Memorial Delirium Assessment Scale or Mini Mental Status Exam is recommended. Clinicians should pay attention to metabolic derangements, which may precipitate delirium such as liver or renal failure (Fig. 68–13). Medications may also be the cause, including use of opioids (responsible for almost 60% of cases[70]), benzodiazepines, some antiemetics, and corticosteroids.

Management

1. Provide patients a safe environment including fall precautions, minimize noise and excessive light, and place patients in a familiar setting with a visible clock and calendar as well as family at the bedside to help reorient patients.
2. Treat underlying causes such as hypercalcemia or pneumonia Treatment of agitation:
3. To treat severe agitation secondary to delirium, it may be necessary to give haloperidol more frequently initially (Table 68–7). In agitated cancer patients with terminal delirium who are refractory to haloperidol, a combination of haloperidol and a benzodiazepine may be necessary. However, in a study by Breitbart et al,[71] lorazepam alone was ineffective in the treatment of delirium and actually contributed to the worsening of delirium and increased cognitive impairment in terminal patients with HIV. Newer atypical antipsychotics may be just as effective as typical antipsychotics but are more expensive. Olanzapine may be more sedating. Sometimes acute dystonia and extrapyramidal side effects are seen with haloperidol, in which case benztropine can be administered. Once symptoms are under control, reducing haloperidol to the minimal effective dose is recommended.[72,73]

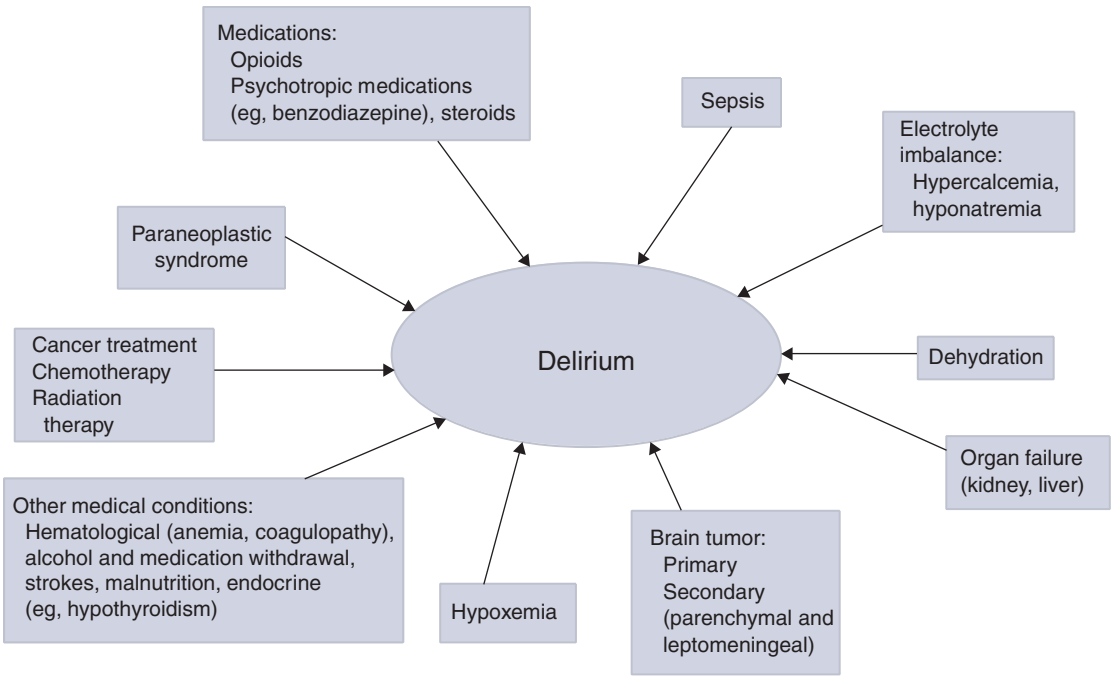


FIGURE 68–13 **Multidimensional Assessment of Delirium. (Reproduced with permission from Elsayem A, Driver LC, Bruera E. *The MD Anderson Palliative Care Handbook*. Houston, TX: MD Anderson Cancer Center; 2002.)**

Table 68–7 Common Pharmacologic Management for Delirium

Haloperidol[a]	IV/PO/IM	Start 1–2 mg q6h and 1–2 mg q2h PRN
Olanzapine	PO/ODT/IM	2.5–5 mg daily, titrated to 5.5–10 mg daily
Risperidone	PO/ODT/IM	0.25–0.5 mg q12h titrated to 1.5 mg q12h
Quetiapine	PO/IM	12.5–25 mg PO q12h titrated to 100 mg q12h
Chlorpromazine	IV/PO/IM	Start 10–25 mg/h and 10–25 mg q2h PRN
Lorazepam	IV/PO/IM	0.5–1 mg q1h until calm; recommend against use as single agent

[a]The oral bioavailability is approximately 60% to 70% when converting from oral to parenteral.

4. Counseling patient's family caregivers and healthcare providers regarding patient expression of previously well-controlled physical symptoms by grimacing or moaning may be inhibition of emotions due to delirium. In such cases, treatment should be directed at controlling delirium and not inappropriately increasing opioids (Fig. 68–14).

Palliative Sedation

Instances of refractory delirium, as well as other uncontrolled symptoms at the end of life, may require palliative sedation. Palliative sedation is defined as "the monitored use of sedative medication to reduce patients' awareness of intractable and refractory symptoms near the end of life when other interventions have failed to control them."[74] It is important to ensure all available symptomatic measures including palliative medicine consultation have been tried before deeming symptoms as refractory. The goal of palliative sedation is to control symptoms, not hasten death, which is differentiated from physician-assisted euthanasia. Therefore, it is imperative to discuss this with the patient and family/caregivers to avoid misunderstanding. Midazolam, titrated to control symptoms, is often used for palliative sedation.

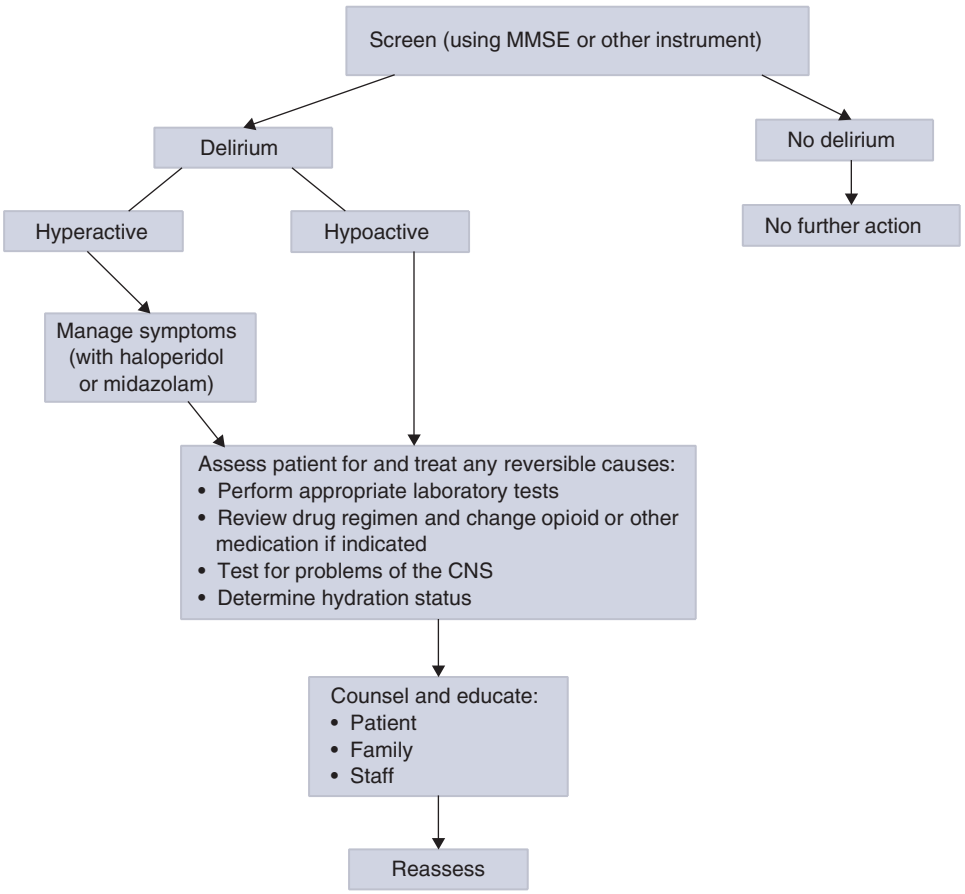


FIGURE 68–14 Algorithm of Delirium Screening and Management. (Reproduced with permission from Elsayem A, Driver LC, Bruera E. *The MD Anderson Palliative Care Handbook*. Houston, TX: MD Anderson Cancer Center; 2002.)

Patients need regular assessments, including the Richmond Agitation Sedation Scale, to monitor for excessive sedation. If underlying symptoms have improved, sedatives may be decreased and even discontinued.

DEPRESSION

Clinical depression is a common mood disorder encountered in patients with cancer and can affect from 25% to 35% of the patient population.[75] Clinical depression increases in frequency in advanced disease,[76] and diagnosis can be challenging in these patients. For instance, symptoms often strongly associated with clinical depression in healthy individuals are often commonly encountered in patients with advanced disease including fatigue, impaired decision-making ability, insomnia, and poor appetite. Per DSM-IV-TR criteria,[77] the cardinal features of clinical depression include anhedonia; feelings of guilt, hopelessness or worthlessness; and suicidal ideation. A thorough patient history directed at assessment for these symptoms is needed.

In addition, the diagnosis of clinical depression can be difficult to differentiate from adjustment disorder, anticipatory grief, or delirium. Validated measures of assessing depression in the primary care setting include the WHO-5 well-being index,[78] the PHQ-9 screening test,[79] Hamilton Rating Scale for Depression (HAM-D),[80] and the Montgomery Asberg Depression Rating Scale[81] (MADRS). Other factors that increase the risk of depression include a history of substance abuse, family history of depression and suicide, concurrent life stressors, and poor social support.

Common Antidepressants

Common initial doses for some antidepressants are:

- Nortriptyline 25 mg/day (at bedtime)
- Amitriptyline 25 mg/day (at bedtime)
- Fluoxetine 10–20 mg/day
- Paroxetine 10 mg/day
- Sertraline 20 mg/day
- Citalopram 20 mg/day
- Venlafaxine 37.5 mg/day
- Mirtazapine 15 mg/day (at bedtime)
- Methylphenidate 5–10 mg in the morning and 5 mg at noon[82]

Escitalopram has a lower side-effect profile and works slightly faster than other first-generation SSRIs. Side effects include reduced appetite, nausea, and anxiety. Antidepressants should be given for a trial of 6 weeks for beneficial effects, and if there is no significant improvement, the dose may need adjustment or an alternate medication prescribed. In patients with cancer who have unclear criteria for clinical depression or suicidal ideation, consultation with a psychiatrist is indicated.

COMMUNICATION

The majority of patients with advanced cancer desire as much information as possible about their diagnosis and treatment.[83] A majority of patients also feel it is important to know about their prognosis[84] and prefer either shared or active decision making with their physician or family/caregivers.[85] Healthcare providers' ability to accurately prognosticate life expectancy of patients with cancer is still very limited. In addition, a patient's acceptance of information regarding prognosis and end-of-life issues is heavily influenced by the manner in which this information is conveyed. It is common that healthcare professionals feel uncomfortable with discussing poor prognosis and other end-of-life issues. Reasons include lack of training, stress, feeling rushed and not having enough time to address the emotional needs of patients, fear of upsetting the patient or family/caregivers, or reluctance to diminish hope about the unavailability of further curative treatment. Avoidance of end-of-life discussions can lead to patient dissatisfaction and further psychological distress.[86]

There are very few trials testing the effectiveness of different strategies in delivering bad news.[87] Most recommendations on discussing bad news agree on the following key features: preparation, content of message, dealing with the patient's responses, and ending the encounter (Table 68–8).[87]

Important guidelines regarding end-of-life discussions have emphasized the following: identify the reason for the discussion and the patient's expectations, elicit their knowledge of their current situation, consider cultural awareness and preferences in regards to disclosure of information, validate feelings and take an empathetic approach, explain information by using language without medical jargon, use terms and phrases that are easy to understand, explain the limitations of prognostication, and avoid exact timelines.[86]

Family meetings initiated by healthcare professionals as a tool to improve communication can be helpful to inform, deliberate, clarify goals, and mediate difficult end-of-life discussions. They can help to formulate acceptable care plans between patient, family/caregivers, and healthcare providers[86] and clarify goals of care so everyone is "on the same page" (Table 68–8).[88,89]

Table 68–8 SPIKES Protocol: Setting Up, Patient's Perception, Invitation, Knowledge, Emotions, and Support[a]

Step 1: Setting Up the Interview	
Goals	**Process**
Prepare for the interview	Have a plan in mind before seeing the patient
Establish rapport	Arrange for uninterrupted time and decide who should be present and whether the patient is ready
Facilitate information exchange	Sit down, try to remain calm, and speak slowly with eye contact; have facial tissues ready
Step 2: Find out the Patient's Perception	
Goals	**Process**
Determine what the patient understands	Ask open-ended questions
Promote rapport with listening	Correct misinformation and misunderstanding
Assess denial	Address denial ("I can see that it is hard to hear this") and unrealistic expectations ("I wish")
Understand expectations and concerns	Define your role
Step 3: Get An Invitation to Give Information	
Goal	**Process**
Determine how much information the patient wants and when they are ready to hear it	Ask "Are you the type of person who wants information in detail or…"
Resolve conflicts with families regarding information disclosure	Explore family concern
Step 4: Giving the Patient Knowledge and Information	
Goal	**Process**
Prepare the patient for bad news	Forecast the arrival of bad news
Ensure understanding	Give information in small parcels and check periodically for understanding
	Avoid medical jargon
	Address questions
Step 5: Responding to Emotions	
Goal	**Process**
Address emotional responses	Anticipate emotional reactions
Facilitate emotional recovery	Have facial tissues ready
Acknowledge our own emotions	Do not speak from you own limbic lobe; resist the temptation to make bad news better than it really is
	Avoid "fix it" responses ("It is not as bad as you think")
	Support with empathic responses to expressions of emotion (ie, crying)
	Clarify emotions you are not sure about ("Tell me more")
	Validate feelings
Step 6: Communicating Strategy and Summary	
Goal	**Process**
Ensure a clear negotiated plan for the future	Treatment recommendations
	Ensure patient understanding about the plan
	Provide options
	Understand barriers and concerns patients may have
	Communicate your role; patients will be comforted knowing you will follow them

[a]Data from Baile WF, Buckman R, Lenzi R, et al: SPIKES-A six-step protocol for delivering bad news: application to the patient with cancer, *Oncologist* 2000;5(4):302-311. Modified with permission from Elsayem A, Driver LC, Bruera E. *The MD Anderson Palliative Care Handbook*. Houston, TX: MD Anderson Cancer Center; 2002.

ADVANCED CARE PLANNING

Advanced directives are routinely comprised of the patient's specific preferences regarding medical care, often in the form of a living will, which details a person's desires for when they are no longer able to express informed consent as well as indicating a medical power of attorney, the patient's surrogate decision maker. The goals of advanced directives are to decrease anxiety and suffering of patients and families and ensure autonomy for the patient if they are unable to express informed consent. Inverse associations between end-of-life discussions before the last 30 days of life and aggressive treatment measures have been observed.[90]

Ideally, goals-of-care discussions are conducted in an outpatient setting during a stable clinical period and initiated by a physician that includes a patient's healthcare proxies and family. It is helpful then to periodically review and edit advanced directives as a patient's condition and prognosis change. Guidelines for developing advanced care plans with patients include the following:

1. Inform the patient of a desire to discuss health preferences related to their medical condition. Transparency on topics to be discussed is important.
2. Arrange for a convenient time and a comfortable setting (without interruptions) to have the discussion. It is important to include surrogate decision makers in addition to loved ones and family who are important to decision making for the patient.
3. Assess, understand, and reflect on the patient's state of health and care options in the context of his or her values and goals.
4. Formulate and document a care plan.
5. Communicate a treatment plan to the surrogate decision maker/family/caregivers/loved ones and the medical team.
6. Review the plan periodically whenever new events or changes to a patient's condition arise.
7. Implement the plan as needed with corresponding circumstances.[91]

Advanced care plans may be forms of medical orders such as the Physician Orders for Life-Sustaining Treatment (POLST) or Medical Orders for Life-Sustaining Treatment (some state programs may vary by name) scanned into the patient's electronic health record. These portable medical orders are an approach to documenting treatment preferences in advance and have been associated with less in-hospital death, hospitalization, and unwanted cardiopulmonary resuscitation.[92]

However, there is still a portion of patients, sometimes more than one-third who receive treatment discordant with their preferences as outlined in their POLST. This was seen with patients with less predictable prognostic trajectories, as opposed to patients with more predictable illness.[92] Advanced care planning documents are one piece of information that are used at the time of decision making, and they depend on prognosticating at a single point in time, which may change. Other challenges to advanced care planning can include additional substantial logistic, financial, and caregiver burdens that arise.

Patients and surrogates may not want to think about issues related to illness and death. Patients may often have a difficult time envisioning disability and forgo aggressive treatments in more stable states, but after experiencing and adjusting to declines in health, they may be willing to accept more invasive treatments. However, some patients may also shift focus from life-prolonging measures to one of comfort after experiencing a decline in their function and health.[93]

These challenges highlight the importance of advanced care planning discussion as an ongoing process, best when started early, revisited periodically to clarify and articulate patients' values over time, and incorporating room to adapt for unforeseen changes in clinical condition, as well as honoring the values of patients and their family/caregivers.

CONCLUSION

Patients with cancer will encounter distressing symptoms that can diminish their quality of life and interfere with the ability to receive cancer therapy. Physical and emotional symptoms are encountered at any point during the illness trajectory from diagnosis, treatment, survivorship, or end of life. An oncologist may be overwhelmed with the challenges of cancer treatment when patients have uncontrolled symptoms. In collaboration with an interdisciplinary palliative care team, healthcare providers may simultaneously treat cancer aggressively while maintaining the integrity of human life and diminishing unnecessary suffering.

There is an urgent need to incorporate assessment and treatment of physical and emotional symptoms facing patients with cancer and integrating palliative medicine teams into the delivery of cancer care. For patients with complex symptoms, early adoption of interdisciplinary palliative care is often indicated to prevent the sequelae of physical and emotional pain. In addition, an open dialogue with patients and family/caregivers regarding issues of treatment options, prognosis, and end-of-life care, including a transition from focus on curing cancer to care directed at controlling symptoms, is needed within the continuum of cancer treatment.

MD ANDERSON PRACTICE TIPS

- The routine use of validated tools in a consistent manner (Edmonton Symptom Assessment Scale, Memorial Delirium Assessment Scale, CAGE-AID) can assist in completing a thorough symptom assessment.
- It is important to consider total pain when prescribing analgesics. Laxatives are essential to consider when prescribing opioid analgesics. Benzodiazepines may cause unintended oversedation, altered mental status, or respiratory suppression. Morphine Equivalent Daily Dose can be a useful baseline calculation for opioid dosing. The process of prescribing opioid analgesics includes discussing potential risks and benefits and is useful for other controlled substances, education on storage and proper disposal of opioid medications, and careful monitoring with prescription monitoring programs.
- For symptomatic relief of fatigue, a short course of corticosteroids, methylphenidate for patients with drowsiness or depression, exercise, and cognitive behavioral therapy may be effective in mitigating fatigue. Physical activity has shown the best evidence-based treatment to date.
- Systemic opioids can help to relieve dyspnea.
- Anorexia-cachexia in patients with cancer can benefit from nutritional counseling, exercise, symptom control, and multiple specific pharmacologic agents directed at the mechanism of cachexia.
- A majority of patients with advanced cancer feel it is important to know about their prognosis. Prognostication is a longitudinal process in which survival estimates may change over time. There is always uncertainty in prognostication, and clinicians can acknowledge this while facilitating decision making over multiple dialogues throughout the disease course.

REFERENCES

1. Portenoy RK, Lesage P. Management of cancer pain. *Lancet.* 1999;353(9165):1695-1700.
2. Solano JP, Gomes B, Higginson IJ. A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease. *J Pain Symptom Manage.* 2006:31(1):58-69.
3. Holtan A, Aass N, Nordoy T, et al. Prevalence of pain in hospitalised cancer patients in Norway: a national survey. *Palliat Med*. 2007;21(1):7-13.
4. Vanden Beuken-Van Everdingen MH, Hochstenbach LM, Joosten EA, et al. Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. *J Pain Symptom Manage.* 2016;51(6):1070-1090.E9.
5. Krech RL, Walsh D. Symptoms of pancreatic cancer. *J Pain Symptom Manage.* 1991;353(9165):1695-1700.
6. World Health Organization. Guidelines for the Pharmacological and Radiotherapeutic Management of Cancer Pain in Adults and Adolescents. Geneva: World Health Organization; 2018.
7. Heung Y, Reddy A, Reddy S. Introduction to pain. In: Dalal S, Bruera E, eds. *The MD Anderson Supportive and Palliative Care Handbook*. 6th ed. UT Health Printing Services; 2018:11-16.
8. Arthur J, Yennurajalingam S, Nguyen L, et al. The routine use of the Edmonton Classification System for Cancer Pain in an outpatient supportive care center. *Palliat Support Care.* 2014: 1-8.
9. Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence, and characteristics. *Pain.* 1990;41:273-281.
10. Bruera E, Kuehn N, Miller MJ, et al. The Edmonton symptom assessment system: a simple method for the assessment of palliative care patients. *J Palliat Care.* 1991;7:6-9.
11. Breitbart W, Bruera E, Chochinov H, et al. Neuropsychiatric syndromes and psychological symptoms in patients with advanced cancer. *J Pain Symptom Manage.* 1995;10:131-141.
12. Coyle N, Breitbart W, Weaver S, et al. Delirium as a contributing factor to 'crescendo' pain: three case reports. *J Pain Symptom Manage.* 1994;9:44-47.
13. World Health Organization. *Cancer Pain Relief*. World Health Organization; 1986.
14. Patrick DL, Cleeland CS, von Moos R, et al. Pain outcomes in patients with bone metastases from advanced cancer: assessment and management with bone-targeting agents. *Support Care Cancer.* 2015;23(4):1157-1168.
15. Reddy A, Yennurajalingam S, Pulivarthi K, et al. Frequency, outcome, and predictors of success within 6 weeks of an opioid rotation among outpatients with cancer receiving strong opioids. *Oncologist.* 2013;18(2):212-220.
16. 27. Reddy S, Hui D, El Osta B, et al. The effect of oral methadone on the QTc interval in advanced cancer patients: a prospective pilot study. *J Palliat Med.* 2010;13(1):33-38.
17. Galer BS, Coyle N, Pasternak GW, et al. Individual variation in the response to different opiods—report of five cases. *Pain.* 1992;49:87-91.
18. Hanks G, Forbes K. Opioid responsiveness. *Acta Anaesthesiol Scand.* 1997;41:154-158.
14. Prommer E. Role of codeine in palliative care. *J Opioid Manage*. 2011;7(5):401-406.
15. Reddy A, Yennurajalingam S, Desai H, et al. The opioid rotation ratio of hydrocodone to strong opioids in cancer patients. *Oncologist.* 2014;19(11):1186-1193.
16. Davis MP, Walsh D. Methadone for relief of cancer pain: a review of pharmacokinetics, pharmacodynamics, drug interactions and protocols of administration. *Support Care Cancer.* 2001;9:63-83.
17. Ripamonti C, Groff L, Brunelli C, et al. Switching from morphine to oral methadone in treating cancer pain: what is the equianalgesic dose ratio? *J Clin Oncol.* 1998;16(10):3216-3221.
18. Ripamonti C, de Conno F, Groff L, et al. Equianalgesic dose/ratio between methadone and other opioid agonists in cancer pain: comparison of two clinical experiences. *Ann Oncol.* 1998;9:79-83.
19. Tarumi Y, Pereira J, Watanabe S. Methadone and fluconazole: respiratory depression by drug interaction. *J Pain Symptom Manage.* 2002;23(2):148-153.
20. Andersen G, Christrup L, Sjogren P. Relationships among morphine metabolism, pain and side effects during long-term treatment: an update. *J Pain Symptom Manage.* 2003;25(1): 74-91.
21. Cruciani RA, Sekine R, Homel P, et al. Measurement of QTc in patients receiving chronic methadone therapy. *J Pain Symptom Manage.* 2005;29(4):385-391.
22. Rhondali W, Tremellat F, Ledoux M, Ciais J-F, Bruera E, Filbet M. Methadone rotation for cancer patients with refractory pain in a palliative care unit: an observational study. *J Palliat Med.* 2013;16(11):1382-1387.
23. Salpeter SR, Buckley JS, Bruera E. The use of very-low-dose methadone for palliative pain control and the prevention of opioid hyperalgesia. *J Palliat Med.* 2013;616(6):616-622.
24. Arthur J, Hui D. Safe Opioid use: management of opioid-related adverse effects and aberrant behaviors. *Hematol Oncol Clin North Am*. 2018;32(3):387-403.
25. Passik SD, Portenoy RK, Ricketts PL. Substance abuse issues in cancer patients. part 1: prevalence and diagnosis. *Oncology (Williston Park).* 1998;12:517-521, 524.
26. Rinaldi RC, Steindler EM, Wilford BB, et al. Clarification and standardization of substance abuse terminology. *JAMA.* 1988;259:555-557.
27. Kwon JH, Hui D, Bruera E. A pilot study to define chemical coping in cancer patients using the Delphi method. *J Palliat Med*. 2015;18:703-706.
28. Dalal S, Tanco K, Bruera E. State of art of managing pain in patients with cancer. *Cancer J.* 2013;19(5):379-389.
29. Del Fabbro E. Assessment and management of chemical coping in patients with cancer. *J Clin Oncol.* 2014;32:1734-1738.
30. Williams N. The CAGE questionnaire. *Occup Med (Lond).* 2014;64:473-474.
31. Bernadt MW, Mumford J, Taylor C, et al. Comparison of questionnaire and laboratory tests in the detection of excessive drinking and alcoholism. *Lancet.* 1982;1:325-8.
32. Dyson V, Appleby L, Altman E, et al. Efficiency and validity of commonly used substance abuse screening instruments in public psychiatric patients. *J Addict Dis.* 1998;17:57-76.
33. Magnani B, Kwong T. Urine drug testing for pain management. *Clin Lab Med*. 2012;32:379-390.
34. de la Cruz M, Reddy A, Balankari V, et al. The impact of an educational program on patient practices for safe use, storage, and disposal of opioids at a comprehensive cancer center. *Oncologist.* 2017;22:115-121.
35. Yennu S, Urbauer DL, Bruera E. Factors associated with the severity and improvement of fatigue in patients with advanced cancer presenting to an outpatient palliative care clinic. *BMC Palliat Care.* 2012;11:16.
36. Piper BF, Cella D. Cancer-related fatigue: definitions and clinical subtypes. *J Natl Compr Canc Netw.* 2010;8(8):958-966.
37. Cella D, Peterman A, Passik S, et al. Progress toward guidelines for the management of fatigue. *Oncology (Williston Park).* 1998;12:369-377.
38. Portenoy RK, Itri LM. Cancer-related fatigue: guidelines for evaluation and management. *Oncologist.* 1999;4:1-10.
39. Demetri GD, Kris M, Wade J, et al. Quality of life benefit in chemotherapy patients treated with epoetin alfa is independent

of disease response or tumor type: results from a prospective community oncology study. *Oncology (Williston Park).* 1998;16: 3412-3425.
40. Yennurajalingam S, Bruera E. Role of corticosteroids for fatigue in advanced incurable cancer: is it a 'wonder drug' or 'deal with the devil'. *www.supportiveandpalliativecare.com*. December 2014:346-351.
41. Bruera E, Yennurajalingam S, Palmer J, et al. Methylphenidate and/or a nursing telephone intervention for fatigue in patients with advanced cancer: a randomized, placebo-controlled, phase II trial. *J Clin Oncol.* 2013;31(19):2421-2427.
42. Bruera E, Brenneis C, Paterson AH, et al. Use of methylphenidate as an adjuvant to narcotic analgesics in patients with advanced cancer. *J Pain Symptom Manage.* 1989;4:3-6.
43. Breitbart W, Mermelstein H. An alternative psychostimulant for the management of depressive disorders in cancer patients. *Psychosomatics.* 1992;33:352-356.
44. Katon W, Raskind M. Treatment of depression in the medically ill elderly with methylphenidate. *Am J Psychiatry.* 1980;137:963-965.
45. Minton O, Richardson A, Sharpe M, Hotopf M, Stone P. Drug therapy for the management of cancer-related fatigue. *Cochrane Database Syst Rev.* 2010;(7):CD006704.
46. Rajagopal A, Vassilopoulou-Sellin R, Palmer JL, et al. Symptomatic hypogonadism in male survivors of cancer with chronic exposure to opioids. *Cancer.* 2004;100(4):851-858.
47. Del Fabbro E, Garcia JM, Dev R, et al. Testosterone replacement for fatigue in hypogonadal ambulatory males with advanced cancer: a preliminary double-blind placebo-controlled trial. *Support Care Center.* 2013;21(9):2599-2607.
48. Yennurajalingam, S, Tannir, NM, Willams, J. A double-blind, randomized, placebo-controlled trial of panax ginseng for cancer-related fatigue in patients with advanced cancer. *J Natl Compr Canc Netw.* 2017 Sep:15(9):1111-1120.
49. Meneses-Echávez JF, González-Jiménez E, Ramírez-Vélez R. Supervised exercise reduces cancer-related fatigue: a systematic review. *J Physiother.* 2015;61(1):3-9.
50. Sadja J, Mills PJ. Effects of yoga interventions on fatigue in cancer patients and survivors: a systematic review of randomized controlled trials. *Explore (NY).* 2013;9(4):232-243.
51. Liu L, Rissling M, Neikruga A, et al. Fatigue and circadian activity rhythms in breast cancer patients before and after chemotherapy: a controlled study. *Fatigue*. 2013;1(1-2):12-26.
52. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international Consensus. *Lancet Oncol.* 2011;12:489-95.
53. Dewys WD, Begg C, Lavin PT, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. *Am J Med.* 1980;69:491-497.
54. Del Fabbro E, Dalal S, Bruera E. Symptom control in palliative care—part II: cachexia/anorexia and fatigue. *J Palliat Med.* 2006;9(2):409-421.
55. Barber MD, Fearon KC, McMillan DC, et al. Liver export protein synthetic rates are increased by oral meal feeding in weight losing cancer patients. *Am J Physiol Endocrinol Metab.* 2000;279:707E-E714E.
56. Wasserman K, Casaburi R. Dyspnea and physiological and pathophysiological mechanisms. *Annu Rev Med.* 1988;39:503-515.
57. Mahler DA, Selecky PA, Harrod CG. Management of dyspnea in patients with advanced lung or heart disease: practical guidance from the American college of chest physicians consensus statement. *Polish Arch Intern Med*. 2010;120(5): 160-166.
58. Hardy JR, Turner R, Saunders M, et al. Prediction of survival in a hospital-based continuing care unit. *Eur J Cancer.* 1994;30:284-288.
59. Escalante CP, Martin CG, Elting LS, et al. Dyspnea in cancer patients: etiology, resource utilization, and survival. *Cancer.* 1996;78:1314-1319.
60. Donald A. Mahler, Denis E. O'Donnell. Recent advances in dyspnea. *Chest.* 2015;147(1):232-241.
61. von Leupoldt A, Sommer T, Kegat S, et al. Down-regulation of insular cortex responses to dyspnea and pain in asthma. *Am J Respir Crit Care Med.* 2009;180(3):232-238.
62. Hui D, Morgado M, Chisholm G, et al. High-flow oxygen and bilevel positive airway pressure for persistent dyspnea in patients with advanced cancer: a phase II randomized trial. *J Pain Symptom Manage.* 2013;46(4):463-473.
63. Weir DC, Gove RI, Robertson AS, et al. Corticosteroids trials in nonasthmatic chronic airflow obstruction: a comparison of oral prednisolone and inhaled beclomethasone diproprionate. *Thorax.* 1991;45:112-117 53.
64. Allcroft P, Margitanovic V, Greene A, et al. The role of benzodiazepines in breathlessness: a single site, open label pilot of sustained release morphine together with clonazepam. *J Palliat Med.* 2013;16(7):741-744.
65. Jones AY, Ngai SP, Hui-Chan CW, Yu HP. Acute effects of Acu-TENS on FEV1 and blood b-endorphin level in chronic obstructive pulmonary disease. *Altern Ther Health Med.* 2011;17(5):8-13.
66. Suzuki M, Muro S, Ando Y, et al. A randomized, placebo-controlled trial of acupuncture in patients with chronic obstructive pulmonary disease (COPD): the COPD-acupuncture trial (CAT). *Arch Intern Med.* 2012;172(11):878-886.
67. Galbraith S, Fagan P, Perkins P, Lynch A, Booth S. Does the use of a handheld fan improve chronic dyspnea? A randomized controlled, crossover trial. *J Pain Symptom Manage.* 2010;39(5):831-838.
68. Bruera E, Bush SH, Willey J, et al. Impact of delirium and recall on the level of distress in patients with advanced cancer and their family caregivers. *Cancer.* 2009;115(9):2004-2012.
69. de la Cruz M, Fan J, Yennu S, et al. The frequency of missed delirium in patients referred to palliative care in a comprehensive cancer center. *Support Care Cancer.* 2015;23(8):2427-2433.
70. Centeno C, Sanz A, Bruera E. Delirium in advanced cancer patients. *Palliat Med*. 2004;18(3):184-194.
71. Breitbart W, Marotta R, Platt MM, et al. A double-blinded trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in the hospitalized AIDS patients. *Am J Psychiatry.* 1996;153:231-237.
72. Hui D, Bush SH, Gallo LE, Palmer JL, Yennurajalingam S, Bruera E. Neuroleptic dose in the management of delirium in patients with advanced cancer. *J Pain Symptom Manage.* 2010;39(2):186-196.
73. Elsayem A, Bush SH, Munsell MF, et al. Subcutaneous olanzapine for hyperactive or mixed delirium in patients with advanced cancer: a preliminary study. *J Pain Symptom Manage.* 2010;40(5):774-782.
74. Sanft T, Hauser J, Rosielle D, et al. Physical pain and emotional suffering: the case for palliative sedation. *J Pain.* 2009;10(3):238-242.
75. Derogatis LR, Marrow GR, Fettig J, et al. The prevalence of psychiatric disorders among cancer patients. *JAMA.* 1983:249;751-757.
76. Wilson KG, Chochinov HM, de Faye B, et al. Diagnosis and management of depression in palliative care. In: Chochinov HM, Breitbart W, eds. *Handbook of Psychiatry in Palliative Care*. Oxford University Press; 2000:25-49, 106.
77. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. American Psychiatric Association; 1994.
78. Bonsignore M, Barkow K, Jessen F, et al. Validity of the five item WHO Well Being Index (WHO-5) in an elderly population. *Eur Arch Psychiatry Clin Neurosci.* 2001;251(suppl 2):II27-II31.

79. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* 2001;16:606-613.
80. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960;23:56-62.
81. Montgomery S, Asberg MA. A new depression scale designed to be sensitive to change. *Br J Psychiatry.* 1979;134:382-389.
82. Elsayem A, Driver LC, Bruera E. *The MD Anderson Palliative Care Handbook*. MD Anderson Cancer Center; 2002.
83. El -Jawahri A, Traeger L, Kuzmuk K, et al. Prognostic understanding, quality of life, and mood in patients undergoing stem cell transplantation. *Bone Marrow Transplant.* 2015;50(8):1119-1124.
84. El-Jawahri A, Traeger L, Park ER, et al. Associations among prognostic understanding, quality of life, and mood in patients with advanced cancer. *Cancer.* 2014;120(2):278-285.
85. Yennurajalingam S, Rodrigues SLF, Shamieh O, et al. Perception of curability among advanced cancer patients: an international collaborative study. *Oncologist.* 2018;23(4):501-506.
86. Clayton JM, Hancock KM, Butow PN, et al. Clinical practice guidelines for communicating prognosis and end-of-life issues with adults in the advanced stages of a life-limiting illness, and their caregivers. *Med J Aust.* 2007;186(suppl 12):S77, S79, S83-S108.
87. Ptacek JT, Eberhardt TL. Breaking bad news: a review of the literature. *JAMA.* 1996;276:496-502.
88. Hudson P, Quinn K, O'Hanlon B, Aranda S. Family meetings in palliative care: multidisciplinary clinical practice guidelines. *BMC Palliat Care.* 2008;7(12).
89. Baile WF, Buckman R, Lenzi R, et al. SPIKES-A six step protocol for delivering bad news: application to the patient with cancer. *Oncologist.* 2000;5:302-211.
90. Mack JW, Cronin A, Keating NL, et al. Associations between end-of-life discussion characteristics and care received near death: a prospective cohort study. *J Clin Oncol.* 2012;30(35):4387-4395.
91. Zhukovsky DS. Principles of advanced care planning. In: *Internal Medicine Issues in Palliative Cancer Care*. Oxford University Press; 2015.
92. Lee RY, Brumback LC, Sathitratanacheewin S, et al. Association of physician orders for life-sustaining treatment with ICU admission among patients hospitalized near the end of life. *JAMA.* 2020;323(10):950-960.
93. Sudore RL, Fried TR. Redefining the "planning" in advance care planning: preparing for end-of-life decision making. *Ann Intern Med.* 2010;153(4):256-261.

This page intentionally left blank

Section XV Biostatistics

Section Editor: Xuelin Huang

69 Statistical Designs for Oncology Clinical Trials

70 Big Data and Machine Learning in Oncology

71 Value-Based Oncology

This page intentionally left blank

69

Statistical Designs for Oncology Clinical Trials

Xuelin Huang
Wei Qiao
Fang Xia
E Lin
Liang Zhu
Jing Ning

KEY CONCEPTS

- Dose selection by a phase I/II trial should be based on efficacy rather than the maximum tolerated dose (MTD), among dose levels with acceptable toxicities.
- A response-adaptive randomization (RAR) schema must control covariate imbalance between the treatment arms to guarantee valid comparison results between them.
- A personalized RAR is used to assign each individual to the treatment arm that fits them best based on their biomarkers.
- An efficient RAR accounts for both tumor response and survival.
- An innovative statistical design for target therapies is proposed to consider both the overall effects and effects for an unknown sensitive subset whose signature is to be identified from the ongoing trial.
- A new enrichment design selectively enrolls sensitive patients during the trial while keeping updating the selection criteria for sensitive patients as the trial proceeds.

A BRIEF INTRODUCTION OF THE DRUG DEVELOPMENT PROCESS

Public Significance of Efficient Statistical Design for Clinical Trials

Based on the analysis of National Institutes of Health (NIH), the medical cost associated with cancer was $124.6 billion in the United States in 2010, and it was expected that the expense would reach $158 billion by 2020 as the prevalence of cancer increases.[1] The skyrocketing cost of drug development is one of the top contributing factors for the high-cost healthcare system in the United States. One generally accepted estimate for preapproval cost of new drug development is about $0.8 billion.[2] Studies have shown that for every 5000 to 10,000 compounds that enter the research and development pipeline, ultimately only one can reach the market.[3] When considering all failed development programs, the cost per successful new drug will be even more expensive. Because all the costs in drug development will eventually be passed down to patients and healthcare system payers, a cost reduction in the drug development process can lower the financial burden on the US health care system.

To effectively reduce the cost and speed up the drug development process, collaborative efforts from all relevant parties are necessary. The role of biostatisticians in a clinical study team is to design a sound clinical trial that can generate high-quality data and analyze data appropriately so the intended scientific questions can be answered correctly with minimum bias and adequate quantification of uncertainty. Therefore, biostatisticians can help to reduce the cost of drug development by implementing innovative statistical methods that can help shorten the duration of a clinical trial and enable physicians to make better informed decisions through more efficient use of existing data.

The Process of Drug Development

The first step in the drug development process is "Discovery," which often begins with the identification of a suitable target. The target normally is a molecule or a protein receptor or a gene that is specifically associated with a disease condition or pathology. For this purpose, researchers are required to have thorough knowledge about the disease mechanism at the molecular, cellular, and genetic levels. Once a target is identified, it needs to be validated in living cells and

in animal models to confirm its role in disease. After the validation, researchers need to search for a molecule or "lead compound" to act on the disease target. Initially, a large number of lead compounds are identified, but most of them are too toxic for the human body. Therefore, early safety tests for drug absorption, distribution, metabolism, and excretion are used to choose a handful of the most promising candidates for further lead optimization. At the lead optimization step, the structures of lead compounds that survive the initial safety screening are altered to enhance safety and effectiveness. Next, additional preclinical laboratory and animal tests are conducted to determine whether the drug is safe for human testing. To identify a potential new drug candidate, this discovery process includes all of the early research explorations and lab testing. During this process, up to 5000 to 10,000 compounds are subject to rigorous screening, which takes approximately 3 to 6 years.[4]

After selecting the drug candidates and establishing their nonclinical safety and efficacy, researchers must file an Investigational New Drug application with the regulatory agencies (such as the Food and Drug Administration (FDA)) and obtain approval to start testing in humans. The FDA reviews the application, which includes information on the chemical structure, manufacturing, safety profile, study results from preclinical studies, and detailed clinical development plan, to make sure trial participants will not be exposed to unreasonable risks. In addition to the FDA approval, all studies must be reviewed and approved by the Institutional Review Boards at study sites.

Once appropriate approvals have been acquired from the FDA and Institutional Review Board, clinical trials can be conducted. According to the NIH, clinical trials are research studies that explore whether a medical strategy, treatment, or device is safe and effective for humans. Based on research questions under study, clinical trials can be classified as treatment trials, prevention trials, screening trials, diagnostic trials, supportive and palliative care trials, or quality-of-life trials. Most cancer clinical trials are treatment trials in which the effectiveness of new treatments or new ways of using current treatments are tested in cancer patients. Based on the phases in the clinical development plan, a clinical trial can be classified into phase 1, 2, or 3.

In phase 1 cancer trials, the candidate drug is tested in humans for the first time in a small group of patients to assess its safety, tolerability, pharmacokinetics, and pharmacodynamics. Most of the cancer drugs are cytotoxic agents, in which higher doses are associated with both greater therapeutic benefits but an increased probability of severe toxicities. Thus, the goal of a phase 1 cancer trial is to establish the maximum tolerated dose (MTD), which is the highest dose associated with an acceptable level of toxicity,[5] and to establish the recommended dose and/or schedule of a drug or drug combination for efficacy testing in subsequent phase 2 trial.[6] Phase 1 trials may not focus on a single tumor type, but rather a broad sample of patients with cancer are recruited and the sample size ranges from roughly 15 to 30 patients.

Once the safety of a new drug or drug combination has been confirmed in the phase 1 trial, a phase 2 cancer trial will be conducted to assess whether the drug has sufficient efficacy to warrant further investigation in a specific patient population.[7] The sample size of phase 2 trials is usually from 30 to 100 patients. If a new drug shows promise in phase 2 trials, a phase 3 cancer trial will be conducted to definitively demonstrate the drug's efficacy and safety. Phase 3 trials are usually large-scale, confirmatory, randomized trials in which the new drug will be compared with the current standard treatment. The primary end point for phase 3 cancer trials is usually related to survival, such as the rate of overall survival (OS) or disease-free survival. Interim tests are commonly performed during phase 3 trials.[8] The sample sizes involved in phase 3 trials may range from 100 to several thousand patients. Because of the longer duration and larger sample size, a phase 3 is the most expensive phase in the drug development. Once all three phases of the clinical trials are completed successfully, a New Drug Application will be filed to FDA requesting the approval to market the drug. Only after the efficacy and safety have been established in all three phases of the clinical trials can a new treatment be considered for marketing approval by the FDA. This whole drug development process is costly and may take more than 10 years.[2]

After a new drug has been approved for marketing, phase 4 trials may be required by regulatory authorities to evaluate the long-term safety and efficacy of the drug. Because they are conducted after the new treatments have been approved for marketing, phase 4 trials are often referred to as "Post Marketing Surveillance Trials." Phase 4 trials usually involve much larger sample sizes and a longer time period compared with phase 2 or 3 trials.

OVERVIEW OF CLINICAL TRIAL DESIGNS

In this section, we introduce statistical designs for phase 1, 2, and 3 trials. The phase 2 trials can be further classified as phase 2a and phase 2b. Phase 2a trials usually involve a single arm compared with historical data, whereas phase 2b trials are usually randomized with two or more arms.

Phase 1 Clinical Trials

For clinical trials evaluating new drugs, phase 1 focuses on the clinical pharmacology and toxicity. In this

phase, humans are administered a new drug, a new dosing schedule, or a new drug combination for the first time. According to Piantodosi,[9] the four main elements of a phase 1 trial design are (1) choosing the initial treatment dose; (2) choosing the dose increments and size of the patient cohorts; (3) defining the dose-limiting toxicity (DLT) level; and (4) setting guidelines to increase or decrease the dose given to subsequent patients. The final goal is to define the MTD in the study. Usually there are several dosage levels or schedules to be tested in an ascending order in terms of dose intensity. Because patient safety is the major concern for a phase 1 trial, in most cases, the lowest dose identified in animal studies of the drug is used as the starting dosage level. Taking a cancer clinical trial as an example, the starting dose may be set at one-tenth the lethal dose in mice or one-third the lowest toxic dose in dogs.[10] Because it is usually assumed in oncology that a more toxic treatment leads to a more efficient treatment effect, the MTD is defined as the highest dose level at which some target percentage of patients (eg, 30%) experience DLT.

Typically, there are two types of phase 1 designs: algorithm-based designs and model-based designs. Algorithm-based designs have prespecified rules for dose escalation or de-escalation. Because of their easy implementation, algorithm-based designs are by far the most frequently used. For example, the "3+3" design is the most popular algorithm-based design.[11,12] In this design, patients are enrolled in the trial in a cohort of three. Based on how many of them experience DLT, specific rules determine whether the dose level should escalate, de-escalate, or stay the same, with the addition of three more patients. Similar decision rules are also specified for action based on data from six patients. The MTD is the highest dose level with 0 or 1 DLTs observed in six patients.

Some alternative algorithm-based designs similar to the traditional "3+3" design include the "2+4," "3+1+1," and "3+3+3" designs.[12] Although these designs are easy to be implemented, they only use the data at the current dose to arrive at the decision and may enroll many patients to receive the ineffective low dose levels and expose some patients to the unsafe toxic dose levels.[13,14] Some publications also show that the performance of the "3+3" design has a low probability of selecting the true MTD[15] and it is highly variable in estimating MTD.[14]

In contrast, model-based designs use all available patient toxicity information to fit a parametric dose-toxicity model, which is a monotonically nondecreasing function. The most well-known model-based design is the continual reassessment method (CRM) proposed by O'Quigley, Pepe, and Fisher.[16] The CRM uses all the accumulated data to select the next dose level for new patients. In contrast, the "3+3" design uses only the data from the most recently enrolled cohort of 3 or 6 patients.

Additional model-based designs based on CRM include dose escalation with overdose control,[5] Bayesian model averaging CRM,[17] time-to-event CRM,[18] Bayesian logistic regression model,[19] and others. Although CRM has shown more desirable operating characteristics than the rule-based designs, such as having a higher probability to more accurately determine the true MTD, its application is still limited because of its conceptual and operational complexities.[6]

Recently, another type of adaptive dose-finding design, termed *model-assisted design*, combines key elements of the rule-based and model-based designs. Similar to rule-based designs, its dose escalation/de-escalation rules are determined before the start of the trial. It also borrows the strength from model-based designs by using a statistical model to aid decision making. Some examples include the modified toxicity probability interval (mTPI) design,[20] its variation mTPI-2,[21] and the Bayesian optimal interval design.[22]

For multiple-agent combination or biological agents, the dose-response function is not a one-dimensional monotone increasing curve. In this case, the rule of "higher dose, higher efficacy" does not apply either (biological agents), or it may not be clear which dose is higher (combination agents: Drug A 3 mg + Drug B 10 mg vs Drug A 10 mg + Drug B 3 mg), so the dose selection should not be purely based on MTD. Both efficacy and toxicity need to be considered for the dose selection. Huang et al[23] provide a parallel phase 1/2 design for dose selection based on efficacy but that is subject to toxicity constraints.

In the parallel phase 1/2 design, toxicity and efficacy of all doses are assessed simultaneously, whereas dose escalation can be done using a traditional "3+3" algorithm,[11] the CRM,[16] or other Bayesian interval designs.[6,22] Adaptive randomization based on efficacy data start after the initial dose escalation, among those safe dose levels. The dose levels with lower efficacy or intolerable toxicity are eliminated. Patients are assigned to the remaining doses with unequal probabilities, where patients have higher probabilities to be assigned to the doses with higher efficacy. Instead of considering each dose level separately, logistic regression models for toxicity and efficacy data from all dose levels can be used to obtain more stable estimation and thus make more reliable decisions for dose selection. Compared with separate phase 1 and phase 2 trials, the integrated phase 1/2 design is more efficient.

Phase 2 Clinical Trials

The MTD or recommended dose found in phase 1 is then applied in a phase 2 study to examine the treatment efficacy and refine the toxicity profile of the agent. In many phase 2 cancer trials, the antitumor activity of a new drug is usually quantified by

tumor response, and the treatment is considered to be successful for an individual patient if his or her tumor burden is reduced by at least 50%.[24] As of this writing, various techniques have been developed for monitoring tumor response to the treatment. However, the most common way is to measure the tumor shrinkage or tumor lesions on computed tomography or magnetic resonance imaging after the therapy, and the Response Evaluation Criteria in Solid Tumors (RECIST 1.1)[25] is the most widely accepted standard method to assess tumor shrinkage. Under RECIST, tumor response can be categorized as complete response (CR), partial response (PR), stable disease (SD), and progressive disease. The proportion of patients who have achieved CR or PR among the total number of evaluable patients is defined as the objective tumor response rate. The objective tumor response rate has been the most widely used primary end point for phase 2 clinical trials because a tumor response can be considered as a clear sign of treatment activity, and tumors rarely shrink by themselves. In addition, tumor response can be obtained quickly after treatment (most often within 4–6 weeks), which results in a shorter duration of clinical trials.

Single-Stage Design

The most common designs of phase 2 oncology trials are single-arm designs. Fleming[26] proposed a single-stage procedure to test a hypothesis against a clinically meaningful efficacy target. Fleming used a normal approximation to estimate the sample size. A'Hern[27] created a sample size table for Fleming's single-stage procedure based on that exact method.

Two-Stage Design

In a single-arm design, all patients are enrolled before the tumor response rate is estimated and a decision is made. If the final response rate turns out to be very low, then all patients have been exposed to the ineffective regimen. For this reason, a two-stage design is proposed to enroll patients in two stages. The data are examined after the first stage and the trial can be terminated if the drug is ineffective. Gehan[28] proposed a two-stage design when the response rate of standard of care is very low. In that case, a new drug with the small response rate is clinically significant and warrants further study. In the first stage, n_1 patients are enrolled and r_1 responses are observed. If $r_1 = 0$, the trial is stopped. If one or more patients have tumor response, they continue to the second stage. In the second stage, n_2 additional patients are accrued and r_2 responses are observed. In Gehan's design, the first-stage sample size n_1 is chosen to give a small probability of the trial ending early (eg, 5%) at a fixed target response rate pa that is considered to be the minimum response rate of interest. The first-stage sample size n_1 is found by solving $\Pr(\text{Stop Early} \mid pa) = \Pr(r_1 = 0) = (1 - p_a)^{n_1} = 0.05$. The second-stage sample size n_2 is chosen to give sufficient precision for estimating the response rate p after all patients are observed.

Simon[7] proposed two types of two-stage designs (Optimal design and Minimax design). The design procedures produce optimal sample sizes for both stages while controlling the type I and II error rates under the null and alternative hypotheses. Using the same notation for Fleming's and Gehan's designs, the Simon Two-Stage Design is as follows. First enroll n_1 patients in Stage 1, reject the alternative hypothesis and terminate the trial for futility if the number of responses $r_1 \leq s_1$, where s_1 is a parameter to be specified. Otherwise, continue to n_2 patients in Stage 2. At the end of Stage 2, reject null hypothesis if the sum of the responses in the two stages $r_1 + r_2 \geq s_2$; otherwise, reject the alternative hypothesis. Simon's two-stage designs are to choose appropriate values for n_1, s_1, n_2, and s_2 to meet specific type I error and power constraints. They are also chosen to meet specific optimality criteria such as minimize the expected total sample size by Simon's Optimal design or minimize the maximum sample size by Simon's Minimax design.

Multistage Design

Fleming[26] also proposed a multistage design to allow an early termination of the trial when intermediate results are extreme, either in favor of the efficacy or the inefficacy of the treatment. Fleming's multistage design can be reduced to a two-stage design when K=2. The difference between a Simon Two-Stage Design and a Fleming Two-Stage Design is that the Simon design does not permit early acceptance of a drug based on a positive Stage I result. Usually, when the drug shows promising activity with a limited number of patients, it is of clinical interest to keep the study ongoing to benefit patients and at the same time to gather more safety information. For this reason, the Simon design is much more commonly used than the Fleming design in oncology phase 2 trials.

Randomized Clinical Trials

In a single-arm design, the tumor response rate of a new drug is typically compared against a fixed rate based on historical data. The variability of historical data is not taken into consideration. Furthermore, the entry criteria of a single-arm trial may not be similar to those of the historical trials on which the fixed response rate is based. The effects from single-arm designs are greatly influenced by entry criteria, supportive care, the definition of response, dose

modification procedures, and compliance patterns or some unknown latent variables.[29]

It is widely acknowledged that randomization is a way to eliminate systematic patients' selection bias and provide a basis for unbiased comparisons of treatment effects.[30] Recently, the use of randomization in phase 2 trials has dramatically increased, especially when the primary end point is progression-free survival (PFS).[31,32] Randomized designs are considered when the aim of a phase 2 trial is to evaluate two or more new agents or new regimens concurrently, or if adequate historical control data are not available.

The randomized selection design was first proposed by Simon.[33] In such a design, patients are randomly assigned to one or more competing regimens or treatments with the same entry criteria. Generally, no control arm is included in the design. The trials are conducted as several independent phase 2 trials simultaneously. Each arm is designed to be evaluated separately, and often there is no adequate power for comparison between arms.[34] At the end of the trial, the results from all arms are considered jointly,[35] and the arm with the highest treatment effect is selected for phase 3. The advantage of this type of design is less selection bias owing to the uniform enrollment and evaluation criteria in each arm. However, when there are multiple arms with similar treatment effects, the probability of selecting the best arm is diminished.

Usually a single-arm phase 2 trial for initially assessing the efficacy of a new treatment is called phase 2a, and the subsequent randomized, multiarm phase 2 trial is called phase 2b. In the current postgenomic and high-throughput era, we have seen a dramatic increase in the number of treatment regimens or agents to be evaluated. Hence, phase 2b serves as a prescreening stage before the large phase 3 trial. The large number of treatment options increases the importance of phase 2b as an intermediate step for the goal of identifying the most efficient treatment options before selecting the candidates to be evaluated in a time-consuming and costly phase 3 study.

Once promising results are found in phase 2 (with or without a phase 2b), a full-scale phase 3 trial is then begun. The phase 3 trials compare the new treatment with the standard treatment in a rigorous manner. The most popular phase 3 trial design is to randomize the patients into different treatment groups. The goal is then to define the best treatment, which has an implication of changing the current practice for that patient population. Randomization, in either a phase 2b or phase 3 setting, has been established as the hallmark for obtaining scientifically valid treatment comparisons in clinical trials. The use of randomization eliminates systematic treatment assignment bias in the trial. It increases the likelihood that the known, and especially the unknown, risk factors are balanced across the treatment groups under study and that the responses observed among the patients result from the treatment and not from confounding factors.

Researchers use clinical trials to assess the effects of specific treatments or other interventions in a target population based on their resulting outcomes. Randomized controlled trials provide the most decisive means for examining clinical interventions and for comparing the characteristics of the competing treatment options, including the associated cost, short-term and long-term effectiveness, and side effects—thus, the overall value. This information is vital to guide health care decisions regarding quality and cost of treatment.

Generally, there are two types of randomization: fixed allocation randomization and adaptive randomization. Because adaptive randomization is relatively complicated, we discuss it in the next section. Fixed randomization means the assignment probability remains fixed throughout the whole process of enrollment of participants to the study. In contrast, adaptive randomization refers to the assignment probability changing during the enrollment period as a function of the treatment assignment, baseline information, and outcomes of previously enrolled subjects.

The most commonly used fixed allocation randomization designs include simple randomization, blocked randomization, and stratified randomization. Simple randomization is similar to conducting a coin flip to determine each patient's treatment assignment in a trial. Conducting a trial with this type of randomization design is straightforward, and therefore easy, but it does not guarantee that the number of patients assigned to each treatment group are equal. For example, with a total of 100 patients, the trial may end up with 47 patients in one treatment arm and 53 patients in the other. Even if the numbers of patients are balanced at the end of trial (eg, 50 per arm), the first 20 patients may be imbalanced as 15 in one arm and five in the other. Especially if patient characteristics change over time (eg, early patients have worse prognosis than later patients), then the early imbalances may introduce bias. Block randomization is often used to avoid this problem. For example, a block randomization with a block size of four may assign the first four patients to ABAB, and the second block of four patients to BBAA, where A and B are the two treatments. Equal sample size is guaranteed within each block, whereas the sequence within each block is a random draw from all possible sequences of equal sizes between A and B. When there are prognostic factors that may affect the treatment response, stratified randomization is often used. For example, if age (≥65 vs <65 years) and a genetic mutation status (yes vs no) are prognostic factors, then four strata are defined by these factors, and the patients are randomly assigned within each stratum.

INNOVATIONS FOR CLINICAL TRIAL DESIGNS

In this section, we first describe different types of adaptive designs, and then introduce our recent publications on innovative clinical trial designs.

An Overview of Adaptive Designs for Randomized Clinical Trials

Traditional randomized clinical trials use a fixed ratio to assign patients to each treatment arm and analyze the treatment effect at the end of the study. In recent years, adaptive designs have become increasingly popular because of their flexibility as an alternative to traditional randomized clinical trials. Adaptive designs allow modifications of the ongoing clinical trials according to the information collected during the trial without undermining its integrity and validity. The use of adaptive design is attractive to investigators, sponsors, and even patients because it may reduce the trial duration, limit the number of patients exposed to the ineffective/inferior treatments, modify the design based on updated information, and increase the probability of success in later-phase drug development. Here we focus on some common types of adaptive designs including (1) response-adaptive randomization (RAR), (2) adaptive group sequential, (3) biomarker-adaptive designs, and (3) seamless phase 2/3 designs. Details of each design are described below.

Response-Adaptive Randomization Design

Equal randomization is commonly used in clinical trial settings to generate reliable data for making inferences about the difference when two treatments are compared. However, when the treatment difference is large and the end point of the study is survival time, it does not seem appropriate to assign a large number of study patients to the inferior treatment arm.[36] A RAR is a data-dependent treatment allocation rule that the probability of assigning the next patient to treatment arms depends on the outcomes of the previously randomly assigned and treated patients.[37–40]

In recent years, increased interest in the RAR design has resulted in more frequent applications of RAR designs in oncology phase 2 studies.[41] This type of randomization is based on the relative success of patients treated, and it tends to put more study patients on the better treatment, which is more likely to be acceptable by patients and their physicians than equal assignment. Examples of RAR designs include play-the-winner,[37,38] urn model,[39] drop-the-loser design,[42] doubly adaptive biased coin design,[43] and Bayesian RAR design.[40,44]

In the play-the-winner design, a success on one treatment arm results in the next patient's assignment to the same treatment, with changes to the alternative treatment only in the event of a failure. The urn model design changes the allocation probabilities during the course of the trial by adding balls of an appropriate color to the urn based on previous patients' outcomes. In the drop-the-loser design, an inferior treatment arm (loser) can be completely dropped from further randomization during the trial to improve the trial efficiency. It may also allow adding additional arms during the trial. For two-arm trials with binary response measurements, Wei and Durham[45] proposed a generalized Friedman urn model for a RAR procedure.

Another approach named doubly adaptive biased coin design was first proposed by Eisele and Woodroofea[46] and further modified by Hu and Zhang[47]. This design depends on the current proportion of patients from each treatment arm and the current estimate of the desired allocation proportion. The advantages of this design include flexibilities to target any given allocation and allowance of multiple types of responses while attaining the lower bound of variance.

A doubly adaptive biased coin design consists of three steps: (1) assign a small proportion of patients using equal randomization as a burn-in period; (2) calculate the optimal allocation probability based on current patient responses; and (3) apply the allocation function to calculate the assignment probability for the next new patient, which targets the optimal allocation probability in step 2.

Several methods of calculating the optimal allocation probability have been proposed. The Neyman allocation[48] minimized the variance of the testing statistic and is a popular choice. The method proposed by Rosenberger et al[49] minimizes the number of failures while keeping the conditional variance of the Wald test statistic at a fixed level. Generalization of this approach has been discussed by Hu et al.[50]

Although adaptive randomization was initiated from the frequentist point of view, it was quickly utilized within the Bayesian framework. Bayesian methods incorporate the prior and historical information with the currently available data to make future assignment decisions. Based on likelihoods, Bayesian inference provides the investigators with greater flexibility and naturally updates the posterior assignment distribution based on the most updated information. For the Bayesian RAR, the allocation probabilities are based on the posterior probabilities of the treatment arm being the best. In such designs, initially, patients are equally randomly assigned to the treatment arms. As efficacy data accrue, patients' assignments are unbalanced in favor of the arm that has the higher treatment effect (higher objective tumor response rate or longer PFS

time). It has the ability to use accumulating data in real time to alter the course of the trial, therefore enabling dynamic allocation of patients to experimental arms and early dropping of ineffective arms.

Berry and Eick[51] provided a thorough comparison of the Bayesian adaptive assignment scheme with balanced randomization. Zhou et al[52] introduced an adaptive randomization design in a trial, namely, biomarker-integrated approaches of targeted therapy of lung cancer elimination (BATTLE), using the hierarchical Bayes model. The method used historical information to define the prior information and "borrowed strength" across patients with different covariate profiles.

Also under the Bayesian framework, Ning and Huang[53] proposed a new RAR schema that controls covariate imbalance between the treatment arms to guarantee valid comparisons between them. A measure of covariate imbalance is provided. As opposed to equal randomization, this design is more likely to assign new patients to the treatment arms that would minimize this covariate imbalance measure. Yuan, Huang, and Liu[54] developed a different method to balance the covariate, either continuous or categorical, by using the Kolmogorov-Smirnov statistic to measure the imbalance across different arms. All these efforts have aimed to incorporate the complex patient heterogeneity and assign future patients to the more promising treatment arm. These new designs achieve scientifically valid results by ensuring patients in different treatment arms are comparable, and also help assign more patients to the better treatment arms.

Adaptive Group Sequential Design

Classical group sequential designs repetitively apply significance testing at prespecified stages. At each stage, they offer a possibility of stopping early without the need of setting a fixed number of sample size. At each interim stage, a decision may be made to support or reject the null hypothesis based on a stopping criterion. A classical group sequential design is required to prespecify the total number and the timing of the analyses. The trial will be stopped until the maximum information is obtained or when a stopping boundary is crossed.

Examples of the stopping boundaries include those by O'Brien and Fleming,[55] Wang and Tsiatis,[56] and Lan and DeMets.[57] O'Brien and Fleming used increasing boundaries. Wang and Tsiatis' boundaries depended on a shape parameter and the prespecified information fraction. Lan and DeMets proposed a flexible alpha-spending function without requiring a prespecified number of interim analyses and the timing of those stops. The alpha-spending function can also approximate the O'Brien and Fleming group sequential boundaries.

Adaptive group sequential design allows adaptations or modifications at interim analyses.[58] Those adaptations may include but are not limited to sample size re-estimation, adding/dropping treatment arms, randomization scheme modification, etc. Although the classical group sequential design is well understood and the Type I error rates can be well controlled under spending functions, adding changes at interim analysis may inflate the Type I error rate. Statistical procedures are still needed to control the study-wise Type I error rate.[59]

Biomarker-Adaptive Design

A biomarker is a biological molecule that is objectively measured and evaluated as an indicator of normal biological, pathogenic processes, or pharmacologic responses to a treatment.[60] The emergence of biomarker development can guide treatment selection for patients according to their biological characteristics or genomic profiles. Based on the type of usage, biomarkers can be classified into prognostic or predictive biomarkers. Prognostic biomarkers assess patient responses independent of treatment, whereas predictive biomarkers provide information regarding the most likely response to a given treatment. Prognostic biomarkers can separate potential patients into good or poor prognosis at diagnosis, whereas predictive biomarkers can separate patients into sensitive or insensitive for a given treatment.[61] Based on the characteristic of predictive biomarkers, they can be used to guide treatment selection to allow a better fit between patients and treatment options.

Many molecular cancer treatments only benefit a subset of patients. A biomarker-adaptive design identifies a subgroup of patients who are most likely to respond to the investigated treatment based on their biomarker profiles. It can allow more patients to benefit from the trial compared with the traditional all-comers design, which may increase the trial efficiency and limit insensitive patients to experience the toxicity of the investigated treatment.

Xu et al proposed a subgroup-based adaptive design for multiarm biomarker trials.[62] This design simultaneously searches for prognostic subgroups using a random partition model and assigns patients to the best subgroup-specific treatment based on posterior predictive probabilities.

If a biomarker is known at patient screening, this trial should only enroll sensitive patients. If the biomarker information is unknown, the adaptive signature design[63] may be used. The adaptive signature design tests the overall treatment effect at a significance level of δ (eg, $\delta = 0.04$). If the overall treatment effect is statistically significant, then it can be concluded that the experimental treatment may benefit all treated patients. Otherwise, the treatment effect is tested in a sensitive patient

subset at a significance level of θ (eg, $\theta = 0.01$). This controls the overall type I error rate at $\alpha = \delta + \theta = 0.05$.

Gu et al proposed a Bayesian two-stage biomarker-based adaptive randomization design (BATTLE-2).[64] This design has three main goals: (1) to test the treatment effect, (2) to identify prognostic and predictive biomarkers for targeted agents, and (3) to provide a better treatment for patients enrolled in the trial. The Bayesian adaptive randomization approach applies to both the biomarker development (stage I) and validation stages (stage II). In stage I, adaptive randomization is applied based on a known biomarker. At the end of the first stage, a Go or No-Go decision is made from testing the overall treatment effect. If a Go decision is made at the end of stage I, a two-step Bayesian Lasso strategy is used to select additional prognostic or predictive biomarkers based on the accumulated data: group lasso is used to select important biomarkers, and adaptive lasso is used to refine the selection and estimation. Patients enrolled in the second stage receive treatment based on the refined adaptive randomization scheme.

Seamless Phase 2/3 Design

During traditional drug development, phase 2 trials select a promising treatment/dose, and phase 3 trials further confirm the treatment efficacy. The seamless phase 2/3 design (also called pick-a-winner design, drop-the-loser design, and adaptive seamless design) is a multistage design that combines phases 2 and 3 into a single trial. It consists of two stages: a selection stage (phase 2b) and a confirmation stage (phase 3).[65] For the selection stage, the objective is to select the best dose/treatment by employing a parallel design with multiple treatment arms and a control arm. The inclusion of a control arm at the selection stage allows the data to be easily combined with those from the confirmation stage for final analysis. The confirmation stage evaluates the efficacy of the selected treatments versus the control treatment.

The general framework for a seamless phase 2/3 design is as follows: patients entering the trial are randomly assigned between the experimental arms and the control arm. At the end of the first stage, the selected dose/treatment moves to the confirmation stage. Newly enrolled patients are randomly assigned to receive the selected dose/treatment or the control treatment. If multiple arms are selected at the end of the first stage, or only the inferior treatments are dropped, each selected arm is compared with the control arm at the confirmation stage.

Thall, Simon, and Ellenberg proposed a two-stage design with binary end points to avoid continuous monitoring.[66] Schaid, Wieand, and Therneau extended their design to the time-to-event end point and allowed early stopping for efficacy after the selection stage.[67] Stallard and Todd generalized their designs to allow more than two stages using the error spending function and it is suitable for all types of end points by using an efficient score for test statistics.[68] Huang, Liu, and Hsiao presented a seamless design that allows prespecifying the probabilities of rejecting an arm at each stage.[69] Bischoff and Miller proposed a two-stage adaptive design based on the means of the normal distribution for treatment selection.[70] Their design requires a minimal number of patients to reach the desired power while controlling the type I error rate and limiting the probability of selecting an inferior treatment after the first stage. Todd and Stallard presented a group sequential design that allows a change of end point for the confirmation stage.[71] Chow and Tu derived formulas for sample size calculation, assuming the same study objectives at different stages.[72] Posch, Maurer, and Bretz presented two methods to control the type I error rate when applying sample size reassessment and/or treatment selection: one uses simulation to adjust the critical value, and the other uses an adaptive Bonferroni-Holm procedure.[73] Stallard described a method to control the type I error rate by adjusting the usual group sequential boundaries when using a short-term end point for the treatment selection at the first interim analysis for a confirmatory seamless phase 2/3 trial.[74]

Instead of running multiple experimental arms versus a control arm in phase 2 and 3 designs, the seamless phase 2/3 design requires a smaller sample size by using data from both stages and can expedite the drug development process.[67,77] Because the results of a seamless 2/3 trial are sensitive to the timing of the analysis for the selection stage, simulations should be done to find an optimal time for the interim analysis.[67]

Recently Proposed Innovative Clinical Trial Designs

In this subsection, we introduce our own work on clinical trial designs with innovations specifically motivated by the need for oncology clinical trials. We describe a new design that can help assign the best individualized treatments to individual participants in the trial.[76] We also provide an innovative design that accounts for both tumor response and survival.[77] Further, we consider biomarker signatures for patients with cancer, selectively enroll patients through an enrichment process, and adaptively assign patients to the treatment that would best fit them based on their biomarker signatures.[78]

A Response-Adaptive Clinical Trial Design Accounting for Patient Heterogeneity

One important ethical question is: In an ongoing trial, what is the best way to assign patients to treatment arms so they are more likely to benefit from the

treatment? To answer this question, we need a flexible design that continuously draws inferences and an ethical design that guides each patient toward the best available regimen during the trial. To meet these needs, Qiao et al[76] provided an adaptive randomization design accounting for patients' characteristics (covariates) under a Bayesian framework.

To present the real situation in which the treatment effect varies in different subgroups, the terms of predictive and prognostic factors in oncology research are introduced here. Italiano[79] provided the following definitions: a prognostic factor is a clinical or biologic characteristic that is objectively measurable and that provides information on the likely outcome of the cancer disease in an untreated individual. Patients with good performance status are likely to do better than those with poor performance status, and performance status would be considered as "prognostic." In contrast, a predictive factor is a clinical or biologic characteristic that provides information on the likely benefit from treatment (either in terms of tumor shrinkage or survival). Such predictive factors can be used to identify subpopulations of patients who are most likely to benefit from a given therapy. A good example of predictive biomarkers used in oncology research is estrogen and progesterone receptors to predict sensitivity to endocrine therapy in patients with breast cancer. Statistically, a prognostic factor can be considered as the main effect and its effect can be concluded in a single-arm trial because the effect does not vary with different treatments. On the contrary, the predictive factor can be considered as the "interaction" term and can be evaluated in a multiarm trial because the effect differs across subgroups.

In our current research environment, we are interested in finding sensitive subgroups of patients for whom the treatments are more effective. Therefore, we focus on studying the predictive factor, that is, the interaction terms of treatment and other covariates. The treatment assignment probability is based on a stable algorithm that accounts for the confidence level of treatment comparisons based on all the observed data.[76] By using RAR, this design results in a greater total number of responders. It also tries to detect the treatment effect difference in subgroups and assign patients to the most beneficial treatment according to their biomarkers. This results in a higher proportion of individuals receiving their best individualized treatment compared with equal randomization. This adaptive design is a step toward precision medicine. It aims to benefit each patient enrolled in a prospective clinical trial.

An Efficient Design Accounting for Both Tumor Response and Survival Outcomes

The survival outcomes in clinical trials take a long time to collect, but early tumor response data are available in a short time after treatment initiation. Huang et al[77] provided an efficient design accounting for both tumor response and survival outcomes. We illustrate the advantages of this new statistical design through an example of consideration for patients with advanced non–small-cell lung cancer (NSCLC) as follows.

NSCLC accounts for approximately 75% to 80% of all lung cancers. NSCLC originates from the "non–small cell" within the lung. Advanced NSCLC is a late stage of the disease characterized by the spread of cancer from the lung to lymph nodes or distant sites in the body. Although OS is the gold standard for clinical benefits of cancer treatments, periodical measurements of the size and locations of tumors are often used as early indicators to determine whether the cancer is responding to treatment. Generally speaking, partial responses (often defined as at least a 50% reduction in tumor) and CRs (often defined as nondetectable cancer) are considered to be successful responses to cancer treatments and are often associated with better long-term survival. However, more patients have disease stabilized through treatments rather than PR or CR. According to an article published in the *Journal of Clinical Oncology*,[80] the addition of disease stabilization to CR and PR at 8 weeks (defined as 8-week disease control rate) can predict long-term outcomes more accurately than the standard measurement of responses for patients with advanced NSCLC. A more recent publication shows that the prediction of survival benefits by 8-week disease control rate is consistent across different ethnicities (Western vs Chinese patients).[81]

Despite developments in the designs of phase 2 trials, there are still many limitations in current phase 2 oncology trial designs. Some of these limitations are caused by the inherent trade-off of the decision-making process in exploratory studies. For example, a short-term outcome such as tumor response rate, which can be obtained in a relatively short time period after treatment (eg, 2–3 months), is often used in phase 2 oncology trials to reduce drug development time and expedite the screening process for drug candidates. However, prolonged survival is still the ultimate goal of cancer treatments, and OS, PFS, or other similar survival outcomes are still the standard end points of phase 3 trials for FDA approval. Efficacy seen in tumor response outcomes may not be readily translated into efficacy in the survival end point. On the other hand, if OS time is used as the primary end point, the final data may require months or years to complete, and the design and the conduct of the trials may be more complex and difficult, especially for RAR designs.[77] Therefore, PFS has been used as an alternative primary end point in many cancer phase 2 trials because it is more relevant to OS compared with tumor response and requires less follow-up time compared with OS.

Although short-term response status can be obtained quickly and can potentially be used to speed up the adaptation of randomization, tumor response status is not incorporated in the decision making in most of the phase 2 RAR oncology trials with PFS as the primary end points.

As mentioned above, the primary goal of phase 2 trials is to screen for promising drug candidates to be studied in phase 3 trials. Because of the limitations in traditional phase 2 oncology trials, the attrition rate in cancer drug development remains high. Only 5% of agents that have anticancer activity in preclinical development demonstrated sufficient efficacy in phase 3 testing.[82] For drug candidates already evaluated in phase 1 trials, data from 1975 to 1994 show that only 10% were approved for clinical use.[83] As of this writing, more than 400 new compounds are available for testing.[84] At the same time, the percentage of patients enrolled in clinical trials remains at a rate of 3% to 5% among the potentially eligible patient populations.[85] These statistics indicate that the phase 2 trials are historically not very successful in screening out "weak" drug candidates. Many "weak" drug candidates are competing with "strong" drug candidates for patients in phase 3 trials, and patients being treated with "weak" drug candidates lose the opportunities to receive clinical benefits. Therefore, current designs for phase 2 oncology trials are far from optimal. Innovative methods should be used to enable more efficient use of scarce resources and achieve more effective elimination of inefficacious agents.

In the traditional phase 2 oncology clinical trials with survival as the primary end point, the interim analysis is usually based on the observed survival information. Patients without events are treated as censored observations. In this subsection, a joint modeling approach between short-term tumor response and long-term survival time is introduced to enable early interim decision making during a clinical trial. In particular, the joint modeling is used to impute censored event time based on baseline covariates and expected tumor response, and the interim decision is made based on results from multiple imputed complete data sets. To be able to impute the censored event time, a Bayesian method with explicit modeling of baseline hazard rate is used. The goal of joint modeling is to improve interim analysis by taking advantage of the correlation between short-term and long-term outcomes. This can enable early decision making while leveraging additional information about long-term outcomes provided by early short-term outcomes.[77]

In addition to NSCLC, the joint modeling approach is potentially applicable to other oncology indications, where early tumor response to treatment in patients with advanced disease could be indicative of longer survival time. The joint modeling approach is also applicable to increase the clinical development process of some rare diseases when the patient population is small or the enrollment rate is slow, as long as early tumor response information is available.

To do a joint modeling, first, a logistic regression model with baseline covariates was assumed for the short-term categorical tumor response with two levels of response status. The long-term PFS outcome was assumed to follow an exponential distribution conditional on the tumor response status. In the adaptation stage, before each new patient was enrolled, the posterior probabilities of different tumor response status conditional on treatment and baseline covariates were calculated first, and then the average posterior mean of PFS was calculated for each treatment arm using posterior tumor response probabilities as the weighting factors. The randomization probability was based on the conditional posterior PFS probability that one arm is superior to the other. A multinomial probit model was used to model the three categories of tumor response. Two binary and one continuous covariate were added to the joint modeling. As a priori, it was assumed that the two binary covariates were interacted with treatment and had effects on tumor response. The continuous covariate had an effect on PFS. The proportional hazards model was assumed for PFS and the randomization probability was based on the posterior probability of the hazard ratio comparing the two treatments.

Two major extensions were made to expand the original joint modeling strategy to more complicated settings: (1) one additional baseline continuous covariate was included in the joint model; and (2) tumor response statuses were expanded to multiple categories (3 categories): disease progression, SD, and response (PR or CR). It was assumed that the baseline continuous covariate was a prognostic biomarker for PFS and was included in the model for PFS. In addition, two baseline binary biomarkers were assumed to be predictive biomarkers for tumor responses, where one biomarker was predictive of a worse treatment effect in the experimental treatment and the other biomarker was predictive of a better treatment effect in the experimental treatment. The choice of biomarkers was to demonstrate that the joint modeling approach is capable of allocating patients more effectively to the better treatment. In principle, the joint modeling approach can accommodate any type of covariate in either the model for tumor response or the model for PFS.

A Signature Enrichment Design with Bayesian Adaptive Randomization

The development in the field of genomics and a better understanding of disease-causing mechanisms have

resulted in a shift toward molecularly targeted treatments. In cancer research, because most human tumors are heterogeneous with regard to molecular pathogenesis, genomic signatures, and phenotypic properties, a target agent is likely to benefit only a subset of patients. For example, trastuzumab works well in a subset of patients with breast cancer whose tumors have high expression levels of HER-2. In this case, reliable assays help to target patients whose tumors will be sensitive to the treatment. However, in most cases, we often do not know an assay or genomic signature that can identify the patients who have a favorable response to a given treatment. Consequently, the conduct of a traditional equally randomized clinical trial with broad eligibility criteria often fails to identify the effective agents and the sensitive patient population. Therefore, for clinical trial practitioners, the following questions arise: Does the treatment work for all patients with the specific diagnosis or for only a subset of patients with certain biomarker profiles? How can these biomarkers be identified in the trial? The assessment of drug efficacy using population statistics at the final look has shown its obvious limitations. Promising new molecular therapies may be discarded because of the absence of statistical criteria to efficiently detect them.

When the group of patients who are likely to benefit from the test treatment is known, the clinical trial should focus on that sensitive subpopulation. The use of biomarkers in adaptive clinical trials can guide the assignment of individually optimal treatments to patients. To address this objective, we proposed a cross-validated signature enrichment design combined with Bayesian RAR.[78] We evaluated the performance of this design using four criteria based on the benefits and losses for individuals inside and outside of the clinical trial. The proposed design allows more patients to receive optimal personalized treatments, thus yielding a higher response rate. This design can identify therapies that are globally beneficial as well as treatments that are effective only in a sensitive subset.

Freidlin and Simon[63] proposed to identify the sensitive patients in the middle of the trial and to test the treatment effect among the subset of sensitive patients selected among the remaining patients. Their approach provides a second chance to assess a treatment effect among the sensitive patients. As a result, it may increase the chance of detecting the treatment effect and enrich our understanding of the treatment-sensitive subpopulation.

The above signature-identification procedure can be implemented in the Bayesian RAR design described above. An adaptive signature component is implemented to identify treatment-sensitive patients and then test the treatment effect among them.[78] To distinguish the sensitive patients from the insensitive patients, we can use different statistical methods, such as the predicted odds ratio for treatment effect, among others. When there is an enormous number of covariates, we need to use variable selection to identify the treatment-sensitive subpopulation or use the covariate adaptive randomization. We conduct an initial exploration for variable selection and implement the machine learning voting methods used by Freidlin and Simon.[63] We can also use the least absolute shrinkage and selection operator method and the smoothly clipped absolute deviation method to identify the most effective variable selection method.[86,87]

The rapid advancement of cancer biomarker development allows for a better fit between patients and treatment options.[88,89] If a treatment targets a particular biomarker, such information can be used to categorize patients into either "sensitive" or "insensitive" patient subgroups to further assess the patients' responses. When the group of "sensitive" patients who are likely to benefit from the experimental treatment is known, the clinical trial should focus on that sensitive subpopulation. Some predictive cancer biomarkers that have been used to guide patient screening include HER-2 for breast cancer,[90,91] BRAF for colorectal cancer and melanoma,[92] estimated glomerular filtration rate for non–small-cell lung cancer and colorectal cancer.[87,93] Furthermore, in 2017, the FDA approved pembrolizumab for any solid tumor with the microsatellite instability-high or mismatch repair–deficient biomarker, which marked the agency's first approval based on biomarkers rather than tumor location.[94]

To use patients' biomarker information for treatment selection, during patient enrollment we apply an enrichment strategy that oversamples the sensitive patient cohort and undersamples the insensitive patients.[78] We also apply Bayesian RAR, adaptively adjusting future allocation probabilities based on the accumulated data. As a result, our design has the advantages of Bayesian adaptive randomization as well as an enrichment strategy, yielding a higher overall response rate on the trial. At the end of the trial, we test the treatment effects in the overall patient group and in the sensitive patient subgroup and control the sum of the type I error rates from these two tests.

The emergence of translating biomarker information into clinical use calls for more efficient and accelerated drug development. A master protocol is an overarching protocol that concurrently operates multiple substudies to simultaneously evaluate one or more interventions in one or more disease types, where each substudy may be conducted based on tumor type or biomarker.[95–97] Based on the characteristics of the study, master protocols are classified into basket, umbrella, and platform trials. The basket trial evaluates one treatment for multiple diseases with a common biomarker; the umbrella trial evaluates

multiple treatments, with each substudy targeting one biomarker for one disease type. The platform trials perpetually assess several treatments for one disease and permit flexible addition and/or exclusion of new treatments during the trial. If basket and umbrella trials allow the addition of new therapies and exclusion of inferior treatments during the trial, they can also be considered as platform trials.[97]

In contrast to the traditional two-arm trial, an umbrella trial is a master protocol that studies multiple drugs within a single indication, which can result in more accurate and efficient drug development. The above Signature Enrichment Design with Bayesian Adaptive Randomization (SEDAR) can be extended to a SEDAR-U design that is suitable for umbrella trials. The SEDAR-U design incorporates multiple arms and early termination rules and allows more enrolled patients to benefit from the promising treatment and achieve favorable operating characteristics.

CONCLUSION

In general, a good clinical trial design should be flexible, adaptive to the data accumulated during the trial. Compared with trials in many therapeutic areas, these features are particularly important for oncology trials. First, most cancer trials are relatively small. When many candidate drugs (trials) competing for eligible patients (recourses in this sense), a trial with small sample size is more feasible. If a trial requires too many patients, it may take a long time to recruit the requisite number of patients and thus the drug under testing may become obsolete owing to the fast advances in medicine. To help save sample sizes, a Bayesian clinical trial design could be used by considering historical information as prior statistical parameters. Second, a large proportion of cancer patients seek treatments through participating in clinical trials. This proportion might be the largest when compared with patients with other diseases. Based on this consideration, it is crucial to maximize the trial participants' benefit from the trial. That is to say, the purposes of an oncology trial include not only scientific research, but also treating patients. This is true for all trials, but because of the large number of patients with cancer participating in clinical trials, this consideration becomes especially important for oncology trial designs. This is why RAR, which assigns more patients to the better treatment arms than equal randomization would, is especially appealing for oncology trials. Because of the complications and regulation considerations, RAR has not been commonly used in phase 3 trials yet. However, for early-phase trials, which have more flexibility, RAR should have broad application.

MD ANDERSON PRACTICE TIPS

- For phase 1/2 trials, dose selection should be based on efficacy among those dose levels with acceptable toxicities. Statistical designs for these trials should reflect this consideration.
- For randomized oncology trials with relatively small sample sizes, we may still consider RAR but need to control covariate imbalance between the treatment arms to guarantee valid comparison results between them. This control can be implemented through continuously monitoring covariate imbalance during the trial and adjusting the randomization ratio for newly enrolled patients to minimize it.
- Each type of cancer is heterogeneous. Each patient with cancer has his/her unique genetic profile. We use personalized RAR aiming to assign each individual to the treatment arm that fits him/her best based on his/her biomarkers.
- Phase 2 trials usually use short-term response as the primary end point, whereas phase 3 trials are usually required to use survival (disease-free survival, PFS, or OS) as the primary end point. To better select successful candidates for phase 3 trials, we use an efficient RAR in phase 2 trials to account for both tumor response and survival.
- Targeted therapies may have "off-target" effects and thus not work as anticipated. We use statistical designs that consider both the overall effects and effects for an unknown sensitive subset whose signature is to be identified from an ongoing trial.
- Patients may be sensitive or insensitive to a targeted therapy. It lowers a trial's chance to succeed if a substantial proportion of enrolled patients are insensitive to the investigational therapy. This also hurts those insensitive patients because they may suffer from the toxicities but do not receive the benefits, and they lose time and opportunities to participate in other trials that may better benefit them. We use enrichment designs to selectively enroll sensitive patients while constantly using the data accumulated during the trial to find out which patients are sensitive.

REFERENCES

1. National Institutes of Health. Cancer costs projected to reach at least $158 billion in 2020. January 12, 2011. Accessed April 17, 2021. https://www.nih.gov/news-events/news-releases/cancer-costs-projected-reach-least-158-billion-2020.
2. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. *J Health Econ.* 2003;22(2):151-185.
3. Pharmaceutical Research and Manufactures of America. Pharmaceutical industry, 2011 profile. Accessed May 17, 2021. http://www.phrma-jp.org/wordpress/wp-content/uploads/old/library/industryprofile/PhRMA%20Profile%202011%20FINAL.pdf .
4. DiMasi JA. New drug development in the united states from 1963 to 1999. *Clin Pharmacol Ther.* 2001;69(5):286-296.
5. Babb J, Rogatko A, Zacks S. Cancer phase I clinical trials: efficient dose escalation with overdose control. *Stat Med.* 1998;17(10):1103-1120.
6. Le Tourneau C, Lee JJ, Siu LL. Dose escalation methods in phase I cancer clinical trials. *J Natl Cancer Inst.* 2009;101(10):708-720.
7. Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials.* 1989;10(1):1-10.
8. Jennison C, Turnbull BW. *Group Sequential Methods with Applications. to Clinical Trials*. Chapman and Hall; 2000.
9. Piantodosi S. *Clinical Trials: A Methodologic Perspective*. 3rd ed. Willey; 2017.
10. Chevret S, editor. *Statistical Methods for Dose-finding Experiments of Statistics in Practice*. John Wiley and Sons; 2006.
11. Storer BE. Design and analysis of phase I clinical trials. *Biometrics.* 1989;45(3):925-.937.
12. Storer BE. An evaluation of phase I clinical trial designs in the continuous dose-response setting. *Stat Med.* 2001;20(16):2399-2408.
13. Korn EL, Midthune D, Chen TT, Rubinstein LV, Christian MC, Simon RM. A comparison of two phase I trial designs. *Stat Med.* 1994:13:1799-1806.
14. Goodman SN, Zahurak ML, and Piantadosi S. Some practical improvements in the continual reassessment method for phase I studies. *Stat Med.* 1995;14:1149-1161.
15. Thall PF, Lee SJ. Practical model-based dose-finding in phase I clinical trials: methods based on toxicity. *Int J Gynecol Cancer.* 2003;13(3):251-261.
16. O'Quigley J, Pepe M, Fisher L. Continual reassessment method: a practical design for phase 1 clinical trials in cancer. *Biometrics.* 1990;46:33-48.
17. Yin G, Yuan Y. Bayesian model averaging continual reassessment method in phase I clinical trials. *J Am Stat Assoc.* 2009;104(487):954-968.
18. Cheung Y, Chappell R. Sequential designs for phase I clinical trials with late-onset toxicities. *Biometrics.* 2000;56:1177-1182.
19. Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. *Stat Med.* 2008;27(13):2420-2439.
20. Ji Y, Wang S. Modified toxicity probability interval design: a safer and more reliable method than the 3 + 3 design for practical phase I trials. *J Clin Oncol.* 2013;31(14):1785-1791.
21. Guo W, Wang SJ, Yang S, Lynn H, Ji Y. A Bayesian interval dose-finding design addressing Ockham's [sic] razor: mtpi-2. *Contemp Clin Trials.* 2017;58:23-33.
22. Yuan Y, Hess KR, Hilsenbeck SG, Gilbert MR. Bayesian optimal interval design: a simple and well-performing design for phase I oncology trials. *Clin Cancer Res.* 2017;22:4291-4301.
23. Huang X, Biswas S, Oki Y, Issa JP, Berry DA. A parallel phase I/II clinical trial design for combination therapies. *Biometrics.* 2007;63(2):429-36.
24. Case LD, Morgan TM. Design of phase II cancer trials evaluating survival probabilities. *BMC Med Res Methodol.* 2003;3:6.
25. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-247.
26. Fleming TR. One-sample multiple testing procedure for phase II clinical trials. *Biometrics.* 1982;38(1):143-151.
27. A'Hern RP. Sample size tables for exact single-stage phase II designs. *Stat Med.* 2001;20(6):859-866.
28. Gehan EA. The determination of the number of patients required in a preliminary and a follow-up trial of a new chemotherapeutic agent. *J Chronic Dis.* 1961;13:346-353.
29. Estey EH, Thall PF. New designs for phase 2 clinical trials. *Blood.* 2003;102(2):442-448.
30. Lachin JM. Statistical properties of randomization in clinical trials. *Control Clin Trials.* 1988;9(4):289-311.
31. Redman MW, Goldman BH, LeBlanc M, Schott A, Baker LH. Modeling the relationship between progression-free survival and overall survival: the phase II/III trial. *Clin Cancer Res.* 2013;19(10):2646-2656.
32. Rubinstein L, Crowley J, Ivy P, Leblanc M, Sargent D. Randomized phase II designs. *Clin Cancer Res.* 2009;15(6):1883-1890.
33. Simon R, Wittes RE, Ellenberg SS. Randomized phase II clinical trials. *Cancer Treat Rep.* 1985;69(12):1375-1381.
34. Scher HI, Heller G. Picking the winners in a sea of plenty. *Clin Cancer Res.* 2002;8(2):400-404.
35. Steinberg SM, Venzon DJ. Early selection in a randomized phase II clinical trial. *Stat Med.* 2002;21(12):1711-1726.
36. Yao Q, Wei LJ. Play the winner for phase II/III clinical trials. *Stat Med.* 1996;15(21-22):2413-2423; discussion 2455-248.
37. Robbins H. Some aspects of the sequential design of experiments. *Bulletin of the American Mathematical Society*. 1952;58(5):527-535.
38. Zelen M. Play the winner and the controlled clinical trial. *J Am Stat Assoc.* 1969;64(325):131-146.
39. Rosenberger WF, Lachin JM. *Randomization in Clinical Trials: Theory and Practice*. Wiley; 2002.
40. Berry DA. Adaptive trials and Bayesian statistics in drug development. *Biopharmaceutical Reports*. 2001;9;1-11.
41. Thall PF, Wathen JK. Practical Bayesian adaptive randomisation in clinical trials. *Eur J Cancer.* 2007;43(5):859-866.
42. Sampson AR, Sill MW. Drop-the-losers design: normal case. *Biom J.* 2005;47(3):257-68; discussion 269-81.
43. Eisele JR. The doubly adaptive biased coin design for sequential clinical trials. *J Stat Plan Inference*. 1994;38(2):249-261.
44. Berry DA. Bayesian statistics and the efficiency and ethics of clinical trials. *Stat Sci.* 2004;19(1):175-187.
45. Wei LJ, Durham S. The randomized play-the-winner rule in medical trial. *J Am Stat Assoc.* 1978;73(364):840-843.
46. Eisele JR, Woodroofe MB. Central limit theorems for doubly adaptive biased coin designs. *Ann Stat.* 1995;23:234-254.
47. Hu F, Zhang LX. Asymptotic normality of urn models for clinical trials with delayed response. *Bernoulli (Andover).* 2004;10:447-463.
48. Neyman J. On the two different aspects of the representative method: the method of stratified sampling and the method of purposive selection. *J R Stat Soc Series B Stat Methodol.* 1934;97:558-606.
49. Rosenberger WF, Stallard N, Ivanova A, Harper CN, Ricks ML. Optimal adaptive designs for binary response trials. *Biometrics.* 2001;57(3):909-913.
50. Hu F, Zhang L, Cheung SH, Chan WS. Doubly adaptive biased coin designs with delayed responses. *Can J Stat.* 2008;36:541-559.
51. Berry DA, Eick SG. Adaptive assignment versus balanced randomization in clinical trials: a decision analysis. *Stat Med.* 1995;14,231-224.
52. Zhou X, Liu S, Kim ES, Herbst RS, Lee JJ. Bayesian adaptive design for targeted therapy development in lung cancer- a step toward personalized medicine. *Clin Trials.* 2008;5 (3):181-193.
53. Ning J, Huang X. Response-adaptive randomization for clinical trials with adjustment for covariate imbalance. *Stat Med.* 2010;29(17):1761-1768.

54. Yuan Y, Huang X, Liu S. A Bayesian response-adaptive covarite-balanced randomization design with application to a leukemia clinical trial. *Stat Med.* 2011;30(11):1218-1229.
55. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics.* 1979;35(3):549-556.
56. Wang SK, Tsiatis AA. Approximately optimal one-parameter boundaries for group sequential trials. *Biometrics.* 1987;43(1):193-199.
57. Lan K, DeMets D. Discrete sequential boundaries for clinical trials. *Biometrika.* 1983;70(3):659-663.
58. Müller HH, Schäfer H. Adaptive group sequential designs for clinical trials: combining the advantages of adaptive and of classical group sequential approaches. *Biometrics.* 2001;57(3):886-891.
59. US Food and Drug Administration. Adaptive design clinical trials for drugs and biologics. Guidance Document. Accessed May 17, 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics-guidance-industry.
60. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther.* 2001;69(3):1-7.
61. O'Neill RT, Wang S, Hung HM. Approaches to evaluation of treatment effect in randomized clinical trials with genomic subset. *Pharm Stat*. 2007;6:227-244.
62. Xu Y, Trippa L, Muller P, Ji Y. Subgroup-based adaptive (suba) designs for multi-arm biomarker trials. *Stat Biosci.* 2016;8(1):159-180.
63. Freidlin B, Simon R. Adaptive signature design: an adaptive clinical trial design for generating and prospectively testing a gene expression signature for sensitive patients. *Clin Cancer Res*. 2005;11(12):7872-7878.
64. Gu X, Chen N, Wei C, et al. Bayesian two-stage biomarker-based adaptive design for targeted therapy development. *Stat Biosci.* 2016;8(1):99-128.
65. Chang M. *Introductory Adaptive Trial Designs: A Practical Guide with R*. Chapman & Hall/Crc Biostatistics; 2015.
66. Thall PF, Simon R, Ellenberg SS. A two-stage design for choosing among several experimental treatments and a control in clinical trials. *Biometrics.* 1989;45:537-547.
67. Schaid DJ, Wieand S, Therneau TM. Optimal two stage screening designs for survival comparisons. *Biometrika.* 1990;77:659-663.
68. Stallard N, Todd S. Sequential designs for phase III clinical trials incorporating treatment selection. *Stat Med.* 2003;22:689-703.
69. Huang W, Liu J, Hsiao C. An alternative phase II/III design for continuous endpoints. *Pharm Stat*. 2011;10:105-114.
70. Bischoff W, Miller F. Adaptive two-stage test procedures to find the best treatment in clinical trials. *Biometrika.* 2005;92:197-212.
71. Todd S, Stallard N. A new clinical trial design combining phases II and III: sequential designs with treatment selection and a change of endpoint. *Ther Innov Regul Sci*. 2005;39:109-118.
72. Chow SC, Tu YH. On two-stage seamless adaptive design in clinical trials. *J Formos Med Assoc.* 2008;107:S52-S60.
73. Posch M, Maurer W, Bretz F. Type I error rate control in adaptive designs for confirmatory clinical trials with treatment selection at interim. *Pharm Stat*. 2011;10:96-104.
74. Stallard N. A confirmatory seamless phase II/III clinical trial design incorporating short-term endpoint information. *Stat Med.* 2010;29(9):959-971.
75. Maca J, Bhattacharya S, Dragalin V, Gallo P, Krams M. Adaptive seamless phase II/III designs- background, operational aspects, and examples. *Drug Inf J.* 2006;40(4):463-473.
76. Qiao W, Ning J, Huang X. A clinical trial design with covariate-adjusted response-adaptive randomization using superiority confidence of treatments. *Statistics in Biopharmaceutical Research*. 2019;11:336-347 .
77. Huang X, Ning J, Li Y, Estey E, Issa JP, Berry DA. Using short-term response information to facilitate adaptive randomization for survival clinical trials. *Stat Med.* 2009;28(12):1680-1689.
78. Xia F, George S, Ning J, Liang L, Huang X. A Signature Enrichment Design with Bayesian Adaptive Randomization. *J Appl Stat*. 2021;48(6):1091-1110.
79. Italiano A. Prognostic or predictive? It's time to get back to definitions! *J Clin Oncol*. 2011;29(35):4718.
80. Lara PN, et al. Disease control rate at 8 weeks predicts clinical benefit in advanced non-small-cell lung cancer: results from Southwest Oncology Group randomized trials. *J Clin Oncol.* 26(3):463-467.
81. Claret L, Gupta M, Han K, et al. Prediction of overall survival or progression free survival by disease control rate at week 8 is independent of ethnicity: Western versus Chinese patients with first-line non-small cell lung cancer treated with chemotherapy with or without bevacizumab. *J Clin Pharmacol.* 2014;54(3):253-257.
82. Hutchinson L, Kirk R. High drug attrition rates--where are we going wrong? *Nat Rev Clin Oncol.* 2011;8(4):189-190.
83. Von Hoff DD. There are no bad anticancer agents, only bad clinical trial designs--twenty-first Richard and Hindar Rosenthal Foundation award lecture. *Clin Cancer Res.* 1998;4(5):1079-1086.
84. Comis RL, Miller JD, Aldige CR, Krebs L, Stoval E. Public attitudes toward participation in cancer clinical trials. *J Clin Oncol.* 2003;21(5):830-835.
85. Cassileth BR. Clinical trials: time for action. *J Clin Oncol.* 2003;21(5):765-766.
86. Tibshirani RJ. Regression shrinkage and selection via the lasso. *J R Stat Soc Series B Stat Methodol.* 1996;58:267-288.
87. Fan J, Li R. Variable selection via nonconcave penalized likelihood and its oracle properties. *J Am Stat Assoc.* 2001;96:1348-1360.
88. Sauter ER. Reliable biomarkers to identify new and recurrent cancer. *Eur J Breast Health*. 2017;13(4):162-167.
89. Janiaud P, Serghiou S, Loannidis JPA. New clinical trial designs in the era of precision medicine: an overview of definitions, strengths, weaknesses, and current use in oncology. *Cancer Treat Rev.* 2019;73:20-30.
90. Ross JS, Fletcher JA, Linette GP, Stec J, Clark E, Ayers M. The HER-2/neu gene and protein in breast cancer 2003: biomarker and target of therapy. *Oncologist.* 2003;8:307-325.
91. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against her2 for metastatic breast cancer that overexpresses her2. *N Engl J Med.* 2001;344(11):783-792.
92. Cheng L, Lopez-Beltran A, Massari F, MacLennan GT, Montironi R. Molecular testing for Braf mutations to inform melanoma treatment decisions: a move toward precision medicine. *Mod Pathol.* 2018;31(1):24-38.
93. Rosell R, Carcereny E, Gervais R, et al; Spanish Lung Cancer Group in collaboration with Groupe Francais de Pneumo-Cancerologie, and Associazione Italiana Oncologia Toracica. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced *EGFR* mutation-positive non-small-cell lung cancer (Eurtac): a multicentre, open-label, randomized phase 3 trial. *Lancet Oncol.* 2012;13(3):239-246.
94. Marcus L, Lemery SJ, Keegan P, Pazdur R. FDA approval summary: pembrolizumab for the treatment of microsatellite instability-high solid tumors. *Clin Cancer Res.* 2019;25(13):3753-3758.
95. US Food and Drug Administration. Master protocols: efficient clinical trial design strategies to expedite development of oncology drugs and biologics. Guidance Document. Accessed May 17, 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/master-protocols-efficient-clinical-trial-design-strategies-expedite-development-oncology-drugs-and.
96. Woodcock J, LaVange LM. Master protocols to study multiple therapies, multiple diseases, or both. *N Engl J Med.* 2017;377(1):62-70.
97. Hirakawa A, Asano J, Sato H, Teramukai S. Master protocol trials in oncology: Review and new trial designs. *Contemp Clin Trials Commun*. 2018;12:1-8.

70

Big Data and Machine Learning in Oncology

Peng Wei
Hai Shu

KEY CONCEPTS

- Machine learning is aimed at developing computer algorithms and statistical models to discover patterns underlying complex and large datasets (unsupervised learning) or to predict an outcome based a set of predictors and a decision rule (supervised learning).
- Deep learning (DL) is a family of machine learning methods based on multilayered artificial neural networks and has been shown to outperform classical supervised learning methods in many applications; however, it requires a large training dataset (at least thousands of samples) because of its model complexity.
- Big data in oncology mainly arise from cancer genomics (such as The Cancer Genome Atlas project), medical imaging (such as magnetic resonance imaging and positron emission tomography–computed tomography), as well as the electronic health record.
- Integrative genomic analysis is a powerful tool to study the biological mechanisms underlying a complex disease, such as cancer, across multiplatform high-dimensional data, such as DNA methylation, copy number variation, and gene expression.
- Radiomics, an emerging field in imaging analysis for diagnosis, prognosis, or treatment response prediction, refers to the extraction of a large number of quantitative features, including shape features, first-order histogram features, and second-order texture features that capture spatial arrangement of the voxel intensities.
- Assessment of prediction model performance should be based on the test error, that is, the prediction error over an independent test sample. On the other hand, minimizing the training error, that is, the prediction error over the sample used to train a model, will lead to overfitting and over-optimism about the model performance. Test error can be objectively evaluated by proper training/test data split or cross-validation.

The term *artificial intelligence* (AI) was first coined by John McCarthy for the famous workshop Dartmouth Summer Research Project on Artificial Intelligence held in 1956,[1] defined as "the science and engineering of making intelligent machines."[2] As a subfield of AI, machine learning is the study of mathematical and statistical approaches that automatically improve the performance of computers through experience.[3] Deep learning (DL), a revolutionary family of machine learning methods based on multilayered artificial neural networks (ANN),[4] has caused a third boom of AI and is integrated into our daily lives in ways such as face recognition,[5] self-driving cars,[6] personal electronic assistants (Siri, Alexa, and Google Assistant), and intelligent medical diagnostics.[7,8]

MACHINE LEARNING

Machine learning, also referred to as statistical learning in the field of statistics, is aimed at developing computer algorithms and statistical models to discover patterns underlying complex and large data sets (unsupervised learning) or to predict an outcome based a set of predictors and a decision rule (supervised learning).[9] The development of machine learning has been bolstered by the big data and emerging analytics challenges in medicine, in particular, oncology, because of the breakthroughs in high-throughput technologies, such as microarray profiling technologies in the late 1990s and early 2000s,[10,11] next-generation sequencing technologies in the mid- to late 2000s,[12,13] and single-cell

sequencing technologies[14,15] in the 2010s. For example, a typical gene expression microarray or RNA-sequencing experiment can interrogate the expression levels of genome-wide messenger RNAs (>20,000 mRNAs) in dozens to hundreds of samples. The Cancer Genome Atlas (TCGA) project, begun in 2005, exemplifies the big data in oncology. It uses a variety of high-throughput platforms to molecularly characterize more than 20,000 primary cancer and matched normal samples spanning 33 cancer types, generating more than 2.5 petabytes of genomic, epigenomic, transcriptomic, and proteomic data.[16,17]

To address the need to uncover cancer subtypes based on high-throughput genomics data, a number of unsupervised machine learning methods have been developed and refined, such as hierarchical clustering, clustering based on multiple types of genomic data (iCluster[18]), and model-based clustering methods.[19] On the other hand, supervised machine learning has also had unprecedented breakthroughs in the past couple of decades, motivated by the need to build prediction models based on high-dimensional predictors (tens of thousands) and relatively small sample sizes (dozens to hundreds), that is, the so called "large p, small n" problem. Major breakthroughs in supervised machine learning include penalized regression methods (lasso,[20] elastic net,[21] and sure independent screening,[22] to name a few); support vector machine,[23] and ensemble-based methods (random forests[24] and boosting[25]); see Hastie et al for a comprehensive introduction.[9]

DEEP LEARNING

DL was notably brought to the public's attention by AlphaGo versus Lee Sedol in 2016, where the DL-trained computer program vanquished the world's Go champion.[26] In the AI community, the spectacular success of DL can be dated 4 years earlier to the well-known ImageNet Large Scale Visual Recognition Challenge 2012 in which the AlexNet, a deep convolutional neural network, achieved a top-5 error rate of 15.3%, more than 10.8% lower than that of the runner up (a non-DL approach).[27] Since then, DL has been successfully applied in various areas of academia and industry,[5–8] which is ascribed to the availability of large datasets (ImageNet,[28] COCO,[29] BraTS[30]), the exponential growth in computing power (graphics processing unit and tensor processing unit), and the well-optimized open-source software libraries (Pytorch, Tensorflow, and Keras).

As the base of DL, an ANN is a nonlinear mathematical model that builds a complex relationship between the input data and the output.[4] In an ANN, the input data are provided to an input layer and then transmitted through one or multiple hidden layers that are linked to an output layer (Fig. 70–1). A layer is a collection of

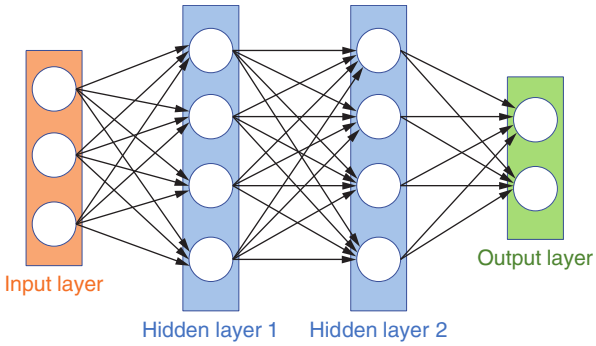


FIGURE 70–1 Architecture of an artificial neural network.

nodes, called neurons, imitating the ones in the human brain, which are connected through edges to the previous and the next layers. Edges are assigned with trainable weights to sum the output values of neurons in the previous layer as the input to each neuron in the next layer. Each neuron nonlinearly transforms the data by applying an activation function. A deep neural network is an ANN with many hidden layers, commonly 10+ and even 100+ layers. A convolutional neural network is a specialized type of ANN designed for image data, which performs a linear operation called a "convolution" that is capable of capturing the spatial dependency in an image.

AI, especially DL, has been recently gaining popularity in medicine, to improve time efficiency, reduce human errors and variability, as well as lower the medical cost.[7,8] The widest application is the field of medical image analysis, mainly because of the remarkable progress in computer vision. For instance, McKinney et al[31] developed a DL model for identifying breast cancer in screening mammograms, which had the area under the receiver operating characteristic curve (AUC) greater than that for the average of six radiologists by an absolute margin of 11.5%. More examples include the BraTS Challenge 2019 for brain tumor magnetic resonance imaging (MRI) segmentation,[32] IDRiD Challenge 2018 for diabetic retinopathy segmentation and grading,[33] and Data Science Bowl 2017 for lung cancer detection in computed tomography,[34] where automated DL algorithms won championships and dominated the challenges. Beyond the medical imaging field, DL is also successfully used on electronic health records for personalized risk predictions and health trajectories and applied in genomic research for predictions of genomic features and functions.[35]

To advance the development and applications of DL and AI in medicine and healthcare, many impressive platforms have been established. Grand Challenge (https://grand-challenge.org/) and Dream Challenges (http://dreamchallenges.org/) post medical and public health competitions in which novel AI algorithms can be devised, for example, the famous U-Net[36] invented for a segmentation challenge. The journals *Artificial Intelligence in Medicine* and *Radiology: Artificial Intelligence*

publish high-quality articles concerning the theory or practice of AI in medicine, and the JAMA Network archives the relevant articles published in its journals (https://sites.jamanetwork.com/machine-learning/).

TRAINING ERROR VERSUS TEST ERROR IN MACHINE LEARNING

Assessment of prediction model performance should be based on the test error, that is, the prediction error over an independent test sample. However, a common mistake in machine learning modeling is the attempt to minimize the training error, that is, the prediction error over the sample used to train a model. Unfortunately, this will lead to overfitting of the model and over-optimism about the model performance. In fact, the training error typically keeps decreasing with increasing number of predictors included in the model, regardless of whether true or noise predictors are included. For example, the training error misclassification rate in a binary outcome prediction problem can be as small as zero with many purely noise predictors. On the other hand, the test error for the same model can be very large.

To objectively estimate the test error, a given data set for prediction modeling should be split into training and test samples (3:1 to 5:1 ratio) with the former being used for model building and the latter for prediction accuracy evaluation. Should the sample size be limited, a K-fold cross-validation can be used to estimate the test error, where commonly used K include 3, 5, 10, or *n* (the sample size, that is, the leave-one-out cross-validation). For example, a five-fold cross-validation entails randomly and equally splitting the entire samples into five groups. Each of the five folds is then held out in turn as the test set and the remaining four folds comprise the training data; the overall prediction accuracy is calculated as the averaged accuracy across all five folds. In the case studies to be detailed later, we used a three-fold cross-validation with a sample size of 74 in Case Study II and a 5:1 training/test data split in Case Study III with a total sample size of 3713. See Chapter 7 of Hastie et al[9] for a comprehensive treatment on this topic.

CASE STUDIES OF MACHINE LEARNING APPLICATION AT MD ANDERSON

In this section we present three case studies to showcase the machine learning research and applications at MDACC, including (1) integrative analysis of cancer genomics data, (2) predictive modeling using MRI radiomics features for treatment response, and (3) DL modeling for mammography.

Case Study I: Integrative Analysis of Cancer Genomics Data

Genomic profiling studies have demonstrated that bladder cancer can be divided into two molecular subtypes, referred to as luminal and basal, with distinct clinical behaviors and sensitivities to frontline chemotherapy.[37,38] Twenty-three mRNA gene expression markers have been reported to play a major role in these molecular subtypes[38]; however, it is not yet known (1) whether those gene expression markers also demonstrate difference at the DNA methylation and copy number variation (CNV) levels, and (2) whether there are other genes associated with the molecular subtyping through any of the three data types (ie, mRNA expression, DNA methylation, and CNV). Although it is common to perform large-scale genome-wide association analysis of an outcome for each data type separately and combine the results ad hoc, it can result in loss of statistical power and uncontrolled overall false discovery rate (FDR).[39] To this end, we proposed a novel multivariate mixture model (IMIX) framework that integrates multiple types of genomic data and allows modeling of interdata-type correlations.[40] IMIX features across-data-type FDR control, computational efficiency, and a user-friendly software package "IMIX" in R (https://github.com/ziqiaow/IMIX). In addition, IMIX only requires summary statistics as its inputs, not individual patient-level data.

We applied IMIX to analyze the TCGA bladder cancer patient cohort, which was profiled by three genomic platforms: DNA methylation (M), mRNA gene expression (GE), and CNV. Our objective was to classify each of the genome-wide genes into one of eight possible classes based on association patterns of the three data types: (M–, GE–, CNV–), (M+, GE–, CNV–), (M–, GE+, CNV–), (M–, GE–, CNV+), (M+, GE+, CNV–), (M+, GE–, CNV+), (M–, GE+, CNV+), and (M+, GE+, CNV+). For example, genes in class (M–, GE–, CNV–) were not associated with the basal/luminal subtype through any of the three data types, whereas those in class (M+, GE+, CNV+) were associated through all three. After quality control, we separately analyzed 373 DNA methylation samples, 391 RNA-sequencing samples, and 387 CNV samples with 15,672 genes with respect to the molecular subtypes, adjusting for the clinical covariates, including age, sex, race, smoking status, and pathologic stage. We applied IMIX to the final *P* values obtained from the association tests of individual-level data. At an FDR of 1%, we identified 61 significant genes in class (M+, GE+, CNV+), ie, genes that were associated with all three data types. We show the DNA methylation, gene expression, and CNV levels of the 61 genes in Fig. 70–2A, where the differential gene expression between luminal and basal subtypes appeared to be positively correlated with CNV levels and negatively correlated with DNA methylation

levels. We further conducted Ingenuity Pathway Analysis (Ingenuity Systems; www.ingenuity.com) on the 61 significant genes. The results showed strong peroxisome proliferator activator receptor (PPAR) pathway activation in luminal samples. This pathway was previously reported by Choi et al,[38] who first proposed the molecular subtypes of muscle-invasive bladder cancer and showed that PPARα and PPARγ activation played essential roles in regulating gene expression signature for the luminal subtype. Specifically, they exposed the PPARγ-selective agonist rosiglitazone in two bladder cancer cell lines and further confirmed that rosiglitazone activated the PPAR pathway and enriched gene signatures in primary luminal samples.

We also present the levels of the luminal and basal markers for DNA methylation, gene expression, and CNV in Fig. 70–2B. Among the 23 markers, we found that 6, 15, and 1 gene belonged to class (M–, E+, CNV–), (M+, E+, CNV–), and (M+, E+, CNV+), respectively. In particular, PPARG belonged to class (M+, E+, CNV+), ie, associated with the subtypes via all three molecular mechanisms. This gene was reported to be one of the driver genes for basal and luminal differentiation. As expected, the luminal samples showed a higher PPARγ gene expression level than did the basal samples; furthermore, we discovered a concordant significant differential pattern in the methylation and CNV levels that has not been previously reported.

In summary, our integrative genomic data analysis revealed that the luminal and basal markers demonstrated substantial differences in at least two data types (Fig. 70–2B). By applying the IMIX framework, we

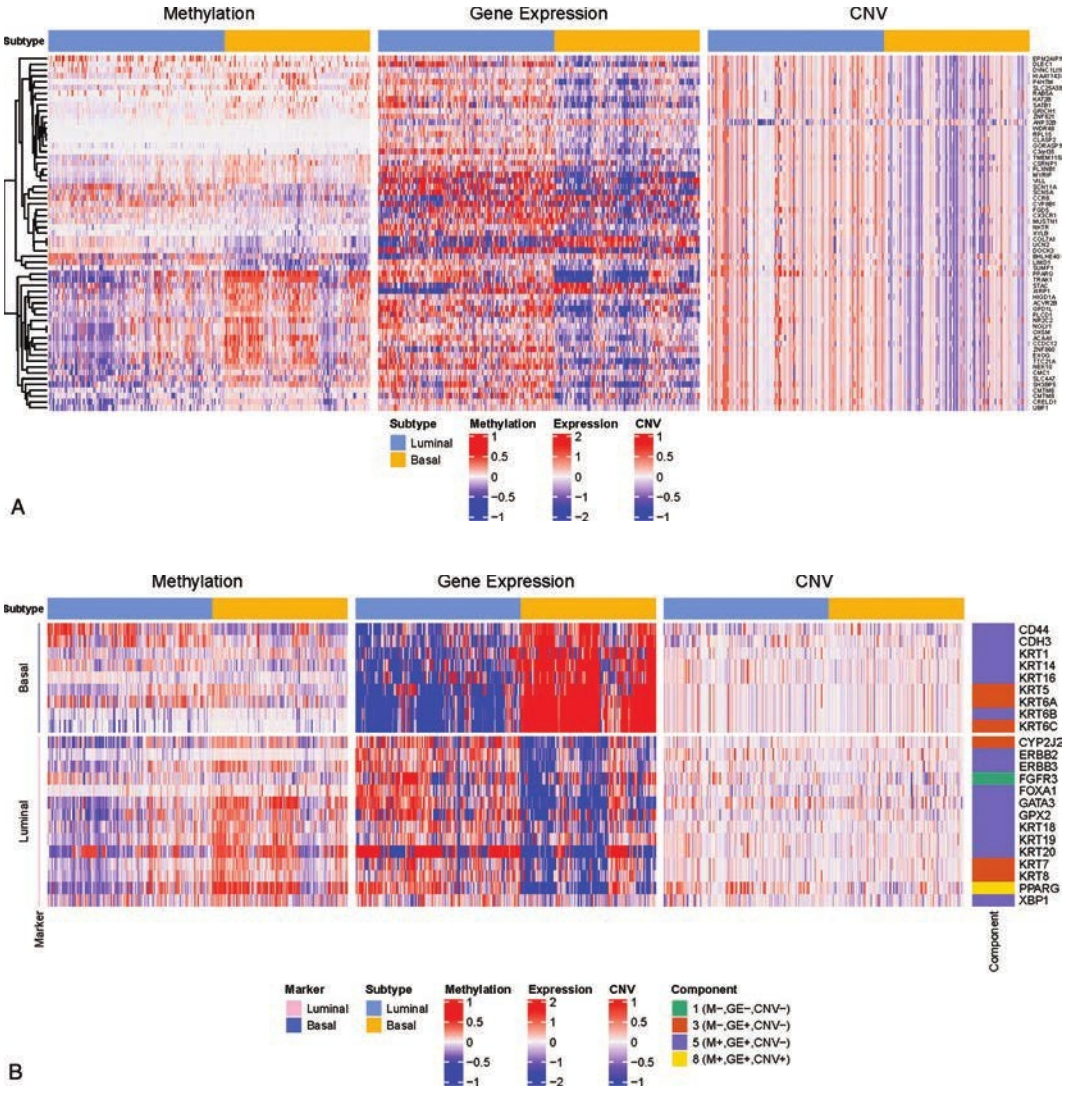


FIGURE 70–2 **A. Heatmaps of genes in IMIX analysis for bladder cancer molecular subtypes in The Cancer Genome Atlas (TCGA). (a) Methylation, gene expression, and copy number variation (CNV) patterns of top significant genes associated with the three data types (M+, GE+, CNV+) identified by IMIX in molecular subtypes of TCGA muscle-invasive bladder cancer patients, with FDR at 1%. B. Expression patterns of luminal and basal markers of TCGA bladder cancer cohort.**

successfully discovered novel genes that were associated with the molecular subtypes across all three data types (Fig. 70–2B) and confirmed the PPAR/RXR activation canonical pathway that was previously reported to play a central role in luminal and basal differentiation.[38]

In addition to being key contributors to the TCGA project,[16,41,42] MDACC investigators have also utilized the TCGA data as a reference to molecularly characterize rare, yet clinically aggressive, cancer subtypes, such as sarcomatoid,[43] small cell carcinoma,[44] and micropapillary[45] variants of bladder cancer, using a multiple-omics approach. A basal to luminal transition score has also been recently developed by applying the lasso regression model[20] to the TCGA bladder cancer cohort (n = 408) as the training data and subsequently validating it in two MDACC cohorts (fresh frozen samples n = 132 and formalin-fixed paraffin-embedded samples n = 89).[37]

Case Study II: MRI Imaging in a Triple-Negative Breast Cancer Clinical Trial

Triple-negative breast cancer (TNBC) accounts for approximately 20% of all breast cancers and is a subtype of breast cancer that lacks estrogen receptor, progesterone receptor, and HER2 expression.[46] Compared with other breast cancer subtypes, TNBC is more aggressive and is associated with a higher rate of relapse and a lower rate of overall survival. Patients with TNBC usually undergo neoadjuvant systemic therapy (NAST) for downstaging of disease to facilitate less invasive surgery. The extent of downstaging is used as a surrogate prognostic marker. Pathologic complete response (pCR) to NAST is seen in about half of the patients with TNBC undergoing the treatment but is weak or absent in the others. The ongoing "A Robust TNBC Evaluation FraMework to Improve Survival" (ARTEMIS) clinical trial (NCT02276443), a part of the MDACC Breast Cancer Moon Shot Program®, is aimed at using longitudinal genomic and imaging signatures to identify patients with TNBC who are sensitive/insensitive to standard NAST chemotherapy. TNBC patients of stage I–III in the study undergo biopsy before treatment, and then immediately begin NAST. Genomic profiling by RNA sequencing and whole-exome sequencing, as well as ultrasound and multiple sequences of MRI imaging (T1, T2, ultrafast dynamic contrast enhanced [DCE]-MRI, and chemical exchange saturation transfer–MRI), are performed at baseline, after two cycles, and at completion of four cycles of NAST. pCR is then ascertained by pathologists after appropriate surgery according to the size of the residual tumor.

Here we introduce a pilot radiomics study that is aimed at using radiomic features of MRI imaging to predict pCR in TNBC patients receiving NAST.[47] Radiomics, an emerging field in imaging analysis, refers to the extraction of a large number of quantitative features, including shape features (eg, volume and maximum diameter), first-order histogram features (eg, mean, median, minimum, maximum, skewness, and kurtosis of intensity distribution), and second-order texture features that capture spatial arrangement of the voxel intensities.[48] To investigate whether radiomic phenotypes can predict pCR, we extracted 390 radiomic features (first-order histogram features and second-order grey-level-cooccurrence matrix) from each of 74 patients with stage I–III TNBC who underwent ultrafast DCE-MRI (temporal-resolution: 9–12 s) at baseline in the ARTEMIS trial using an in-house MATLAB library. AUC was used to determine how well radiomic features could predict pCR. Given the relatively small sample size and large number of radiomic features, we used three-fold cross-validation and a penalized logistic regression model with the elastic net penalty to build a prediction model. The elastic net penalty is appealing because it enables feature selection while accommodating potentially correlated features as is the case for radiomics.[21,49,50] The resulting radiomic model consisting of 24 features had an AUC of 0.80 for predicting pCR. This model is being validated in an independent set of ARTEMIS patients. Other ongoing research efforts include integrating molecular, genomic, and imaging biomarkers to tailor personalized treatment for patients with TNBC and developing DL models for longitudinal MRI imaging to predict pCR.

Case Study III: Deep Learning Approach to Mammography

MERIT (Mammography, Early detection biomarkers, Risk assessment and Imaging Technologies) is a multidisciplinary MDACC initiative designed for discovery, evaluation, and validation of biomarkers for early detection of breast cancer. In this section, we describe a MERIT project that proposed a DL approach to recover for-processing full-field digital mammograms for breast density and texture feature analysis. Interested readers are referred to the article by Shu et al for details.[51]

Full-field digital mammography generates two types of imaging data[52]: the raw "for-processing" images in which the greyscale is proportional to the x-ray attenuation through the breast, and the processed "for-presentation" images that are optimized for visual cancer detection. For-processing images are more appropriate for quantitative analyses (eg, breast density evaluation and texture feature analysis) than for-presentation images because they reflect the original physical properties of the breast. The literature has reported significant differences in breast density and texture measures between the two image types.[53,54] However, in clinical settings, for-processing images are rarely archived because of cost and storage constraints; only for-presentation images are routinely stored. Moreover,

mammography equipment manufacturers do not disclose raw-to-processed-image conversion steps, and inversion algorithms are not available. Hence, retrospective calculations of breast density and texture features using preferred for-processing image-based algorithms and software[55,56] are not applicable to most historical images stored only in the for-presentation format.

This motivated our research to recover for-processing images from for-presentation images. We developed an image recovery approach by utilizing the powerful DL technique, the U-Net.[36] The U-Net and its variants[57,58] have exhibited state-of-the-art performance in various medical image segmentation tasks.[32,33,59] We extended the use of U-Net to image estimation, in which the recovered image can be viewed as a continuous-valued segmentation map. We mathematically used U-Net as a nonlinear regression function to fit for-processing images based on for-presentation images. Specifically, in the original U-Net we changed the loss function to the mean square error from the cross-entropy of classification and the final activation function to the continuous ReLU function from the categorical softmax function.

All for-processing and for-presentation mammograms were generated using the Selenia Dimensions Mammography System (Hologic). The for-presentation images were retrieved from the Picture Archiving and Communication System, and the for-processing images were stored on a Picture Archiving and Communication System–based research server. The data set contained 3713 pairs of for-processing and for-presentation mammograms from 884 women (age range, 28–80 years; mean ± standard deviation [SD] age, 56.7 ± 9.9 years), including 1891 pairs in the mediolateral oblique view and 1822 pairs in the craniocaudal view. The dataset was randomly split into disjoint training and testing sets, consisting of images from 737 and 147 women (737:147»5:1) with 1569 and 322 pairs in the mediolateral oblique view and 1519 and 303 pairs in the craniocaudal view. Both for-processing and for-presentation images were used in model training. In testing, the for-presentation images were input into the trained model to generate the estimated for-processing images, and the original for-processing images were used only to evaluate image recovery performance.

In the testing data set, the estimated for-processing images had acceptable mean absolute percentage error (mean ± SD = 0.115 ± 0.059) and high structural similarity index (0.986 ± 0.007) for the breast portion. The estimated and original images had a strong correlation in breast density percentage (Pearson r = 0.946; 95% CI 0.926, 0.966) and a strong agreement in breast density grade (Cohen κ = 0.875; 95% CI 0.845, 0.905). The breast density percentage and grade were evaluated by Volpara software (version 1.5.4.0; Volpara Solutions). We also considered the widely used 28 mammographic texture features listed in Gastounioti et al.[53] The estimated images had satisfactory correlations with the originals in 22 texture features (Pearson $r \in$ [0.762, 0.986] and [0.503, 0.668] for 18 and two features, respectively; Spearman ρ ³ 0.705 for another two) and were well complemented by for-presentation images for the other six features ($r \in$ [0.832, 0.846] and = 0.650 for four and one features, respectively; Spearman's ρ = 0.553 for the other one). We obtained comparable results for the training dataset. Hence, our DL approach performed well in recovering for-processing mammograms with strong consistency in image error and similarity metrics, breast density, and the majority of 28 widely used texture features. Figure 70–3 illustrates examples of our recovered for-processing images.

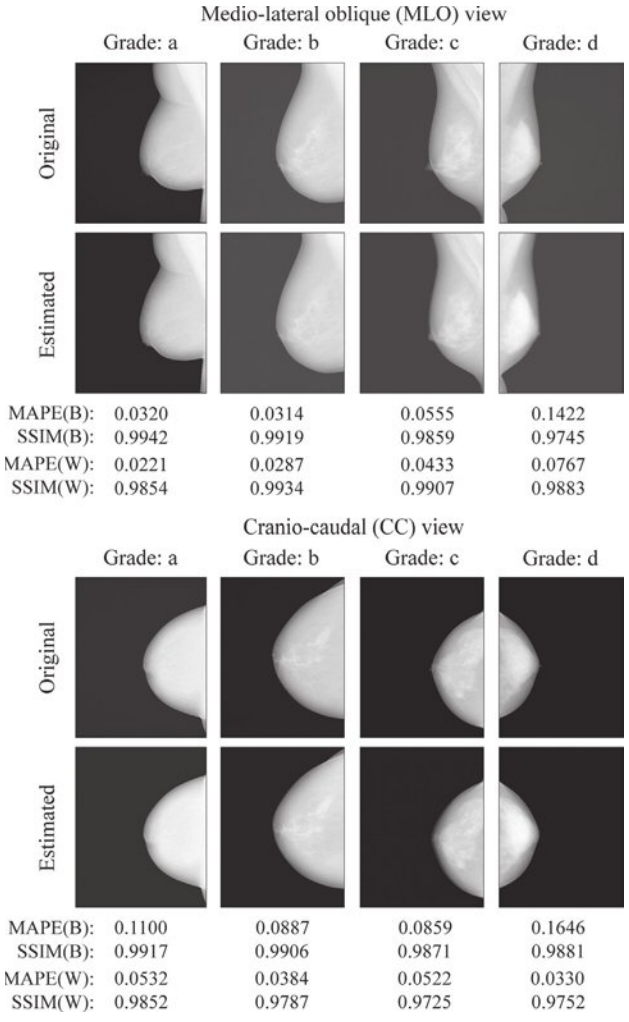


FIGURE 70–3 **Comparison of original and estimated for-processing images for four randomly selected patients with different true Volpara breast density grades. The images were negative log–transformed to improve readability. (B), (breast portion); MAPE, mean absolute percentage error; SSIM, structural similarity index measure; (W), (whole image).**

CONCLUSION AND FUTURE DIRECTIONS

Big data in oncology arise from cancer genomics, medical imaging, and the electronic health record. Recent advances in machine learning methods, particularly, DL, have revolutionized precision oncology and, more broadly, precision medicine.[60] A promising direction is to integrate genomics and medical imaging data to build prediction models for diagnosis, prognosis, or treatment response.[61]

Two emerging directions in AI are the deep reinforcement learning[62] and deep causal inference,[63] which are the combination of DL with reinforcement learning and causal inference, respectively. DL enables them scale to problems that were previously intractable. Reinforcement learning is to learn a strategy for an agent to take actions in an environment to maximize expected cumulative rewards. A prominent application of deep reinforcement learning in medicine is robotic surgery, which is expected to improve precision, increase safety, and reduce time and expenses.[64,65] In contrast with the relatively acceptable robot-assisted surgery, that is, under a human surgeon's supervision, the autonomous robotic surgery may face ethical issues.[66] Causal inference studies the causal relationships among different components of a system. Deep causal inference is useful to address complex medical problems, such as the causal effect estimation in the presence of high-dimensional covariates and high cardinality treatments.[67]

MD ANDERSON PRACTICE TIPS

- Machine learning research in oncology requires a team-science approach by investigators from multiple disciplines including medical oncologists, radiologists, pathologists, medical physicists, biostatisticians, bioinformaticians, and computer scientists.
- Team-science research at MDACC is facilitated by the National Cancer Institute Cancer Center Support Grant, Specialized Programs of Research Excellence grants, and MDACC's Breast Cancer Moon Shot Program®.
- Machine learning, in particular DL research, needs strong computational infrastructure, including high-performance computing (HPC) with a large number of central processing unit and graphics processing unit computing nodes, large memory, and storage space. MDACC investigators have access to institutional HPC with dedicated IT support, as well as world-class HPC resources at the Texas Advanced Computing Center as afforded by the University of Texas Research Cyberinfrastructure Initiative.
- Public data sets such as those form TCGA, the database of Genotypes and Phenotypes (dbGaP), and the Gene Expression Omnibus, which can be effectively leveraged to compare and combine with data generated from local patient samples.
- Given a data set for prediction modeling, it should be split into training and test samples (3:1 to 5:1 ratio) with the former being used for model building and the latter for prediction accuracy evaluation. Should the sample size be limited, cross-validation can be employed to estimate the test error. Ideally, an independent data set from a different source, for example, institution, should be further used to validate the prediction model.
- DL has been shown to outperform classical machine learning methods in imaging and other applications; however, because of the model complexity, it requires a large training data set (at least thousands of samples). For prediction modeling with moderate sample sizes, traditional machine learning methods, such as penalized regression, random forests, and boosting, can still be good options.

ACKNOWLEDGMENTS

This work was supported by the National Institutes of Health (NIH) grants R01HL116720 and R01CA169122; P.W. was partially supported by NIH grants P50CA091846 and P50CA217674.

REFERENCES

1. Moor J. The Dartmouth College Artificial Intelligence Conference: The Next Fifty Years. AI Magazine 2006;27:87.
2. McCarthy J. What is AI? / Basic Questions. http://jmc.stanford.edu/artificial-intelligence/what-is-ai/index.html.
3. Mitchell TM. *Machine Learning*. McGraw-Hill; 1997.
4. Goodfellow I, Bengio Y, Courville A. *Deep Learning*. MIT Press; 2016.
5. Sun Y, Wang X, Tang X. Deeply learned face representations are sparse, selective, and robust. Proceedings of the IEEE Conference on Computer Vision and Pattern Recognition. 2015:2892-2900.
6. Bojarski M, Del Testa D, Dworakowski D, et al. End to end learning for self-driving cars. arXiv:160407316 [cs] 2016.
7. Mintz Y, Brodie R. Introduction to artificial intelligence in medicine. *Minim Invasive Ther Allied Technol*. 2019;28:73-81.
8. Shimizu H, Nakayama KI. Artificial intelligence in oncology. *Cancer Sci*. 2020;111:1452-1460.
9. Hastie T, Tibshirani R, Friedman JH. *The Elements of Statistical Learning: Data Mining, Inference, and Prediction*. 2nd ed. Springer; 2009.
10. Golub TR, Slonim DK, Tamayo P, et al. Molecular classification of cancer: class discovery and class prediction by gene expression monitoring. *Science*. 1999;286:531-537.
11. Ramaswamy S, Golub TR. DNA microarrays in clinical oncology. *J Clin Oncol*. 2002;20:1932-1941.
12. Berger MF, Mardis ER. The emerging clinical relevance of genomics in cancer medicine. *Nat Rev Clin Oncol*. 2018;15:353-365.
13. Goodwin S, McPherson JD, McCombie WR. Coming of age: ten years of next-generation sequencing technologies. *Nat Rev Genet*. 2016;17:333-351.
14. Turajlic S, Sottoriva A, Graham T, Swanton C. Resolving genetic heterogeneity in cancer. *Nat Rev Genet*. 2019;20:404-416.
15. Lim B, Lin Y, Navin N. Advancing cancer research and medicine with single-cell genomics. *Cancer Cell*. 2020;37:456-470.
16. Robertson AG, Kim J, Al-Ahmadie H, et al. Comprehensive molecular characterization of muscle-invasive bladder cancer. *Cell*. 2017;171:540-56 e25.
17. Hutter C, Zenklusen JC. The Cancer Genome Atlas: creating lasting value beyond its data. *Cell*. 2018;173:283-285.
18. Mo Q, Wang S, Seshan VE, et al. Pattern discovery and cancer gene identification in integrated cancer genomic data. *Proc Natl Acad Sci U S A*. 2013;110:4245-4250.
19. Richardson S, Tseng GC, Sun W. Statistical methods in integrative genomics. *Annu Rev Stat Appl*. 2016;3:181-209.
20. Tibshirani R. Regression shrinkage and selection via the Lasso. *J R Stat Soc Series B Stat Methodol*. 1996;58:267-288.
21. Zou H, Hastie T. Regularization and variable selection via the elastic net (vol B 67, pg 301, 2005). *J R Stat Soc Series B Stat Methodol*. 2005;67:768.
22. Fan JQ, Lv JC. Sure independence screening for ultrahigh dimensional feature space. *J R Stat Soc Series B Stat Methodol*. 2008;70:849-883.
23. Schölkopf B, Smola AJ. *Learning with Kernels: Support Vector Machines, Regularization, Optimization, and Beyond*. MIT Press; 2002.
24. Breiman L. Random forests. *Mach Learn*. 2001;45:5-32.
25. Freund Y, Schapire RE. A decision-theoretic generalization of on-line learning and an application to boosting. *J Comput Syst Sci*. 1997;55:119-139.
26. Silver D, Schrittwieser J, Simonyan K, et al. Mastering the game of Go without human knowledge. *Nature*. 2017;550:354-359.
27. Krizhevsky A, Sutskever I, Hinton GE. ImageNet classification with deep convolutional neural networks. In: Pereira F, Burges CJC, Bottou L, Weinberger KQ, eds. *Advances in Neural Information Processing Systems 25*. Curran Associates, Inc; 2012:1097-1105.
28. Deng J, Dong W, Socher R, Li L-J, Kai L, Li F-F. ImageNet: A large-scale hierarchical image database. 2009 IEEE Conference on Computer Vision and Pattern Recognition; 2009;06:248-255.
29. Lin T-Y, Maire M, Belongie S, et al. Microsoft COCO: Common Objects in Context. In: Fleet D, Pajdla T, Schiele B, Tuytelaars T, eds. Computer Vision – ECCV 2014. Lecture Notes in Computer Science, vol 8693. Springer International Publishing; 2014:740-755. https://doi.org/10.1007/978-3-319-10602-1_48.
30. Menze BH, Jakab A, Bauer S, et al. The multimodal Brain Tumor Image Segmentation Benchmark (BRATS). *IEEE Trans Med Imaging*. 2015;34:1993-2024.
31. McKinney SM, Sieniek M, Godbole V, et al. International evaluation of an AI system for breast cancer screening. *Nature*. 2020;577:89-94.
32. Bakas S, Reyes M, Jakab A, et al. Identifying the best machine learning algorithms for brain tumor segmentation, progression assessment, and overall survival prediction in the BRATS challenge. arXiv preprint arXiv:181102629 2018.
33. Porwal P, Pachade S, Kokare M, et al. IDRiD: Diabetic retinopathy—segmentation and grading challenge. *Med Image Anal*. 2020;59:101561.
34. Data Science Bowl 2017. https://www.kaggle.com/c/data-science-bowl-2017.
35. Deep learning for genomics. *Nat Genet*. 2019;51:1.
36. Ronneberger O, Fischer P, Brox T. U-Net: convolutional networks for biomedical image segmentation. In: Navab N, Hornegger J, Wells WM, Frangi AF, eds. Medical Image Computing and Computer-Assisted Intervention - MICCAI 2015. Lecture Notes in Computer Science, vol 9351. Springer International Publishing; 2015:234-241. https://doi.org/10.1007/978-3-319-24574-4_28.
37. Guo CC, Bondaruk J, Yao H, et al. Assessment of luminal and basal phenotypes in bladder cancer. *Sci Rep*. 2020;10(1):9743.
38. Choi W, Porten S, Kim S, et al. Identification of distinct basal and luminal subtypes of muscle-invasive bladder cancer with different sensitivities to frontline chemotherapy. *Cancer Cell*. 2014;25:152-165.
39. Benjamini Y, Hochberg Y. Controlling the false discovery rate—a practical and powerful approach to multiple testing. J Roy Stat Soc Series B Stat Methodol. 1995;57:289-300.
40. Wang Z, Wei P. IMIX: a multivariate mixture model approach to association analysis through multi-omics data integration. Bioinformatics. 2021;36:5439-5447.
41. Akbani R, Ng PK, Werner HM, et al. A pan-cancer proteomic perspective on The Cancer Genome Atlas. *Nat Commun*. 2014;5:3887.
42. Cancer Genome Atlas Research Network; Weinstein JN, Collisson EA, et al. The Cancer Genome Atlas Pan-Cancer analysis project. *Nat Genet*. 2013;45:1113-1120.
43. Guo CC, Majewski T, Zhang L, et al. Dysregulation of EMT drives the progression to clinically aggressive sarcomatoid bladder cancer. *Cell Rep*. 2019;27:1781-1793, e4.
44. Yang G, Bondaruk J, Cogdell D, et al. Urothelial-to-neural plasticity drives progression to small cell bladder cancer. *iScience*. 2020;23:101201.
45. Guo CC, Dadhania V, Zhang L, et al. Gene expression profile of the clinically aggressive micropapillary variant of bladder cancer. *Eur Urol*. 2016;70:611-620.
46. Bao C, Lu Y, Chen J, et al. Exploring specific prognostic biomarkers in triple-negative breast cancer. *Cell Death Dis*. 2019;10:807.
47. Elshafeey NA, Adrada BE, Kotrosou A, et al. Radiomic phenotypes from ultrafast dynamic contrast enhanced (DCE) MRI for prediction of the treatment response to neoadjuvant systemic therapy (NAST) of Triple Negative Breast Cancer (TNBC).

Radiological Society of North America (RSNA) 2020 Annual Meeting (virtual); November 29-December 5, 2020.
48. Lambin P, Leijenaar RTH, Deist TM, et al. Radiomics: the bridge between medical imaging and personalized medicine. *Nat Rev Clin Oncol.* 2017;14:749-762.
49. Yang T, Wei P, Pan W. Integrative analysis of multi-omics data for discovering low-frequency variants associated with low-density lipoprotein cholesterol levels. Bioinformatics 2020;36(21):5223-5228.
50. Yang T, Wu C, Wei P, Pan W. Integrating DNA sequencing and transcriptomic data for association analyses of low-frequency variants and lipid traits. *Hum Mol Genet*. 2020;29: 515-526.
51. Shu H, Chiang T, Wei P, Do KA, Lesslie MD, Cohen EO, Srinivasan A, Moseley TW, Chang-Sen LQ, Leung JWT, Dennison JB, Hanash SM, Weaver OO. A Deep Learning Approach to Re-creating Raw Full-Field Digital Mammograms for Breast Density and Texture Analysis. Radiology: Artificial Intelligence. 2021;3(4):e200097. https://doi.org/10.1148/ryai.2021200097.
52. International Atomic Energy Agency. *Quality Assurance Programme For Digital Mammography*. Vienna: International Atomic Energy Agency; 2011.
53. Gastounioti A, Conant EF, Kontos D. Beyond breast density: a review on the advancing role of parenchymal texture analysis in breast cancer risk assessment. *Breast Cancer Res*. 2016; 18:91.
54. Burton A, Byrnes G, Stone J, et al. Mammographic density assessed on paired raw and processed digital images and on paired screen-film and digital images across three mammography systems. *Breast Cancer Res*. 2016;18:130.
55. Wang C, Brentnall AR, Cuzick J, Harkness EF, Evans DG, Astley S. A novel and fully automated mammographic texture analysis for risk prediction: results from two case-control studies. *Breast Cancer Res*. 2017;19:114.
56. Wang J, Azziz A, Fan B, et al. Agreement of mammographic measures of volumetric breast density to MRI. *PloS One.* 2013;8:e81653.
57. Milletari F, Navab N, Ahmadi S-A. V-Net: fully convolutional neural networks for volumetric medical image segmentation. 2016 Fourth International Conference on 3D Vision (3DV). 2016;10:565-571.
58. Jegou S, Drozdzal M, Vazquez D, Romero A, Bengio Y. The one hundred layers tiramisu: fully convolutional DenseNets for semantic segmentation. Proceedings of the IEEE Conference on Computer Vision and Pattern Recognition Workshops; 2017:11-19.
59. Aresta G, Araújo T, Kwok S, et al. BACH: grand challenge on breast cancer histology images. *Med Image Anal*. 2019;56:122-139.
60. Goecks J, Jalili V, Heiser LM, Gray JW. How machine learning will transform biomedicine. *Cell.* 2020;181:92-101.
61. Zhang NS, Wu J, Yu JM, Zhu H, Yang M, Li RJ. Integrating imaging, histologic, and genetic features to predict tumor mutation burden of non-small-cell lung cancer. *Clin Lung Cancer*. 2020;21: E151-E163.
62. Arulkumaran K, Deisenroth MP, Brundage M, Bharath AA. Deep reinforcement learning: a brief survey. IEEE Signal Processing Magazine. September 28, 2017.
63. Luo Y, Peng J, Ma J. When causal inference meets deep learning. *Nat Mach Intell*. 2020;2:426-427.
64. Nguyen ND, Nguyen T, Nahavandi S, Bhatti A, Guest G. Manipulating soft tissues by deep reinforcement learning for autonomous robotic surgery. 2019 IEEE International Systems Conference (SysCon). 2019;04:1-7.
65. Tan X, Chng C-B, Su Y, Lim K-B, Chui C-K. Robot-assisted training in laparoscopy using deep reinforcement learning. *IEEE Robot Autom Lett*. 2019;4:485-492.
66. Stahl BC, Coeckelbergh M. Ethics of healthcare robotics: towards responsible research and innovation. *Rob Auton Syst*. 2016;86:152-161.
67. Sharma A, Gupta G, Prasad R, Chatterjee A, Vig L, Shroff G. Hi-CI: deep causal inference in high dimensions. Proceedings of the 2020 KDD Workshop on Causal Discovery; 2020 2020/08/19/: PMLR. p. 39-61.

This page intentionally left blank

71 Value-Based Oncology

Casey J. Allen
Aileen Chen
Ryan W. Huey
Ya-Chen Tina Shih

KEY CONCEPTS

- As the demand to curb costs and improve the quality of cancer care increases, cancer care delivery should align with patients' value and preference.
- Value assessment is of paramount importance to the delivery of value-based cancer care effectively and efficiently.
- There are evolving value-based practices specific to the fields of medical, radiation, and surgical oncology.
- To serve the need for value assessment in today's health care environment, there is ongoing development of various value frameworks.
- Management science and health economics and outcomes research both contribute to value assessment frameworks.
- Our ability to effectively communicate value will facilitate shared decision making among all stakeholders involved in value-based health care.

OVERVIEW OF VALUE-BASED HEALTHCARE

As projections indicate that healthcare spending will account for nearly one-fifth of the Gross Domestic Product in the United States in 2021, the rate at which healthcare costs are growing will limit our country's growth and possibly even bankrupt the nation.[1] Cancer care in particular is of great concern because of its relatively high costs to deliver treatment. Furthermore, cancer care costs are expected to grow 40% from 2010 to a projected $175 billion in 2020.[2]

The rising cost of cancer care impacts many stakeholders including patients and their families, providers, payers, and manufacturers. If the costs of cancer care continue to rise unchecked, it will be become unaffordable for many Americans—a concern raised by an Institute of Medicine (now National Academies of Sciences, Engineering, and Medicine) consensus study in 2013.[3] Financial hardship, or financial toxicity, describes the impact of direct and indirect healthcare costs that lead to significant financial burden for patients and their caregivers, resulting in increased psychosocial distress, worse outcomes, and poorer quality of life (QOL).[4,5] In addition, as specialized cancer care continues to become more centralized, one well-recognized disadvantage is the limited access to high-quality care in patients with low socioeconomic status.[6–8] Barriers to access treatment may impact patient-centric outcomes.

Moreover, there is now widespread recognition that high-cost care does not necessarily translate into high-quality care or improved outcomes. The per capita healthcare spending in the United States far exceeds that in other developed countries, yet when juxtaposed against life expectancies, it is clear there is a great deal of wasted expense in our healthcare system.[9]

As the demand to curb costs and improve quality increases, there is a societal consensus that healthcare should be more greatly assessed on value. Thus, the United States healthcare system is now in the midst of transitioning to a value-incentivized system.[10] As policymakers and those covering the costs (insurers and patients) seek ways to assure the best use of limited resources, they are turning to business leaders, physicians, and health economists for a better understanding—and definition—of value. There is a growing understanding that true healthcare reform will require major strategic and organizational changes in the way healthcare is actually measured, delivered, and reimbursed.[11,12] Also, because the federal government and individual states are beginning to mandate insurers

and providers to improve price transparency by offering patients information about their healthcare costs,[13] patients will likely want to be more actively engaged in their interactions with clinicians to ensure that the treatment choice aligns with their value and preference.

CONCEPTUAL FRAMEWORK OF VALUE ASSESSMENT

Value Assessment from Management Science Approach

The value-based healthcare movement is based on the work of leading authorities on competitive business strategy Michael E. Porter and Elizabeth O. Teisberg. Their landmark book, *Redefining Health Care Creating Value-Based Competition on Results*,[14] was published after more than a decade of research into why the healthcare industry failed to conform to the standard economic principles of competition. They described how healthcare had fallen into dysfunction as providers competed for the wrong things. Value-based healthcare's central tenet is that value for patients must be the overarching principle in the organization and management of healthcare delivery systems.

The Value Equation

As originally proposed by Porter and Teisberg, "value" for patients is determined by assessing the relationship between the outcomes that matter to them and the cost incurred to deliver those outcomes across the full cycle of care.[14] To capture the multiple dimensions of a patient's health, they proposed the concept of a three-tiered outcome measures hierarchy.[14,15] This hierarchy highlights the importance of survival but also accounts for degree of recovery, time to recovery, harm caused during treatment, recurrences, and long-term consequences of care.

The Expanded Value Equation

Adhering to Porter's principles, MDACC has favored a definition that integrates the outcomes component of the value framework with traditional quality, safety, and patient experience measures.[16] Our detailed equation incorporates the dimension of time by including short-term complications with long-term disability, and both early and late survival with functional recovery. It also expands the definition of cost to include the costs to both payers and patients. As depicted in Equation (1), our value equation includes components specified to metrics of quality (survival, functional recovery, experiences); harm/safety (complications, pain, disability); and/or cost (patient-borne, third-party payer, institutional).

$$VALUE = \frac{QUALITY\ (survival,\ functional\ recovery,\ experience) - HARM/SAFETY\ (complications,\ pain,\ disability)}{COSTS\ (institutional,\ patient,\ payer)} \quad EQ(1)$$

Value Assessment from Health Economics and Outcomes Research Approach

Recognizing the urgent need for better understanding and assessing value in today's healthcare environment, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), a leading organization in health economics and outcomes research (HEOR), formed a Special Task Force on Value Assessment in 2016.[17] A series of reports from this ISPOR Special Task Force, alone with other articles covering the conceptual, theoretical, empirical, and practical aspects of value assessment, were published in a themed issue in *Value in Health* in 2018.[18] In this section, we provide a broad overview of value assessment from the HEOR approach. Readers who are interested in deeper learning on this topic are encouraged to read this themed issue.

Elements of Value

The biggest challenge in value assessment is to define "value" because the word is inherently subjective and multifaceted. HEOR experts acknowledged 12 elements of value: (1) quality-adjusted life-years (QALYs); (2) net costs; (3) productivity; (4) adherence-improving factors; (5) reduction in uncertainty; (6) fear of contagion; (7) insurance value; (8) severity of disease; (9) value of hope; (10) real option value; (11) equity; and (12) scientific spillovers.[19] QALY is a measure that weighs life-years (LYs) gained from interventions with health utility associated with various health states in that duration, with weight 1.0 giving to perfect health and 0 to death. Net costs refer to the additional (or incremental) cost associated with a new intervention compared with alternative(s)—often the current standard of care. QALYs and net costs are the two value elements most commonly found in value assessment in HEOR because they form the basic components of cost-effectiveness analysis (CEA). Productivity captures health-related work impairment and consists of two components: absenteeism and presenteeism. The former quantifies time absent from work because of illness, whereas the latter measured reduction in the quality of work performed when coming to work while sick.[20] Adherence-improving factors reflect value through improving health outcomes as a result of better adherence to treatment, which can be achieved with certain product features (eg, switch medications from twice daily to once daily) or technologies (eg, MEMS® Cap device). In the context of oncology value assessment, all four value elements discussed above are important to consider.

The remaining eight elements of value are relatively underexplored in the HEOR literature; several are especially relevant in the discussions of value-based oncology. For example, the value of an intervention can be enhanced by reducing uncertainty in outcomes (element #5) with the use of tests or algorithms to identify subgroups most likely to benefit from an intervention (eg, pharmacogenomic tests to better differentiate responders and nonresponders of certain chemotherapy regimens or risk-stratified screening strategies). Severity of disease (element #8) debates whether the value of an intervention differs by the severity of disease intended for the intervention, raising the question of whether higher values should be placed on end-of-life care or treatment of late-stage cancers. Value of hope (element #9) is especially relevant when comparing values between two oncology products: a high-risk treatment with a small chance of achieving large survival benefit versus a lower-risk treatment with moderate survival benefit. Real option value (element #10) refers to the situation in which life extended from a treatment creates an opportunity for patients to benefit from treatment advances in the future. With a large pipeline of oncology products, this value element is particularly meaningful. Indeed, research has found that the inclusion of option value increases the value of treatment for chronic myeloid leukemia by 10%.[21] The other elements are equally applicable to oncology as well as other diseases. Interestingly, fear of contagion (element #6) is traditionally thought to be more relevant to infectious diseases and less relevant to oncology. However, current experience with a highly contagious virus like Covid-19 sounded the alarm that value assessment of oncology may need to consider the overall public health environment and how cancer care interacts with other diseases in such an environment.

Methods to Quantify Value

The ultimate goal of value assessment is to assist stakeholders in making informed decisions. The transition from "value framework" to "decision making" requires methods that synthesize and quantify information into a metric useful to decision makers. Two commonly used approaches to generate such metric is CEA and multicriteria decision analysis (MCDA).

Cost-Effectiveness Analysis

CEA summarizes study findings in terms of the incremental cost-effectiveness ratio (ICER).[22,23] The ICER, as shown in Equation (2) below, estimates the additional resource consumption needed to achieve an increase in an additional unit of effectiveness, often measured by LYs saved or QALYs gained.

$$ICER = \frac{E(COST_{NEW}) - E(COST_{OLD})}{E(EFFECTIVENESS_{NEW}) - E(EFFECTIVENESS_{OLD})} \quad EQ(2)$$

Incremental cost, the numerator of ICER, calculated the difference in the mean cost of the new treatment and that of the old (existing) treatment. Incremental effectiveness, the denominator of ICER, is the difference in the mean effectiveness of the new treatment and that of the old treatment. The ICER is then compared with a threshold value; an intervention is considered cost-effective if the ICER is below the threshold value. Although many countries have explicitly specified the threshold value acceptable for the new treatment,[24] there is no threshold value published by the US government. A survey of medical oncologists in the US and Canada indicated that the majority of oncologists considered $100,000/QALY an acceptable threshold value.[25] A review of economic evaluation methods in the context of oncology can be found in an article published in *CA: A Cancer Journal for Clinicians* in 2008.[26] More recently, researchers have extended the conventional CEA to incorporate broader topics of interest to health policymakers, such as equity, distributional benefits, and financial protections.[27,28]

The value equation proposed by Porter and Teisberg[14] resembles the concept of average cost-effectiveness ratio (ACER) in the HEOR literature. The ACER quantifies the average cost per effect for an intervention, whereas ICER emphasizes the concept of incremental efficiency that captures the additional costs consumed to gain an additional unit of effectiveness. It is generally agreed in the HEOR literature that ICER is supported by economic theories and better reflects the nature of decision making in that decision makers often determine the value of a new treatment by comparing its improvement in outcomes as well as the additional costs with the existing treatment. It has been documented that ACER can lead to the wrong choice in healthcare decision making.[29]

Multicriteria Decision Analysis

One of the key requirements in CEA is to explicitly specify the study perspective, with societal perspective being the preferred choice.[30] However, this single-metric approach creates a challenge for decision makers to incorporate the viewpoints from multiple stakeholders simultaneously. MCDA is an emerging approach in HEOR that offers an analytical framework to explicitly incorporate the subjective and multidimensional features of value into decision making.[31] MCDA involves four key steps to prepare the data for decision makers. First, researchers need to determine the elements of value to be considered. For example, the value elements for oncology care may include median survival,

progress-free survival, toxicity profile (eg, nausea/vomiting, anemia, febrile neutropenia), pain, anxiety, total cost of treatment, and out-of-pocket cost for patients, among others. The next step is to define the boundary values for each of these value elements or "attributes." For some attributes, it is obvious that the boundary values would have to be confined within a range that meets the statistical property of that attribute, such as probabilities are bound between [0,1] range. For other attributes, such as costs, the boundary values are less obvious and will rely on additional research to determine these values. Next, scores need to be assigned to each attribute based on each patient's preference through some forms of value function. The last step is to solicit weights for each attribute. One approach is to simply ask stakeholders to rank order the attributes and convert the ranking into weights using methods such as the rank order centroid method.[31] For ease of illustration, assume that there are three treatments (X, Y, and Z), three patients (A, B, and C), and three attributes: probability of 5-year survival, probability of severe side effects, and costs. Using the rank order centroid method and in the case of three attributes, the weight for each attribute, ranked by the order of importance, is calculated as (1+1/2+1/3)/3 (~0.61), (1/2+1/3)/3 (~0.28), and (1/3)/3 (~0.11), respectively.

After completing the first two steps described above, results can be summarized in the input table for MCDA (Table 71–1A), followed by soliciting preference scores for each patients (Table 71–1B). A patient's value for each treatment can then be calculated by taking the weighted average across attribute values (Table 71–1C). As an emerging method, many methodological details of MCDA are still under development, such as the scoring algorithm for the attributes and the weighting methods. The most critical issue is the decision rule to determine which treatment/intervention yields highest "value" at the population level. As shown in Table 71–1C, although the treatment choice of each patient is clear, the best choice for the society as a whole may not be obvious. Readers who are interested in learning more about MCDA are recommended to read the task force reports by ISPOR MCDA Emerging Good Practices Task Force.[32,33]

Value Assessment in Oncology

Cancer care is an opportune context in which to target value-based healthcare delivery. As clearly stated by the President of the American Society of Clinical Oncology (ASCO) in 2014, Dr Clifford A. Hudis: "*In oncology, we face the fascinating challenge of determining the value of today's cancer treatments….What is the worth … of three or four more weeks of time … relative to the cost and side effects of the treatment? … The answers to these kinds of questions may vary widely among different patients, families, healthcare providers, and communities, but we must confront these difficult issues with courage, compassion, and integrity.*"[34]

Value assessment is of paramount importance to the delivery of value-based cancer care effectively and efficiently. Despite the desire to transition into a value-driven system, our capability of quantifying value is in flux and there had been no objective way to quantify and communicate the many outcomes and cost components of value to patients, stakeholders, or healthcare providers. For these reasons, frameworks have been developed to provide a comprehensive measure of healthcare value.

Value frameworks have gained broader use in the field of oncology. The benefits of new and promising therapies might not necessarily be uniformly distributed. When considering a cancer treatment—especially one that could financially imperil a patient—a value framework has become critically important. This environment of increasing costs of drugs and healthcare services (and increased patient cost sharing) versus inconsistent benefits propelled the development of various cancer-focused value frameworks. Herein we detail some existing value frameworks in oncology, and propose the advantages of new, theoretical models.

The American Society of Clinical Oncology Value Framework

ASCO has proposed assigning a numeric score, Net Health Benefit (NHB), to cancer treatments based on an assessment of their clinical benefit, side effects, associated symptoms, effect on QOL, and costs.[35] The framework determination, on the basis of consensus among framework developers, is weighted most heavily by clinical benefit, with overall survival being the most important, progression-free survival less important, and response rate the least important. The framework also includes bonus points for extended survival to reflect "tail of the curve" survival for those therapies that benefit only a meaningful minority, but that help those few patients tremendously. Toxicity is included as a liability and detracts from the clinical benefit. Finally, the patient's out-of-pocket costs (a major source of financial toxicity) are also included in the value framework.

The National Comprehensive Cancer Network Evidence Blocks

The National Comprehensive Cancer Network Evidence Blocks (NEB) proposed by the National Comprehensive Cancer Network (NCCN) presents assessments of treatments as a visual matrix.[36] Guided by staff from the NCCN, in consultation with the group's members, their approach uses a standardized scale to provide consensus-based scoring of efficacy, safety, quality of evidence, and costs of a particular treatment. Each of the five measures in the NCCN's approach is displayed as a solid block using a scale from 1 to 5, where 1 is

Table 71–1 Example of Multicriteria Decision Analysis

A: Inputs of MCDA

		Attributes		
		5-year survival prob (0–1)	Prob. of side effect (0–1)	Cost ($5000–$300,000)
Treatment option	Treatment attribute values			
	X	0.8	0.7	$30,000
	Y	0.6	0.4	$10,000
	Z	0.2	0.1	$5,000
Patient	Patient rankings (weights) of attribute			
	A	1 (0.61)	2 (0.28)	3 (0.11)
	B	2 (0.28)	3 (0.11)	1 (0.61)
	C	3 (0.11)	1 (0.61)	2 (0.28)

B: Preference score for Patient A–C

	Attributes		
Treatment Option	5-year survival prob (0–1)	Prob. of side effect (0–1)	Cost ($5,000–$300,000)
Patient A			
X	80	20	30
Y	40	30	20
Z	20	40	10
Patient B			
X	40	10	10
Y	30	20	50
Z	20	30	80
Patient C			
X	60	10	30
Y	55	65	48
Z	10	70	50

C: Patient Value by Treatment Option

	Treatment X	Treatment Y	Treatment Z
Patient A	**57.7**	35	24.5
Patient B	18.4	41.1	**57.7**
Patient C	21.1	**59.14**	57.8

Note: For each patient, the bold entry marks the treatment option that yields the highest value for the patient.

considered least favorable and 5 is most favorable. An example of the NEB is depicted in Fig. 71–1. Here we provide a theoretical comparison of "Drug A" versus "Drug B." "Drug A" scores better on efficacy and quality of evidence; however, "Drug B" scores better on safety and affordability. The total "score" for "Drug A" is 15 and the total "score" for "Drug B" is 16, thus inferring "Drug B" is the superior choice. However, if a patient or provider seeks the more efficacious drug (over safety and affordability), "Drug A" may be the preferred treatment. Therefore, although the NEB creates a robust comparison, the preference of the stakeholder is not incorporated into the comparative capabilities of the framework.

Here we reference other existing value frameworks in oncology including Memorial Sloan Kettering Cancer Center's DrugAbacus tool,[37] the Institute for Clinical and Economic Review's Value Assessment Framework,[38] and the European Society for Medical Oncology (ESMO)'s Magnitude of Clinical Benefit Scale.[39]

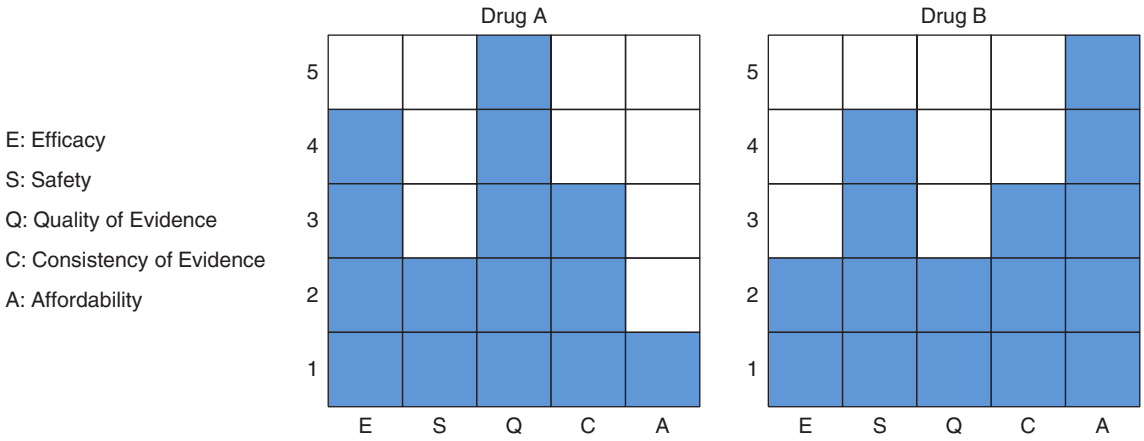


FIGURE 71–1 **Example of NCCN Evidence Blocks (NEB), comparison of "Drug A" versus "Drug B".**

Novel Framework with Use of Radar Charts

To address limitations of existing value frameworks, and to promote adoption through a more robust tool, a group of investigators at MDACC have developed a novel, alternative framework to visualize and communicate value. With so many individual components in the value equation, we found that data visualization is absolutely crucial to all stakeholders. A radar chart is a graphic method of displaying data in which quantitative variables are represented on multiple axes. The simple radar chart is a practical tool with which to improve shared decision making between stakeholders because it provides clinicians, patients, administrators, and policymakers with a readily understandable snapshot that can facilitate value assessment. At MDACC, we have embraced the utility of radar charts as a novel framework to effectively measure and communicate value,[40] most recently reporting how the implementation of clinical care pathways for patients undergoing pancreatectomy provides an overall value advantage by improving several metrics (Fig. 71–2).[41]

Although each of the value frameworks discussed above has targeted patients, physicians, and/or payers using a unique interpretation of value, the relevance of each of the frameworks to stakeholders will depend on their adoption. Factors that may drive framework adoption include appreciation for real-world evidence, the relation of cost to affordability, ability to accurately estimate costs, transparency regarding the quantification process, and the framework's applicability to individual decision making.

Limitations of How We Currently Assess Value

Despite the major advancement in value assessment, there remain multiple limitations to how we effectively assess total value. The ASCO NHB score is useful, but the extent to which value can be summarized by a single number using data generated across multiple dimensions is unclear. Furthermore, there is currently no reason to believe that total value would be accurately represented by the linear sum of such metrics. The NEB from the NCCN attempts to address these limitations by quantifying consensus-based scores of various value elements, but it does not provide a final summation directly from data that reflect stakeholders' differential preferences across value elements. Neither the NCCN's nor the ASCO's framework is optimized to allow visualization of value from the perspective of different stakeholders. The radar chart may be different in that it facilitates intuitive understanding of value differences through robust graphic depiction of actual data across multiple metrics and can compare alternate processes within a single figure. Still, future research is needed to guide not only the selection of metrics used by different stakeholders, but also how stakeholders' preferences may be reflected into more aggregate indexes of value.

There are also important limitations to our current abilities to quantify many domains considered in value assessment, although several domains can be measured using data readily available in electronic health records, registries, hospital billing records, and/or insurance claims. However, other metrics—especially patient-reported outcomes (PROs) such as pain measures, functional outcomes, QOL, and measures of financial toxicity—are not routinely available. Also challenging is the ability to accurately estimate out-of-pocket expenses given the sophistication of insurance benefit designs and the complexity of cancer care.[42]

For practical reasons, many value assessments are assessing process measures, and the assessment often takes place at a snapshot in time, often at the beginning of treatment. For many cancers, it can take many years to observe outcomes such as survival and long-term

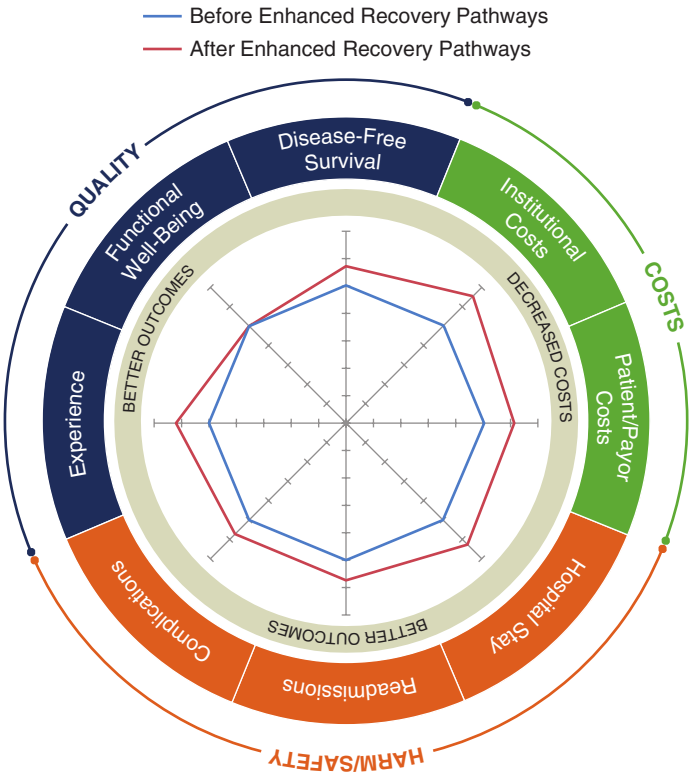


FIGURE 71–2 **Radar chart comparing value before and after implementation of risk-stratified clinical care pathways for patients undergoing pancreatectomy for pancreatic adenocarcinoma. Post-implementation metrics are displayed using relative change from an index value. Blue depicts quality metrics, green depicts cost metrics, and orange depicts harm/safety metrics. (Reproduced with permission from Allen CJ, Thaker NG, Prakash L, et al: Communicating Value: Use of a Novel Framework in the Assessment of an Enhanced Recovery Initiative, *Ann Surg* 2021 Jan 1;273(1):e7-e9.)**

treatment-related toxicities, and by that time treatment has been administered and paid by payers and patients. This suggests the need to incorporate long-term outcomes data as one of the metrics in value assessment. Finally, many factors beyond the control of providers can contribute to outcomes such as survival and financial toxicity; these factors introduce uncertainties in value assessment. How to address uncertainties is an underexplored area in value assessment and value communication.

Opportunities and Challenges of Using Administrative Claims Data to Aid Value Assessment

With the rising importance of data-driven decision making, administrative claims data are emerging as valuable tools in assessing value in hopes of improving healthcare delivery. These data sets provide the information from which companies including *US News & World Report*[43] and The Leapfrog Group[44] rank and compare hospitals across the country. In addition to private groups, the Center for Medicare and Medicaid Services (CMS) is working in collaboration with consumers, hospitals, doctors, employers, accrediting organizations, and other federal agencies to develop Hospital Compare, a publicly available data source informing the quality of care of more than 4000 Medicare-certified hospitals across the country.[45] Multiple stakeholders can utilize Hospital Compare to identify and compare the value of their own care delivery.

These administrative data sets are available from a myriad of sources including hospitals, payers, data organizations, departments of health, and federal agencies, and can act as tools to identify areas in which to improve healthcare delivery. Many quality measures are created using hospital administrative discharge data. Administrative claims data make it possible to identify individuals or cohorts who meet specific inclusion/exclusion criteria, define episodes of care, estimate costs, measure outcomes,[46] and present advantages over other data sources (eg, single-institution data, trials or surveys) because of its larger sample size, completeness, and availability. For inpatient care, these data provide patient demographics, diagnoses, procedures, discharge status, length of hospital stay, as well as estimated hospital costs, charges, and patient out-of-pocket payments; and they have been shown to be more accurate than data collected through

qualitative means.[47] This can help providers access complete, accurate, and longitudinal clinical data along the care continuum. Quality experts regard claims data as a reliable and usable source for the purpose of assessing hospital quality.[37] For cancer care overall, the linked Surveillance, Epidemiology, and End Results Program (SEER)-Medicare data offer unique opportunities to examine treatment patterns, costs, and outcomes for Medicare beneficiaries diagnosed with cancer.[48]

Despite the reliability and widespread uses of claims data, they also have important limitations. Administrative data are primarily used to support the billing process and often do not contain detailed clinical information, thus lacking important value measures. Long-term survival is not available in some administrative claims data, especially those from private insurance companies. PROs including pain measures, functional outcomes, and QOL are not available, regardless of the source of claims. There is also no formal system to accurately report costs of care to all stakeholders. Although we have a partial surrogate for payer and patient costs through variables of charges and/or payments, the majority of the financial burden (financial toxicity) of treatment is not currently measured. Some major organizations are already making these realizations. For example, the Oncology Care First Model, as recently proposed by CMS, mandates hospitals to collect PROs along with all other outcome and cost metrics.[40]

As we continue to use administrative claims data in our assessment of value-based healthcare, we need to emphasize the importance of collecting and reporting more long-term and patient-centric outcomes.

Future Endeavors

The ultimate goal of these efforts is to engage patients, caregivers and providers with data to make informed decisions regarding their care. Cancer treatment can often be physically taxing, emotionally draining, and financially toxic to patients. Bringing the patient into the conversation about their care allows treatment to be reframed from the patient's perspective based on their value, preference, and priorities in life. To the extent that patients are increasingly engaged in their healthcare,[41] it is critical that the patient perspective is accurately reflected by any value measurement. By also communicating value in a manner that is accessible to all stakeholders, better decision making will aid in the continual effort to deliver better value to patients.

Thus, in order to enhance the value of care, interventions should aim at improving end points that matter to patients. Gathering reliable and valid QOL data, designing patient preference studies that use reliable and generalizable methods, and using the results to develop decision aids for shared decision-making strategies are recommended going forward.

Until we have access to multiple disparate outcomes, each measured routinely and reliably, it will be difficult to assess the total value of any care process. As we develop better data, our ability to effectively communicate value will facilitate shared decision making among all stakeholders involved in value-based healthcare.

VALUE-BASED ONCOLOGY IN PRACTICE

Value-Based Practice in Medical Oncology

As the cost of oncology drugs continues to increase, the notion of value-based care has become increasingly important. Historically, data on survival and QOL have been the most important factors in the choice of systemic therapies. However, financial toxicity has been increasingly recognized as an important factor for patients.[49]

Efforts to promote value-based care in medical oncology have centered on physician-patient conversations about cost, drug pricing and reimbursement models, standardization of practice patterns, and the elimination of low-value care.

Price Transparency/Conversations About Cost

Attitudes surrounding discussing the cost of cancer care differ among patients and oncologists. The majority of patients are interested in discussing costs of cancer care, but oncologists are less comfortable with these conversations.[50] Although cost communication is recognized by the ASCO Cost of Cancer Care Guidance Statement[51] and the Institute of Medicine Committee on Improving the Quality of Cancer Care[3] as an essential component for high-quality cancer care, a recent review article showed low prevalence of cost communication reported by patients and physicians (27% and 47%, respectively).[52] In addition, some oncologists consider the value of a treatment only if it poses a significant financial burden to the patient.[53] However, these conversations remain important, because financial toxicity has important implications not only for a patient's QOL, but data suggest some patients skip doses of oral chemotherapy to reduce the burden of prescription refills or copayments, which could ultimately compromise the efficacy of a treatment.[54] Furthermore, the lack of price transparency both to patients and providers remains a substantial barrier, because this information is crucial for informing patient-provider discussions.[42,55] Recent public policy has focused on making the prices of cancer treatment services available to patients, but a lack of standardization has made it difficult to interpret such data, and more work is needed to provide value to patients.[56]

Drug Pricing

Although one may expect the introduction of competitor drugs or generic drugs to result in lower prices, in oncology this is not necessarily the case, and the opposite is often true.[57] In fact, studies exploring the drug prices of targeted oral anticancer medications have reported a trend toward not only higher prices at launch over time but also a sustained increase in prices post-launch.[58–60] Health policy plays a role in drug pricing, because Medicare is required to cover drugs approved by the Food and Drug Administration but is not allowed to negotiate drug prices. Reimbursement structures are also important for drug pricing, and the notion of value-based drug pricing has gained momentum in recent years. Value-based drug pricing is a concept that centers around tying the price of a drug to its efficacy or outcomes for a specific indication.[61] For instance, some have suggested that if a drug has multiple indications for use (eg, in multiple cancers), then its price should be tied to the clinical benefit it provides to a specific set of patients. Another proposed payment model is outcomes-based, in which a pharmaceutical company only receives reimbursement for a drug if the patient has a favorable outcome. CMS explored using outcomes-based pricing for the chimeric antigen receptor T-cell therapy Kymriah, but ultimately suspended the payment deal before launch.[62] Future efforts by policymakers and payers will continue to focus on innovative payment and drug reimbursement models.

Value Pathways and Drug Formularies

Standardization of physician practice patterns has emerged as an important method to improve quality and reduce cost. In oncology, providers and payers are increasingly using clinical pathways.[63] These clinical pathways use a variety of tools to promote guideline-concordant, evidenced-based care. One component typically involves a committee of experts in a field who review clinical benefit, toxicities, and cost of drugs to develop recommendations and/or algorithms. A common second component is a decision-support tool with electronic health record integration that assists providers in making clinical decisions, providing education and recommendations at the point of care. Clinical pathways have been demonstrated to reduce costs while maintaining or improving outcomes.[64,65]

Drug formularies can also play an important role in the utilization of drugs and in some instances can affect pricing as well. A notable example was highlighted in an op-ed in *The New York Times* by a group of physicians at Memorial Sloan Kettering Cancer Center who detailed a new cancer drug that had similar efficacy and mechanism of action to other drugs but was more than twice the cost.[66] This gained significant attention and criticism directed at the pharmaceutical company, which subsequently announced a price reduction for the drug.[67] Drug formularies are important for helping to determine the utilization of a drug, but price reductions based on well-publicized articles in the media are the exception rather than the norm.

Choosing Wisely

In 2012, the Choosing Wisely initiative was launched by the American Board of Internal Medicine Foundation in partnership with several specialty societies, with the goal of helping reduce waste in the US healthcare system.[68] ASCO was one of the specialty societies to join this initiative, and over the next 2 years created a Top 10 List of "Things Physicians and Patients Should Question," identifying and discouraging the use of low-value tests and interventions for patients with cancer.[69,70] Of these 10 items, four relate to the use of imaging, three address indications for chemotherapy, two focus on supportive care medicines such as antinausea drugs or hematopoietic growth factors, and one discusses cancer screening. The goal of the Choosing Wisely initiative is not to restrict necessary and appropriate care, but rather to highlight evidence and educate physicians and patients regarding the use of low-utility tests and interventions.

Value-Based Practice in Radiation Oncology

Radiation oncology represents approximately 4% of overall cancer spending and, similar to overall cancer spending, increased by 62% from 2004 to 2014.[71] The primary drivers of radiation cost from the payer's perspective include: (1) costs associated with radiation technologies used, and (2) number of radiation treatments delivered. Furthermore, there can be downstream costs associated with radiation, including management of toxicities from treatment. In addition to direct costs of care, patients may also incur substantial costs from daily radiation treatments, such as travel costs and time lost from work for patients and their family or friends who accompany patients to their radiation treatment. The most commonly measured treatment outcomes, as with other treatment modalities, include cancer-specific outcomes, such as overall survival, as well as treatment toxicity and QOL. Though there have been efforts to define standard sets of cancer outcomes for the purpose of measuring value, these have not yet been widely adopted.[72]

Radiation Technologies

Although value-based practice in radiation oncology shares many features with both medical and surgical

oncology, the adoption of high-cost technologies is of particular importance. The delivery of radiation therapy is a multistep process involving simulation, treatment planning, and radiation delivery, each with a variety of technological options associated with different costs. Unlike for most chemotherapy and drugs, the introduction of many new technologies in radiation oncology have not been subject to the same rigorous approval process. In the past, Medicare has covered new technologies, such as intensity-modulated radiation therapy (IMRT), based on promising dosimetric and clinical studies, but before large, randomized studies comparing its effectiveness with that of conventional radiation therapy.[73]

In many cases, comparative effectiveness studies may not be feasible without incurring high upfront fixed costs, often largely borne by providers. An example of this was the adoption of proton therapy, which required the construction of proton therapy centers, with costs that exceeded $100 million. However, it was not until a critical mass of proton therapy centers were built that large-scale multi-institutional trials could be performed, leading to a conflict between the need for evidence before coverage versus the need for coverage to support evidence development.[74]

The multistep process of radiation therapy can also make clean comparisons of new technologies challenging, and technologies may become outdated by the time randomized studies are completed. For example, a randomized study comparing proton therapy with photon therapy for lung cancers failed to show a difference in toxicity or local failure,[75] which was a surprise to many proponents of proton therapy. However, on closer examination, the trial was not a straightforward comparison of protons versus photons, because at the time, more advanced treatment planning and imaging technologies were available to patients undergoing photon IMRT versus patients receiving proton IMRT. Additional trials are now underway evaluating more modern proton techniques.

Number of Radiation Treatments

Though most curative intent radiation regimens have a fairly standard number of treatments, there has been recent interest in decreasing the number of treatments delivered, or hypofractionation, in a number of cancer types, with most studies supporting the efficacy and safety of this approach.[76–78] This has the potential benefit of reducing costs to both payers and patients. For palliative intent treatments, there is considerable provider discretion in the number of treatments delivered. Reducing the use of extended fractionation for the treatment of bone metastases has long been a target of value-based efforts in radiation oncology, with multiple guidelines, including a National Quality Foundation (NQF 1822) measure, all supporting shorter regimens than what is commonly being done.[79–82] The NQF measure has been adopted by the CMS programs that provide financial incentives for reporting data on care quality.

Value-Based Payments Models in Radiation Oncology

The traditional fee-for-service payment model incentivizes both the use of high-cost technologies and a greater number of radiation treatments. Value-based payment models seek to increase physician accountability and risk for cancer spending. Though there have been a variety of models proposed in radiation oncology, the most common are described below:

Guidelines, Clinical Pathways, and Quality Measures

The primary goal of most guidelines, clinical pathways, and quality measures is to improve physician accountability and reduce variation in care. Examples of such efforts in radiation oncology include clinical guidelines issued by NCCN, the Choosing Wisely initiative, and the American Society for Radiation Oncology (ASTRO). Increasingly, payers are using these guidelines and pathways to determine coverage of care and to provide financial incentives to providers.[83,84] However, a frequent challenge is that use of pathways and guidelines may result in burdensome reporting requirements and lag new developments in clinical practice.

Episode-Based Payment Models

Episode-based payment models in radiation oncology aim to increase the proportion of financial risk providers bear for costs of care and to incentivize lower-cost care while maintaining quality standards.

Radiation oncology has been incorporated both into broader condition-based models, as well as radiation modality–specific models. One example of a cancer condition–based model is the United Healthcare and MDACC bundled payment pilot in patients with head and neck cancer, which included multidisciplinary oncology care over a one-year period.[85] Another example is the Oncology Care Model, a voluntary episode-based payment program sponsored by the CMS, which is centered on 6-month chemotherapy episodes and incorporates total costs of care during the episode, including radiation therapy.[86] One challenge of this model is that benchmarks are based on total costs of care, which oncologists may not be able to fully control. Furthermore, the model could potentially introduce disincentive to care that is not well-captured by quality measures, such as palliative radiation. More recently, the Oncology Care First Model has been proposed as a successor to the Oncology Care Model, with a target start date in 2021.[84]

Radiation modality–specific episode-based models have previously been developed between individual payers and radiation therapy practices.[87] Nationally, a Radiation Oncology Model has been announced by the CMS to test a prospective episode-based payment model, with a target start date in 2022. Participation in the model would be mandatory for radiation oncology providers in selected Core-Based Statistical Areas for 17 different cancer types. Provider payments would be based on 90-day episodes of care and linked to reporting and performance on quality measures. The goal would be to test whether episode-based payments lead to shorter courses of treatment and higher-value care delivery in radiation oncology, while allowing providers flexibility for individual patients.[88]

Value-Based Practice in Surgical Oncology

Because cancer surgery may frequently be associated with large physical, emotional, and financial demands, with often only a marginal survival benefit, the determination of value is prominent in this setting. Within the field, most recent efforts to improve perioperative outcomes and cost are through the development of enhanced recovery protocols and through preoperative optimization with prehabilitation programs.

Enhanced Recovery and Prehabilitation

Enhanced Recovery After Surgery (ERAS) is an evidence-based, multimodal, multidisciplinary approach to the care of the surgical patient. In short, the goal of any ERAS process is to achieve early recovery for patients undergoing major surgery. ERAS process implementation involves a team consisting of surgeons, anesthesiologists, nurses, and staff from units that care for the surgical patient. It has been shown that, regardless of the surgical site, ERAS programs result in major improvements in clinical outcomes and cost,[88] making ERAS an important example of value-based care applied to surgery.

Although cancer surgery may be curative, the efficacy of surgery depends heavily on whether patients' performance status and functional fitness will allow for successful postoperative recovery. Frailty is seen in patients with gastrointestinal malignancy and is a predictor of poor survival, including patients treated with curative intent.[89] Because ERAS focuses on in-hospital care in the immediate perioperative period, prehabilitation is a growing approach that is based on the principle that structured and sustained exercise over a period of weeks before surgery will optimize a patient's cardiovascular, respiratory, and muscular condition. Because several recent preoperative fitness programs involving patients with cancer show how prehabilitation may improve patient outcomes and reduce direct and indirect healthcare costs,[90] this approach is an important factor that influences not only the treatment and survival of patients undergoing major operations for malignancy, but also has important implications regarding the healthcare economy.

The American College of Surgeons (ACS) is the leading organizational body for improving overall surgical care in the nation. With regarding to oncology, the organization has created the ACS Cancer Programs, aimed at developing resources that enable providers to deliver comprehensive, high-quality, multidisciplinary, evidence-based, patient-centered care to patients with cancer. The various programs include the Commission on Cancer, the American College of Surgeons Clinical Research Program (ACS-CRP), the National Accreditation Program for Breast Centers, the National Accreditation Program for Rectal Cancer, the National Cancer Database, and the American Joint Committee on Cancer. Among other functions, these programs provide education and training opportunities, establish and promote evidence-based systems for the classification and management of cancer, and emphasize program structure, patient care processes, performance improvement, and performance measures across the country.

American College of Surgeons Clinical Research Program

Through a relationship between the Alliance for Clinical Trials in Oncology and the ACS Cancer Programs, the ACS-CRP was created to improve cancer care outcomes by disseminating validated management strategies. The program has several committees that work together to reach the program's overall goals. Within these, the Cancer Care Delivery Research Committee is currently developing the Value of Care Workgroup. Their specific mission is to improve care delivery processes by improving the infrastructure in defining value, measuring costs, developing multisite datasets, building value-based care models, and networking the various member sites—ultimately integrating value assessment into cancer care delivery research.[91]

Transforming Healthcare Resources to Increase Value and Efficiency

In 2019, the Harvard Business School's Institute for Strategy and Competitiveness partnered with the ACS and announced Transforming Health-care Resources to Increase Value and Efficiency. The program's mission is to assist providers in delivering value-based surgical care by improving patient outcomes while lowering costs. Focused on measuring the full cycle of care, the program is currently piloting their value measurement process for three surgical conditions at select institutions throughout the country: colon cancer, breast

cancer, and morbid obesity/bariatric surgery. Their goal is to use the results from the initiative to create a robust approach to measure and improve value at hospitals around the county.

Within the field of surgical oncology, although there has been growing recognition and emphasis to improve value of care delivery, the concept of complete value-cased care in the field remains in its infancy.

MD ANDERSON PRACTICE TIPS

- To enhance the value of care, interventions should aim at improving end points that matter to patients, providers, and society as a whole.
- Gathering reliable and valid PRO data, designing patient preference studies that use valid instruments and apply reliable and generalizable methods, and using the results to develop decision aids for shared decision-making strategies are recommended going forward.
- Efforts to promote value-based care in medical oncology should center on cost, drug pricing and reimbursement models, standardization of practice patterns, and the elimination of low-value care.
- Because cancer surgery may frequently be associated with large physical, emotional, and financial demands, efforts to improve outcomes and cost by developing enhanced recovery protocols and prehabilitation programs is recommended.
- When designing value-based models of care, it is important to consider how changing the incentives of providers, patients, and payers might impact the quality of care.
- Engagement in value workgroups through organizational bodies including the ASCO, the ASTRO, and the American College of Surgeons (ACS) will further enhance value-based care transformation nationwide.

REFERENCES

1. Keehan SP, Cuckler GA, Sisko AM, et al. National health expenditure projections: modest annual growth until coverage expands and economic growth accelerates. *Health Aff (Millwood).* 2012;31(7):1600-1612.
2. Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010-2020. *J Natl Cancer Inst.* 2011;103(2):117-128.
3. Institute of Medicine. Delivering high-quality cancer care: charting a new course for a system in crisis. Institute of Medicine; 2013.
4. Pisu M, Henrikson NB, Banegas MP, Yabroff KR. Costs of cancer along the care continuum: hat we can expect based on recent literature. *Cancer.* 2018;124(21):4181-4191.
5. Yabroff KR, Bradley C, Shih YT. Understanding financial hardship among cancer survivors in the United States: strategies for prevention and mitigation. *J Clin Oncol.* 2020;38(4):292-301.
6. Smith AK, Shara NM, Zeymo A, et al. Travel patterns of cancer surgery patients in a regionalized system. *J Surg Res.* 2015;199(1):97-105.
7. Schlottmann F, Strassle PD, Charles AG, Patti MG. Esophageal cancer surgery: spontaneous centralization in the US contributed to reduce mortality without causing health disparities. *Ann Surg Oncol.* 2018;25(6):1580-1587.
8. Raoof M, Dumitra S, Ituarte PHG, et al. Centralization of pancreatic cancer surgery: travel distances and disparities. *J Am Coll Surg.* 2016;223:e166.
9. Bradley EH, Taylor LA. *The American Health Care Paradox: Why Spending More is Getting Us Less*. PublicAffairs; 2013.
10. Porter ME, Lee TH. From volume to value in health care: the work begins. *JAMA.* 2016;316(10):1047-1048.
11. Burwell SM. Setting value-based payment goals--HHS efforts to improve U.S. health care. *N Engl J Med.* 2015;372(10):897-899.
12. Offodile AC 2nd, Mehtsun W, Stimson CJ, Aloia T. An overview of bundled payments for surgical oncologists: origins, progress to date, terminology, and future directions. *Ann Surg Oncol.* 2019;26(1):3-7.
13. A Presidential Document by the Executive Office of the President on 06/27/2019. https://www.federalregister.gov/documents/2019/06/27/2019-13945/improving-price-and-quality-transparency-in-american-healthcare-to-put-patients-first. Accessed 7/19/2021.
14. Porter ME, Teisberg EO. *Redefining Health Care : Creating Value-Based Competition On Results*. Harvard Business School Press; 2006.
15. Porter M, Lee T. The strategy that will fix health care. Harvard Business Review. 2013.
16. Aloia TA. Should zero harm be our goal? *Ann Surg.* 2020;271(1):33-36.
17. Neumann PJ, Willke RJ, Garrison LP Jr. A health economics approach to US value assessment frameworks-introduction: an ISPOR Special Task Force Report [1]. *Value Health.* 2018;21(2):119-123.
18. Norman R, Chalkidou K, Culyer AJ. A health economics approach to US value frameworks: serving the needs of decision making. *Value Health.* 2018;21(2):117-118.
19. Lakdawalla DN, Doshi JA, Garrison LP Jr, et al. Defining elements of value in health care-a health economics approach: An ISPOR Special Task Force Report [3]. *Value Health.* 2018;21(2):131-139.
20. Prasad M, Wahlqvist P, Shikiar R, Shih Y-CT. A review of self-report instruments measuring health-related work productivity: a patient-reported outcomes perspective. *Pharmacoeconomics.* 2004;22(4):225-244.
21. Sanchez Y, Penrod JR, Qiu XL, et al. The option value of innovative treatments in the context of chronic myeloid leukemia. *Am J Manag Care.* 2012;18(suppl 11):S265-S271.
22. Gold MR, SJ, Russell LB, Weinstein MC, eds. *Cost-Effectiveness in Health and Medicine*. Oxford University Press; 1996.
23. Drummond MF, O'Brien B, Stoddart GL, Torrance GW, eds: *Methods for the Economic Evaluation of Health Care Programmes*. 2nd ed. Oxford University Press; 1997.
24. Danzon PM, Drummond MF, Towse A, Pauly MV. Objectives, budgets, thresholds, and opportunity costs-a health economics approach: an ISPOR Special Task Force Report [4]. *Value Health.* 2018;21(2):140-145.
25. Ubel PA, Berry SR, Nadler E, et al. In a survey, marked inconsistency in how oncologists judged value of high-cost cancer drugs in relation to gains in survival. *Health Aff (Millwood).* 2012;31(4):709-717.
26. Shih YC, Halpern MT. Economic evaluations of medical care interventions for cancer patients: how, why, and what does it mean? *CA Cancer J Clin.* 2008;58(4):231-244.
27. Verguet S, Kim JJ, Jamison DT. Extended cost-effectiveness analysis for health policy assessment: a tutorial. *Pharmacoeconomics.* 2016;34(9):913-923.
28. Cookson R, Mirelman AJ, Griffin S, et al. Using cost-effectiveness analysis to address health equity concerns. *Value Health.* 2017;20(2):206-212.
29. Hoch JS, Dewa CS. A clinician's guide to correct cost-effectiveness analysis: think incremental not average. *Can J Psychiatry.* 2008;53(4):267-274.
30. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. *JAMA.* 2016;316(10):1093-1103.
31. Phelps CE, Madhavan G. Using multicriteria approaches to assess the value of health care. *Value Health.* 2017;20(2):251-255.
32. Marsh K, Ijzerman M, Thokala P, et al. Multiple criteria decision analysis for health care decision making--emerging good practices: report 2 of the ISPOR MCDA Emerging Good Practices Task Force. *Value Health.* 2016;19(2):125-137.
33. Thokala P, Devlin N, Marsh K, et al. Multiple criteria decision analysis for health care decision making--an introduction: report 1 of the ISPOR MCDA Emerging Good Practices Task Force. *Value Health.* 2016;19(1):1-13.
34. Hudis CA. Science and society: fifty years later--the 2014 presidential address. *J Clin Oncol.* 2015;33(2):127-132.
35. Schnipper LE, Davidson NE, Wollins DS, et al. Updating the American Society of Clinical Oncology Value Framework: revisions and reflections in response to comments received. *J Clin Oncol.* 2016;34(24):2925-2934.
36. Tombu M, Jolicoeur P. Virtually no evidence for virtually perfect time-sharing. *J Exp Psychol Hum Percept Perform.* 2004;30(5):795-810.
37. Memorial Sloan Kettering Cancer Center (MSKCC) Drug Pricing Lab. The DrugAbacus Tool. Accessed April 14, 2020. http://drugpricinglab.org/tools/drug-abacus/
38. Institute for Clinical and Economic Review. 2020-2023 Value Assessment Framework. 2020. https://icer.org/wp-content/uploads/2020/10/ICER_2020_2023_VAF_102220.pdf. Accessed 7/19/2021.
39. Cherny NI, Sullivan R, Dafni U, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). *Ann Oncol.* 2017;28(11):2901-2905.
40. Allen CJ, Thaker NG, Prakash L, et al. Communicating value: use of a novel framework in the assessment of an enhanced recovery initiative. *Ann Surg.* 2021;273(1):e7-e9.

41. Thaker NG, Ali TN, Porter ME, et al. Communicating value in health care using radar charts: a case study of prostate cancer. *J Oncol Pract*. 2016;12(9):813-820.
42. Shih YT, Nasso SF, Zafar SY. Price transparency for whom? In search of out-of-pocket cost estimates to facilitate cost communication in cancer care. *Pharmacoeconomics*. 2018;36(3):259-261.
43. Shanafelt TD, West CP, Sinsky C, et al. Changes in burnout and satisfaction with work-life integration in physicians and the general US working population between 2011 and 2017. *Mayo Clin Proc*. 2019;94(9):1681-1694.
44. National Academy of Medicine. Individual strategies to promote well-being. Accessed June 30, 2020. https://nam.edu/clinicianwellbeing/solutions/individual-strategies/
45. Sell NM, Silver JK, Rando S, et al. Prehabilitation telemedicine in neoadjuvant surgical oncology patients during the novel COVID-19 coronavirus pandemic. *Ann Surg*. 2020;272(2):e81-e83.
46. Birnbaum HG, White AG, Schiller M, Waldman T, Cleveland JM, Roland CL. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. *Pain Med*. 2011;12(4):657-667.
47. Short ME, et al. How accurate are self-reports? Analysis of self-reported health care utilization and absence when compared with administrative data. *J Occup Environ Med*. 2009;51(7):786-796.
48. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. *Med Care*. 2002;40(suppl 8):IV-3-18.
49. Zafar SY, Peppercorn JM, Schrag D, et al. The financial toxicity of cancer treatment: a pilot study assessing out-of-pocket expenses and the insured cancer patient's experience. *Oncologist*. 2013;18(4):381-390.
50. Bullock AJ, Hofstatter EW, Yushak ML, Buss MK. Understanding patients' attitudes toward communication about the cost of cancer care. *J Oncol Pract*. 2012;8(4):e50-e58.
51. Meropol NJ, Schrag D, Smith TJ, et al. American Society of Clinical Oncology guidance statement: the cost of cancer care. *J Clin Oncol*. 2009;27(23):3868-3874.
52. Shih YT, Chien CR. A review of cost communication in oncology: patient attitude, provider acceptance, and outcome assessment. *Cancer*. 2017;123(6):928-939.
53. Gidwani-Marszowski R, Nevedal AL, Blayney DW, et al. Oncologists' views on using value to guide cancer treatment decisions. *Value Health*. 2018;21(8):931-937.
54. Bestvina CM, Zullig LL, Rushing C, et al. Patient-oncologist cost communication, financial distress, and medication adherence. *J Oncol Pract*. 2014;10(3):162-167.
55. Henrikson NB, Shankaran V. Improving price transparency in cancer care. *J Oncol Pract*. 2016;12(1):44-47.
56. Agarwal A, Dayal A, Kircher SM, Chen RC, Royce TJ. Analysis of price transparency via National Cancer Institute-designated cancer centers' chargemasters for prostate cancer radiation therapy. *JAMA Oncol*. 2020;6(3):409-412.
57. Experts in Chronic Myeloid Leukemia. The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts. *Blood*. 2013;121(22):4439-4442.
58. Bennette CS, Richards C, Sullivan SD, Ramsey SD. Steady increase in prices for oral anticancer drugs after market launch suggests a lack of competitive pressure. *Health Aff (Millwood)*. 2016;35(5):805-812.
59. Shih Y-CT, Smieliauskas F, Geynisman DM, Kelly RJ, Smith TJ. Trends in the cost and use of targeted cancer therapies for the privately insured nonelderly: 2001 to 2011. *J Clin Oncol*. 2015;33(19):2190-2196.
60. Dusetzina SB. Drug pricing trends for orally administered anticancer medications reimbursed by commercial health plans, 2000-2014; *JAMA Oncol*. 2016;2(7):960-961.
61. Kaltenboeck A, Bach PB. Value-based pricing for drugs: theme and variations. *JAMA*. 2018;319(21):2165-2166.
62. Karlin-Smith S, Pittman D. CMS Quit Test of Pricey Cancer Treatment amid Concerns over Industry Role." POLITICO, July 9, 2018. Accessed May 21, 2021. www.politico.com/story/2018/07/09/cms-quit-test-of-pricey-cancer-treatment-amid-concerns-over-industry-role-674086
63. Daly B, Zon RT, Page RD, et al. Oncology clinical pathways: charting the landscape of pathway providers. *J Oncol Pract*. 2018;14(3):e194-e200.
64. Kreys ED, Koeller JM. Documenting the benefits and cost savings of a large multistate cancer pathway program from a payer's perspective. *J Oncol Pract*. 2013;9(5):e241-e247.
65. Jackman DM, Zhang Y, Dalby C, et al. Cost and survival analysis before and after implementation of dana-Farber Clinical Pathways for patients with stage IV non-small-cell lung cancer. *J Oncol Pract*. 2017;13(4):e346-e352. https://ascopubs.org/doi/10.1200/JOP.2017.021741.
66. Bach PBS, Saltz LB Wittes RE. In Cancer Care, Cost Matters. *The New York Times*. 2012. https://www.nytimes.com/2012/10/15/opinion/a-hospital-says-no-to-an-11000-a-month-cancer-drug.html
67. Pollack A. Sanofi Halves Price of Cancer Drug Zaltrap After Sloan Kettering Rejection. *New York Times*. 2012.
68. Cassel CK, Guest JA, Choosing wisely: helping physicians and patients make smart decisions about their care. *JAMA*. 2012;307(17):1801-1802.
69. Schnipper LE, Smith TJ, Raghavan D, et al. American Society of Clinical Oncology identifies five key opportunities to improve care and reduce costs: the top five list for oncology. *J Clin Oncol*. 2012;30(14):1715-1724.
70. Schnipper LE, Lyman GH, Blayney DW, et al. American Society of Clinical Oncology 2013 top five list in oncology. *J Clin Oncol*. 2013;31(34):4362-4370.
71. Fitch K, Pelilzzari PM, Pyenson B. Cost drivers of cancer care: a retrospective analysis of Medicare and commercially insured population claim data 2004-2014. Accessed May 21, 2021. https://communityoncology.org/pdfs/Trends-in-Cancer-Costs-White-Paper-FINAL-20160403.pdf
72. Mak KS, van Bommel ACM, Stowell C, et al. Defining a standard set of patient-centred outcomes for lung cancer. *Eur Respir J*. 2016;48(3):852-860.
73. Pearson SD, Bach PB. How Medicare could use comparative effectiveness research in deciding on new coverage and reimbursement. *Health Aff (Millwood)*. 2010;29(10):1796-1804.
74. Bekelman JE, Hahn SM. Reference pricing with evidence development: a way forward for proton therapy. *J Clin Oncol*. 2014;32(15):1540-1542.
75. Liao Z, Lee JJ, Komaki R, et al. Bayesian adaptive randomization trial of passive scattering proton therapy and intensity-modulated photon radiotherapy for locally advanced non-small-cell lung cancer. *J Clin Oncol*. 2018;36(18):1813-1822.
76. START Trialists' Group; Bentzen SM, Agrawal RK, Aird EGA, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet*. 2008;371(9618):1098-1107.
77. Whelan TJ, Pignol J-P, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med*. 2010;362(6):513-520.
78. Dearnaley D, Syndikus I, Mossop H, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the

randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol.* 2016;17(8):1047-1060.
79. Cieri N, Di Bartolo O, Corradini P. Rituximab for indolent lymphomas before and after allogeneic hematopoietic stem cell transplantation. *Curr Opin Hematol.* 2015;22(6):469-475.
80. Chen AB, Cronin A, Weeks JC, et al. Palliative radiation therapy practice in patients with metastatic non-small-cell lung cancer: a Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) Study. *J Clin Oncol.* 2013;31(5):558-564.
81. Bekelman JE, Epstein AJ, Emanuel EJ. Single- vs multiple-fraction radiotherapy for bone metastases from prostate cancer. *JAMA.* 2013;310(14):1501-1502.
82. Hahn C, Kavanagh B, Bhatnagar A, et al. Choosing wisely: the American Society for Radiation Oncology's top 5 list. *Pract Radiat Oncol.* 2014;4(6):349-355.
83. Steingisser L, Acker B, Berman S, et al. Bending the cost curve: a unique collaboration between radiation oncologists and Blue Cross Blue Shield of Massachusetts to optimize the use of advanced technology. *J Oncol Pract.* 2014;10(5):e321-e327.
84. Derenzini E, Casadei B, Pellegrini C, Argnani L, Pileri S, Zinzani PL. Non-Hodgkin lymphomas presenting as soft tissue masses: a single center experience and meta-analysis of the published series. *Clin Lymphoma Myeloma Leuk.* 2013;13(3):258-265.
85. Spinks T, Guzman A, Beadle BM, et al. Development and feasibility of bundled payments for the multidisciplinary treatment of head and neck cancer: a pilot program. *J Oncol Pract.* 2018;14(2):e103-e112.
86. Krause SW, Gerken M, Andreesen R, Hofstädter F, Klinkhammer-Schalke M. Treatment of B cell lymphoma with chemotherapy plus rituximab: a survival benefit can be demonstrated in the routine data of a regional cancer registry. *Ann Hematol.* 2012;91(4):561-570.
87. Falit BP, Chernew ME, Mantz CA. Design and implementation of bundled payment systems for cancer care and radiation therapy. *Int J Radiat Oncol Biol Phys.* 2014;89(5):950-953.
88. Ljungqvist O, Scott M, Fearon KC. Enhanced recovery after surgery: a review. *JAMA Surg.* 2017;152(3):292-298.
89. Ngo-Huang A, Holmes HM, des Bordes Jude KA, et al. Association between frailty syndrome and survival in patients with pancreatic adenocarcinoma. *Cancer Med.* 2019;8(6):2867-2876.
90. Silver JK, Baima J. Cancer prehabilitation: an opportunity to decrease treatment-related morbidity, increase cancer treatment options, and improve physical and psychological health outcomes. *Am J Phys Med Rehabil.* 2013;92(8):715-727.
91. Kent EE, Mitchell SA, Castro KM, et al. Cancer care delivery research: building the evidence base to support practice change in community oncology. *J Clin Oncol.* 2015;33(24):2705-2711.

This page intentionally left blank

Index

Note: Page numbers followed by f and t indicate figures and tables.

A
ABC. *See* Activated B-cell subtype
ABCB, biliary tract cancer, 650
Abdominoperineal resection (APR)
  anal cancer, 765, 773
  CRC, 742
Abemaciclib, 1334–1335
  MBC, 833, 836–837
aBFM. *See* Augmented Berlin-Frankfurt-Münster regimen
Abiraterone, 131
Abiraterone acetate and prednisone, prostate cancer, 1062
Absolute eosinophil count (AEC), CEL/HES, 141, 145
Absolute lymphocyte count (ALC)
  BCL CART-T, 365, 366
  CLL, 50
  GVHD, 405
  RSV HCT, 1354t
ABV. *See* Doxorubicin, bleomycin, and vinblastine
ABVD. *See* Doxorubicin, bleomycin, vinblastine, and dacarbazine
ABVE-PC, HL, 1274
AC. *See* Doxorubicin and cyclophosphamide
Acalabrutinib
  CLL, 57
  MCL, 236, 242–243
AC and bevacizumab, TNBC, 817
AC and paclitaxel, breast cancer, 813
ACC. *See* Adrenocortical carcinoma
Accelerated hyperfractionated RT (AHRT), SCLC, 480
Accelerated partial breast irradiation (APBI), 810, 825
Accelerated phase chronic myeloid leukemia (AP-CML), 68
ACE. *See* Angiotensin-converting enzyme inhibitors; Dactinomycin, cisplatin, and etoposide
ACER. *See* Average cost-effectiveness ratio
Acetaminophen, hydrocodone, 1558–1559
Acitretin, CTCL, 278
aCML. *See* Atypical CML
Acquired hemophilia, 1430, 1431
Acquired immunodeficiency syndrome (AIDS). *See* Human immunodeficiency virus/acquired immunodeficiency syndrome
Acquired polycystic kidney disease, RCC, 1007
Acquired von Willebrand disease (AVWD), ET, 130–131, 133, 134, 154
Acral lentiginous melanoma, 1134, 1135t
Acrolein
  bladder cancer, 1028
  hemorrhagic cystitis, 1421
ACS. *See* Acute coronary syndrome
ACT. *See* Adoptive T-cell therapy
ACTH. *See* Adrenocorticotropic hormone
Actinomycin D, ARDS, 1423
Activated B-cell subtype (ABC), 191
Active surveillance
  penile cancer, 1074
  prostate cancer, 1058, 1058t
  seminoma, 1087
  SRM, 1009
Activities of daily living (ADLs), 1534, 1538, 1548
Activity Measure for Post-Acute Care (AM-PAC), 1532
ACUPs. *See* Adenocarcinoma of unknown primary site
Acute coronary syndrome (ACS), 1503–1504
Acute graft-versus-host disease (aGVHD)
  AHSCT, 411–413, 412t, 464–465
  HaploSCT, 448, 450
Acute lymphoblastic leukemia (ALL), 3–18
  AHSCT, 398, 416
  AYA, 12, 15
  bispecific antibodies, 1314
  CAR-T, 363
  CLL, 58
  diagnosis, 4t–7t, 7f, 48
  emerging therapies, 17–18
  epidemiology and etiology, 3–4
  frontline therapy, 8–14, 13f
  older patients, 12–13
  pediatric cancer, 1271, 1272–1273
  salvage therapy, 14–17, 14t, 17t
Acute myeloid leukemia (AML), 23–44, 25t–27t, 37f, 38t–43t
  AHSCT, 398, 416, 459
  AYA, 30–31
  CBF, 34–35
  clinical presentation, 24
  diagnosis and classification, 24–26, 25t, 26t
  epidemiology, etiology, and risk factors, 24
  ET, 119, 128–129
  FLT3, 23, 35, 38
  FLT3-mutated, 33
  fungal infections, 1364
  GVHD, 465
  HaploSCT, 449–450
  IDH, 34, 35
  induction therapy, 28–30, 30t
  maintenance therapy, 35, 36f
  MDSs, 91, 94, 99, 101, 105, 107
  older patients, 31–34
  pediatric cancer, 1273
  PMF, 135, 139
  PV, 119, 124
  relapsed or refractory, 37–38, 37f
  risk stratification, 26–27, 27t
  supportive care, 38–39
  targeted therapy, 33–34
  TP53, 27, 34
  treatment, 27–28
Acute pancreatitis, pancreatic cancer, 623
Acute pericarditis, 1451, 1452t, 1453f
Acute promyelocytic leukemia (APL), 24, 39–42, 39t–42t
  ARDS, 1466
  bleeding, 1420–1421
Acute pulmonary failure, AML, 39
Acute respiratory distress syndrome (ARDS), 1486
ACVR1, HGGs, 1275
Acyclovir, 1346t
  HSV, 1346
  VZV, 1348
ADAMTS-13, TMAs, 1500, 1501
Adaptive group sequential design, 1585
Adaptive randomization, 1583
Adenocarcinoma. *See also* Colorectal cancer
  anal cancer, 775–776
  appendiceal tumors, 716–727, 718f, 719t, 720t, 721f–724f, 726f
  biliary tract cancer, 647–648
  bladder cancer, 1032
  cervical cancer, 956, 971
  CUP, 1256, 1257, 1260, 1264
  EOC, 904
  esophageal cancer, 594, 600, 603
  gallbladder carcinoma, 648–650
  gastric cancer, 580
  liver cancer, 1262
  MPE, 1482
  NSCLC, 499–500, 500f, 500t, 501t
  pancreatic cancer, 619–640, 620t, 623f, 623t, 625f, 626t, 627f, 628f, 629t, 630t, 633f–635f
  prostate cancer, 1054
  SBA, 707–716, 711t, 712t, 714t, 715f
Adenocarcinoma in situ (AIS), cervical cancer, 959, 960, 961
Adenocarcinoma of unknown primary site (ACUPs), 1259
Adenoid cystic carcinoma
  cervical cancer, 956
  esophageal cancer, 594
Adenomatous polyposis coli (*APC*)
  ACC, 1215t
  appendiceal tumors, 723
  brain tumors, 1109
  HCC, 678
  SBA, 709

Adenomyomatosis, 650
Adenosarcoma, 948–949
Adenosine diphosphate (ADP)
  EOC, 897
  EOS, 910
5-adenosine monophosphate-activated protein kinase (AMPK), 1443
Adenosine triphosphate (ATP)
  c-kit, 1331
  encorafenib, 1324
Adenosquamous carcinomas
  cervical cancer, 956, 971
  CUP, 1257
Adenovirus, 1345, 1351–1352
  GVHD, 466, 467
ADIC. *See* Doxorubicin and dacarbazine
Adiponectin, prostate cancer, 1051
Adjuvant medications, 1561, 1561t
ADLs. *See* Activities of daily living
Adolescent and young adults (AYA)
  ALL, 12, 15
  AML, 30–31
  CLL, 60
  CML, 76
  HCC, 678
  MCL, 239–240
  PMF, 135
  PTCLs, 254
Adoptive T-cell therapy (ACT), 1311, 1312f
Ado-trastuzumab-emtansine (Kadcyla), 1291t, 1332
  PABC, 878
ADP. *See* Adenosine diphosphate
Adrenal insufficiency, 1392
Adrenocortical carcinoma (ACC), 1211–1217, 1212t, 1213f, 1214f, 1215t, 1216f, 1217f
Adrenocorticotropic hormone (ACTH, corticotrophin), 1391
  ACC, 1212
  adrenal insufficiency, 1392
  pheochromocytoma, 1205
  primary adrenal insufficiency, 1397, 1428
  SCLC, 476, 489
ADT. *See* Androgen deprivation therapy
Adult respiratory distress syndrome (ARDS), 1423
  bleeding, 1420
  hyperleukocytosis, 1417
Adult T-cell leukemia/lymphoma (ATLL), 280
Advanced care planning, 1571
Advanced SM (AdvSM), 149, 151–152
AEC. *See* Absolute eosinophil count
AEDs. *See* Antiepileptic drugs
Afatinib (Gilotrif), 1291t, 1329–1330
  NSCLC, 537–538
Afinitor. *See* Everolimus
Aflatoxin, HCC, 683
Aflibercept, CRC, 749
AFP. *See* a-fetoprotein
AFP-L3. *See* Lectin-reactive isoenzyme of AFP
Aggressive variant prostate cancer (AVPC), 1054–1055
aGVHD. *See* Acute graft-versus-host disease
A'Hern, R. P., 1582
AHPCT. *See* Autologous hematopoietic progenitor cell transplant
AHRT. *See* Accelerated hyperfractionated RT
AHSCT. *See* Allogeneic hematopoietic stem cell transplantation
aHUS. *See* Atypical hemolytic uremic syndrome
AI. *See* Artificial intelligence
AIC. *See* Autoimmune cytopenia
AIDS. *See* Human immunodeficiency virus/acquired immunodeficiency syndrome
AIHA. *See* Autoimmune hemolytic anemia
Airway obstruction, 1422, 1422t
  CAO, 1461
  MCAO, 1479–1480, 1480t, 1481f
AIs. *See* Aromatase inhibitors
AIS. *See* Adenocarcinoma in situ
AITL. *See* Angioimmunoblastic T-cell lymphoma
Ajani, J. A., 589–590
AKT
  EOC, 900
  glial tumors, 1109
  MBC, 855
  melanoma, 1136
  meningiomas, 1111
  osteoporosis, 1388
  SCC, 502t
  targeted therapy, 1329
AL. *See* Systemic light chain amyloidosis
Alagille syndrome, HCC, 678
Albers, P., 1093
ALC. *See* Absolute lymphocyte count
ALCL. *See* Anaplastic large-cell lymphoma
Alcohol
  brain tumors, 1108
  breast cancer, 805
  HCC, 678, 682
  HNSCC, 555, 570
  NETs, 782
  SBA, 708
Alectinib, 1337
  NSCLC, 538, 539
Alemtuzumab
  adenovirus, 1352
  CMV, 1349
  CTCL, 281
  GVHD, 465
  HBV, 1356
  hypothyroidism, 1394
  PLL, 63
Alexandrov, L. B., 1286
Alisertib, PTCLs, 263
ALK. *See* Anaplastic lymphoma kinase
ALK-positive large B-cell lymphoma (ALK+ LBCL), 199, 212, 215
ALL. *See* Acute lymphoblastic leukemia
Allergies, brain tumors, 1108
Allogeneic hematopoietic stem cell transplantation (AHSCT), 397–417, 399f, 401, 401f, 402, 403f, 407f–408f, 410t, 411–413, 412t, 414t–415t
  AHPCT, 384
  ALL, 3, 8, 10, 13–14, 13f
  VOD, 15, 16
  CAR-T, 363
  cellular therapy, 457–468, 458f, 460f, 462t, 463f, 465f, 466f
Allogeneic stem cell transplant (all-SCT)
  AML, 28, 29, 35, 42–44
  BL, 215
  CEL/HES, 145–146
  cHL, 315–316
  CLL, 59, 59t, 61
  CML, 82, 83t, 84
  HaploSCT, 447–448
  MDSs, 91, 92, 94, 101, 103, 108–109
    total therapy with, 111
  PMF, 141
Allopurinol
  TLS, 1426
  tumor lysis syndrome, 38
All-SCT. *See* Allogeneic stem cell transplant
All-*trans*-retinoic acid (ATRA)
  APL, 39–40
  ARDS, 1423, 1466
  cardiac tamponade, 1413
  DAH, 1466
  pleural effusions, 1467
Alpelisib, 1328
  MBC, 838
Alpha-blockers
  pheochromocytoma, 1207
  urinary tract obstruction, 1421
Alpha-ketoglutarate (aKG), AML, 34
Alprazolam, seizures, 1412
Alteplase, 1419t
Altered mental status, 1413
  AML, 24
  bleeding, 1420
  gabapentin, 1561
  LGGs, 119
  pediatrics, 1271, 1275
Alveolar soft parts sarcoma (ASPS), 1163, 1169–1170
AM. *See* Anal margin
Amantadine, 1346t
Americans With Disabilities Act of 1990, 1546
AMH. *See* Anti-Müllerian hormone
Amitriptyline, depression, 1569
AML. *See* Acute myeloid leukemia
AM-PAC. *See* Activity Measure for Post-Acute Care
Amphotericin B, 1369t
  aspergillosis, 1372–1373
  candidiasis, 1368, 1369
  coccidioidomycosis, 1377
  cryptococcosis, 1374
  fusariosis, 1375
  histoplasmosis, 1376
  mucormycosis, 1375
Amphotericin B-deoxycholate (D-AMB), 1369t, 1370
  aspergillosis, 1372
  coccidioidmomycosis, 1377
  cryptococcosis, 1374
AMPK. *See* 5-adenosine monophosphate-activated protein kinase
Amputation
  penile cancer, 1075
  rehabilitation, 1529, 1537–1538
Amyloidosis, 1437
  arterial ischemia, 1446

Amyloid P component (SAP), AL, 324
Anagrelide, ET, 133
Anal cancer, 765–776, 766f, 770t, 771t, 773f, 774t
  cervical cancer, 975
  HIV/AIDS, 1242, 1242t, 1245f
  metastatic, 773–775
Anal margin (AM), 765
Anal transition zone (ATZ), 765–766
Anal verge (AV), 765, 766
Anaplastic astrocytoma, 1116, 1117f, 1121–1122
Anaplastic large-cell lymphoma (ALCL), 259
  CAR-T, 372
Anaplastic lymphoma kinase (*ALK*)
  CUP, 1258
  DVT and VTE, 1488
  FGFR, 663
  NSCLC, 514, 518, 520, 538–539
  OP, 1465
  pancreatic cancer, 620–621
  PD-1 ICIs, 1308
  PTCL-NOS, 256
  PTCLs, 254, 260
  sALCL, 256–258
  targeted therapy, 1337
Anaplastic meningioma, 1113f
Anaplastic oligodendrogliomas, 1115–1116, 1116f, 1120–1121
Anaplastic thyroid carcinoma (ATC), 1202–1203, 1202f
Anastrozole (Arimidex)
  breast cancer, 815
  DCIS, 887–888
  MBC, 838
  osteoporosis, 1387, 1387f
Anastrozole (Arimidex), Tamoxifen, Alone or in Combination (ATAC), breast cancer, 815
"AND"-gate CARs, 374–375
Androgen deprivation therapy (ADT)
  osteoporosis, 1387, 1388
  prostate cancer, 1049, 1055, 1059, 1061–1062
Androgen receptor (AR)
  breast cancer, male, 881
  targeted therapy, 1326t, 1335
Androgens
  MBC, 838–839
  PMF, 139
  prostate cancer, 1050–1051, 1051f
Anemia. *See also* Fanconi anemia; Iron deficiency anemia
  CNL, 148
  CRAB, 341, 343, 345, 345t, 355
  GTD, 996
  LGLs, 63
  MDSs, 105
  parvovirus B19, 1356
  PMF, 135, 140
  SM, 120, 149, 152
  WM, 334
ANF. *See* Atrial natriuretic factor
Angioimmunoblastic T-cell lymphoma (AITL), 254, 255–256, 257f–258f, 259
Angiosarcoma, 1168
  HCC, 685
Angiotensin-converting enzyme (ACE) inhibitors
  cardiomyopathy, 1439
  myocardial toxicity, 1442
Anidulafungin, 1368t
ANN. *See* Artificial neural networks
Anorexia-cachexia, 1564–1565, 1565f
Anthracyclines
  AML, 28–29
  APL, 39
  atrial fibrillation, 1504
  breast cancer, 820, 1397–1398
  LABC and IBC, 867
  MBC, 842, 850–851
  myocardial toxicity, 1440, 1442
  PABC, 877, 879
  sarcoma, 1166–1167
  TNBC, 817, 819, 853
Antibiotics
  acute pericarditis, 1451
  AML, 31, 39
  ICANS, 1313
  MALT, 185–186
  MDSs, 105
  NHL, 1235
  oncocardiology, 1435
  seizures, 1412
Antibody drug conjugate
  bladder cancer, 1039, 1041–1042
  MM, 353
Anticoagulants. *See also* Direct oral anticoagulants
  bleeding, 1499
  PE, 1478
  thrombocytopenia, 1499
  VTE, 1478, 1494–1495, 1495t–1497t
Anticonvulsants
  brain tumor seizures, 1126
  pain management, 1561, 1561t
  PCNSL, 1239–1240
Antidepressants, 1569
  CYP2D6, 1558
  fatigue, 1563
  pain management, 1561, 1561t
  SIADH, 1386
Antidiuretic hormone (ADH). *See* Syndrome of inappropriate antidiuretic hormone
Antiepileptic drugs (AEDs)
  seizures, 1413
  SIADH, 1386
Antifungals
  acute pericarditis, 1451
  AML, 31
  MDSs, 105
  methadone, 1560
  oncocardiology, 1435
Antigen-presenting cell (APC)
  AHSCT, 458, 459
  CTCL, 273
Antigen receptor complex (ARC), 374
Antihistamines, SM, 152
Anti-Müllerian hormone (AMH), SCSTs, 924, 925
Antiplatelet therapy
  ACS, 1504
  ET, 15
  radiation-induced cardiovascular toxicity, 1456
  VTE, 1503
Antipsychotics
  oncocardiology, 1435
  SIADH, 1386
Antithymocyte globulin (ATG)
  aGVHD, 464–465
  aplastic anemia, 1430
  MDSs, 108
α-1 antitrypsin deficiency, HCC, 682–683
Antivirals, 1346t. *See also* Highly active antiretroviral therapy
  AML, 31
  DAAs, HCC, 679–680
  HSV, 1346–1347
  MDSs, 105
  oncocardiology, 1435
Antonarakis, E. S., 1063
Anxiety, fatigue, 1563
Apalutamide, 131
  prostate cancer, 1049
APBI. *See* Accelerated partial breast irradiation
APC. *See* Antigen-presenting cell; Argon plasma coagulation
APC. *See* Adenomatous polyposis coli
AP-CML. *See* Accelerated phase chronic myeloid leukemia
Aphasia, spinal cord injury, 1535
Apixaban, VTE, 1478, 1494
APL. *See* Acute promyelocytic leukemia
Aplastic anemia, 1430
  AHSCT, 398
  bleeding, 1420
APOA5, 1384
APOBEC, 1288
  HIV/AIDS, 1225
APOC3A, 1384
Appendiceal carcinoid tumors, 716, 720
Appendiceal epithelial tumors, 716, 721–722
Appendiceal NETs, 788
Appendiceal tumors, 716–727, 718f, 719t, 720t, 721f–724f, 726f
APR. *See* Abdominoperineal resection
Apraxia, spinal cord injury, 1535
AR. *See* Androgen receptor
ARAF, RAS-RAF-MEK pathway inhibitors, 1324
ARC. *See* Antigen receptor complex
ARDS. *See* Adult respiratory distress syndrome
Argatroban8, 1498t
Arginase-1, FLHCC, 684
Arginine vasopressin (AVP). *See* Vasopressin
Argon plasma coagulation (APC)
  airway obstruction, 1422, 1422t
  hemoptysis, 1423
ARID1A
  biliary tract cancer, 662
  FL, 170
Arimidex. *See* Anastrozole
Aromatase inhibitors (AIs)
  breast cancer, 814, 815
  MBC, 837–838
  osteoporosis, 1387, 1387f
Arsenic trioxide (ATO), APL, 39–40
Arterial ischemia, 1444–1448, 1445f, 1445t, 1447f, 1447t, 1448t
Artificial intelligence (AI), 1593
Artificial neural networks (ANN), 1593, 1594, 1594f

Asbestos
  NSCLC, 496
  RCC, 1007
  SCLC, 476
ASC. *See* Atypical squamous cells
Asciminib, CML, 81
ASCT. *See* Autologous stem cell transplant
Aseptic meningitis, 1429–1430
Aspergillosis (*Aspergillus* spp.), 1370–1373, 1371f, 1372t, 1376t
  HCC, 683
Aspirin
  acute pericarditis, 1453f
  CRC, 736
  ET, 15
  myocardial ischemia, 1416
  PV, 125, 126, 154
ASPS. *See* Alveolar soft parts sarcoma
Asthenia, rehabilitation, 1538–1540
Asthma, brain tumors, 1108
Astrocytoma, 1105, 1107, 1115, 1115f
  anaplastic, 1116, 1117f, 1121–1122
ATAC. *See* Anastrozole (Arimidex), Tamoxifen, Alone or in Combination
Ataxia telangiectasia
  ALL, 4
  AML, 24
  B-NHL, aggressive, 192t
  HCC, 678
  pancreatic cancer, 620–621
  spinal cord injury, 1535
Ataxia telangiectasia mutated (*ATM*)
  CLL, 50
  MCL, 228, 230
  pancreatic cancer, 637
  prostate cancer, 1052, 1064
  sarcoma, 1160
  SLL/CLL, 188
ATC. *See* Anaplastic thyroid carcinoma
Atezolizumab. *See also specific drug combinations*
  bladder cancer, 1040
  MBC, 855
  NSCLC, 516, 518, 537
  PD-1 ICIs, 1299–1311, 1300t–1303t
  RCC, 1010
  SCLC, 483
  TNBC, 852–853
Atezolizumab and bevacizumab
  FLHCC, 695
  HCC, 691–692
ATG. *See* Antithymocyte globulin
Atherosclerotic disease, 1456
  arterial ischemia, 1445
ATLL. *See* Adult T-cell leukemia/lymphoma
ATM. *See* Ataxia telangiectasia mutated
ATO. *See* Arsenic trioxide
ATP. *See* Adenosine triphosphate
ATR
  pancreatic cancer, 637
  prostate cancer, 1064c
  sarcoma, 1160
ATRA. *See* All-*trans*-retinoic acid
Atrial fibrillation, 1435, 1504
Atrial natriuretic factor (ANF), SIADH, 1424
Atrial tachycardia, 1449
ATRX
  MDS, 97
  SBA, 709
ATRX, glioblastoma, 1110
Atypical CML (aCML), MPDs, 120
Atypical glandular cells, cervical cancer, 960
Atypical hemolytic uremic syndrome (aHUS), TMAs, 1500–1501
Atypical squamous cells (ASC), cervical cancer, 960
ATZ. *See* Anal transition zone
Augmented Berlin-Frankfurt-Münster (aBFM) regimen, ALL, 11, 12
Auristatin, 1041
Aurora A kinase inhibitors, SCLC, 488
Autoimmune cytopenia (AIC), CLL, 60
Autoimmune hemolytic anemia (AIHA), CLL, 50, 60
Autologous hematopoietic progenitor cell transplant (AHPCT), 383–392, 385f, 387f, 388f, 390f
Autologous stem cell transplant (ASCT)
  B-NHL, aggressive, 214
  CAR-T, 365, 366
  cHL, 312–315, 316
  HL, 291
  MCL, 235, 237, 240, 243–244
  MM, 341, 349–350
  neuroblastoma, 1276
  NLPHL, 304
  PBL, 212
  PCNSL, 211
  POEMS, 357
  WM, 335, 336
AV. *See* Anal verge
Avapritinib, 1332
  SM, 120, 153, 154
Avastin. *See* Bevacizumab
AVD
  cHL, 305, 310–312
  HL, 1242
Avelumab
  bladder cancer, 1037
  endometrial cancer, 941–942
  GEJ cancer, 607
  mRCC, 1013
  PD-1 ICIs, 1299–1311, 1300t–1303t
Average cost-effectiveness ratio (ACER), 1605
AVPC. *See* Aggressive variant prostate cancer
AVWD. *See* Acquired von Willebrand disease
Axicabtagene ciloleucel, 1312
Axillary lymph nodes
  breast cancer, 807–808, 810
  DCIS, 885
Axitinib (Inlyta), 1292t. *See also specific drug combinations*
  mRCC, 1033
  RCC, 1010
Axitinib and pembrolizumab, ASPS, 1170
AXL, mRCC, 1013, 1015
AYA. *See* Adolescent and young adults
5-azacitidine (AZA)
  AML, 23, 32, 33, 35
  MDSs, 103, 106–107, 109
Azathioprine, B-NHL, aggressive, 192

B
Bacillus Calmette-Guérin (BCG), 1297
  bladder cancer, 1027, 1032, 1035, 1036
  HP, 1467
Baclofen, spasticity, 1536
Bakitas, M., 1520
BAL. *See* Bronchoalveolar lavage
Balkan nephropathy, 1029
B-ALL. *See* B-cell acute lymphoblastic leukemia
Baloxavir (Xofluza), 1346t
  influenza, 1354
BAP
  ccRCC, 1008
  RCC, 1007
Baraclude. *See* Entecavir
Bar-Eli, M., 1255
Barker, J. N., 428, 432
Barrett esophagus (BE), 594, 598f
Bartsch, G. C., 1035
Basic fibroblast growth factor, PMF, 135
BATTLE. *See* Biomarker-integrated approaches of targeted therapy of lung cancer elimination
Bayesian RAR, 1588–1589
BBB. *See* Blood brain barrier
B-cell acute lymphoblastic leukemia (B-ALL), 3, 5
  CAR-T, 365
B-cell lymphoma 2 (*BCL-2*)
  AHSCT, 416
  AML, 23, 32–33
  B-cell lymphomas, 206
  CAR-T, 365
  CLL, 57
  DLBCL, 196
  FL, 166–167, 170, 176
  HGBL, 201, 202, 213
  MCL, 230
  MM, 354
  NHL, 1274
  pediatric cancer, 1273
  prostate cancer, 1054
  T-ALL, 12
  WM, 336
B-cell lymphoma 6 (*BCL-6*)
  DLBCL, 196
  FL, 165, 166
  HGBL, 213
  HL, 292
  ISPN, 168
  MALT, 185, 195
  NHL, 199, 1274
  pcMZL, 284
  SOX, 230
B-cell lymphoma, unclassifiable, 202, 215
B-cell maturation antigen (BCMA), CAR-T, 461
B-cell non-Hodgkin lymphoma (B-NHL), 227. *See also* Mantle cell lymphoma
  aggressive, 191–220, 192t, 194f–197f, 194t, 200f, 201t, 202f–205f, 203t, 207t, 208t, 216t, 217t, 218f, 219f
B cell-prolymphocytic leukemia, MCL, 233
B-cell receptor (BCR), MCL, 228, 230–231
B-cells
  bladder cancer, 1031
  GC, MM, 342

MALT, 185
nodal MZL, 186
PLL, 63
SMZL, 187
B-cell signaling pathway inhibitors, CLL, 56
BCG. *See* Bacillus Calmette-Guérin
BCL-2. *See* B-cell lymphoma 2
BCL-6. *See* B-cell lymphoma 6
BCMA. *See* B-cell maturation antigen
BCNU. *See* Carmustine
BCR. *See* B-cell receptor
BCR-ABL
ALL, 3, 7, 11
cancer genomics, 1290
CEL/HES, 145
CML, 67, 70
GISTs, 1171, 1172
malignant melanoma, 1148
MPN, 120
PH, 1469
BCS. *See* Breast conserving surgery; Budd-Chiari syndrome
BD. *See* Bortezomib and dexamethasone
BE. *See* Barrett esophagus
BEACOPP. *See* Bleomycin, etoposide, doxorubicin, procarbazine, cyclophosphamide, vincristine, and prednisone
BEAM. *See* Carmustine, etoposide, cytarabine, and melphalan
Beatson, G. T., 814
Beckwith-Wiedemann syndrome
ACC, 1214, 1215t
WT, 1276
Behavox, TMAs, 1501
Belinostat, PTCLs, 263, 264t
Bempegaldesleukin
bladder cancer, 1031
mRCC, 1018
Bendamustine
diabetes insipidus, 1386
MCL, 236
Bendamustine with rituximab (BR), MCL, 237, 238t, 240, 241
Benign prostatic hypertrophy (BPH), urinary tract obstruction, 1421
Bentivegna, E., 970
Benzodiazepines
delirium, 1567
seizures, 1412, 1413
Benztropine, delirium, 1567
BEP. *See* Bleomycin, etoposide, and cisplatin
Berenbaum, M. C., 449
Bergman, L., 945
Berry, D. A., 1585
Bevacizumab (Avastin), 1291t. *See also specific combination drugs*
arterial ischemia, 1446t, 1447
cervical cancer, 976
CRC, 748, 749
DVT and VTE, 1488
EOC, 902, 917–918
glioma, 1121t
hypertension, 1454, 1454t
mRCC, 1033
NSCLC, 518, 520–522, 526
sarcoma, 1168
thrombosis, 1502
Bevacizumab and carboplatin, glioma, 1121t
Bevacizumab and erlotinib, CUP, 1266
Bevacizumab and lomustine, glioma, 1121t
Bevacizumab and sunitinib, prostate cancer, 1063
Bexarotene
central hypothyroidism, 1393
CTCL, 277, 278
lipid disorders, 1384
BH3 mimetics
ALL, 16–17
MDSs, 109
Big data, 1593
Bilateral prophylactic mastectomies (BPMs), 889–890
Biliary tract cancer, 647–670, 648f, 649t, 658t–662f, 664, 666t–668t
Binimetinib, 1325, 1326
Biomarker-adaptive design, 1585–1586
Biomarker-integrated approaches of targeted therapy of lung cancer elimination (BATTLE), 1585, 1586
Bischoff, W., 1586
Bispecific antibodies, 1314
cHL, 316
Bispecific T-cell engager (BITE), MM, 354
Bisphosphonates
bone cancer, MBC, 832
hypercalcemia, 1389, 1426
hypocalcemia, 1390
osteoporosis, 1388
SM, 152
BITE. *See* Bispecific T-cell engager
Bivalirudin8, 1498t
BK virus, 1356–1357
GVHD, 407, 437, 467–468
hemorrhagic cystitis, 1421
BL. *See* Burkitt lymphoma
Bladder cancer, 1027–1043, 1030f, 1034f, 1038f, 1042f
ICIs, 1382
prostate cancer, 1050
targeted therapy, 1327t
urinary tract obstruction, 1421
Bladder management, spinal cord injury, 1536
Blaes, A., 407
Blastic phase chronic myeloid leukemia (BP-CML), 68
Blasts
CEL/HES, 142
CNL, 148, 154
MDSs, 99, 105, 109
PMF, 141
Bleeding, 1419–1421
anticoagulants, 1499
gastrointestinal, 1426–1427
Bleomycin. *See also specific drug combinations*
EP, 1466
HP, 1467
MPE, 1484
NSIP, 1466
PH, 1469
Bleomycin, busulfan, cyclophosphamide, gemcitabine, and carmustine, DILI, 1462
Bleomycin, etoposide, and cisplatin (BEP)
GTD, 996–997
MOGCTs, 922–923, 924t
SCSTs, 925
seminoma, 1088
Bleomycin, etoposide, doxorubicin, procarbazine, cyclophosphamide, vincristine, and prednisone (BEACOPP), 291
cHL, 305, 307, 309–310, 312
HL, 1241
NLPHL, 303
Bleomycin, methotrexate, and cisplatin (BMP), 1076, 1077
Bleomycin, vincristine, and cisplatin (BOP), 1092
Blepharitis, 1431
Blinatumomab, ALL, 14–15, 17–18
β-blockers, 1428
cardiomyopathy, 1439
choriocarcinoma, 1091
hypertension, 1455
myocardial toxicity, 1442
pheochromocytoma, 1207
Block randomization, 1583
Blood brain barrier (BBB)
brain tumors, 1107, 1111–1112
ICANS, 368
lomustine, 1124
Bloom syndrome
ALL, 4
AML, 24
MDSs, 92
B-lymphoblastic leukemia/lymphoma, 25t
BMB. *See* Bone marrow biopsy
BMD. *See* Bone mineral density
BMDex. *See* Bortezomib, melphalan, and dexamethasone
BMI. *See* Body mass index
BMP. *See* Bleomycin, methotrexate, and cisplatin
BMT. *See* Bone marrow transplantation
B-NHL. *See* B-cell non-Hodgkin lymphoma
BNP. *See* B-type natriuretic peptide
Body mass index (BMI)
DLBCL, 193
endometrial cancer, 932
gallbladder carcinoma, 650
HCC, 681
pancreatic cancer, 620–621
prostate cancer, 1051
RCC, 1007
SBA, 709
Body surface area (BSA), CTCL, 272, 273t
Bone cancer
bladder cancer, 1038
DTC, 1197
MBC, 832
mRCC, 1014
osteosarcoma, pediatric cancer, 1277
penile cancer, 1073
prostate cancer, 1050
rehabilitation, 1537
sarcoma, 1172–1180, 1173t, 1174f, 1175t, 1176f, 1177f
Bone health, rehabilitation, 1539–1540

Bone marrow biopsy/aspiration (BMB)
AML, 24–25
B-NHL, aggressive, 205
CEL/HES, 146
CML, 69, 82
ET, 129
HL, 291, 300–301
MCL, 231
MDSs, 93–98, 93t, 95f–98f, 101
PMF, 136
PTCLs, 259
PV, 124, 125
SCLC, 479
SM, 149–151
Bone marrow transplantation (BMT)
AHSCT, 397
CMV, 1350
gastrointestinal bleeding, 1426
osteoporosis, 1387
Bone mineral density (BMD), osteoporosis, 1387, 1388
BOOP. *See* Bronchiolitis obliterans organizing pneumonia
BOP. *See* Bleomycin, vincristine, and cisplatin
Borras, G., 964
Borrelia burgdorferi
MALT, 185
MCL, 228
primary cutaneous B-cell lymphomas, 284
Bortezomib
DLBCL, 209
MCL, 236, 239t, 240, 241
MM, 348, 351, 352
NSIP, 1466
POEMS, 357
PTCLs, 263
Bortezomib and dexamethasone (BD), MM, 348, 349
Bortezomib, cyclophosphamide, and dexamethasone (CyBorD)
AL, 327, 328
MM, 348
Bortezomib, lenalidomide, and dexamethasone (VRD)
AHPCT, 383
AL, 327–328
MM, 348–349
Bortezomib, melphalan, and dexamethasone (BMDex), 328
Bortezomib, thalidomide, and dexamethasone (BTD), 349
BOS. *See* Bronchiolitis obliterans syndrome
Bosutinib (Bosulif), 1291t
CML, 75, 76, 79, 80, 82
QT prolongation, 1452t
Botulinum toxin, spasticity, 1536
Bowel management, spinal cord injury, 1536–1537
BP-CML. *See* Blastic phase chronic myeloid leukemia
BPH. *See* Benign prostatic hypertrophy
BPMs. *See* Bilateral prophylactic mastectomies
BR. *See* Bendamustine with rituximab
Brachytherapy
airway obstruction, 1422, 1422t
cervical cancer, 969, 973, 974
prostate cancer, 1057
Bradyarrhythmias, 1448–1449
BRAF, 1286
ATC, 1202
biliary tract cancer, 647, 662, 664
CRC, 736, 748, 750–752, 753
DTC, 1190, 1191, 1199
HCL, 62–63
inhibitors, 1324
LGGs, 1275
LGSC, 920
melanoma, 1133, 1135–1136, 1144, 1147, 1148–1150, 1152
MM, 342
mutations, 1287
NSCLC, 514, 535, 541–542
sarcoid-like reactions, 1467
SBA, 709
targeted therapy, 1324, 1325t, 1326f
Brain
cancer
bladder cancer, 1032
GTD, 988, 993
penile cancer, 1073
rehabilitation, 1532–1535
SIADH, 1424
ICP, 1409–1412, 1410f–1412f
tumors, 1105–1127, 1112f–1118f, 1118t, 1119t, 1121t
classification of, 1106, 1107t
metastases, 1106–1107, 1111–1112, 1114f, 1125–1126
primary, 1107–1108
quality of life, 1126–1127
seizures, 1126
BRCA
biliary tract cancer, 669
breast cancer, 804, 888–890
male, 881
EO4, 911
EOC, 898, 899, 900, 918
EOS, 910
LABC and IBC, 864
male breast cancer, 883
MBC, 831, 839–840
pancreatic cancer, 620–621, 622, 637
prostate cancer, 1049, 1052, 1064
sarcoma, 1160
targeted therapy, 1325t
TNBC, 853
Breast cancer, 1397–1398
brain tumors, 1114f
cardiac tamponade, 1413
contralateral, 882
CUP, 1258, 1261, 1263
DCIS, 804–805, 804t, 884–888, 885f, 887t
early-stage, 803–825, 804t, 806t–809t, 813f, 816f, 817t, 818f, 819f, 821f–823f, 824t
HBOC, prostate cancer, 1049
HRPBC, AHPCT, 390
IBC, 863–871, 866f
LABC, 803–825, 804t, 806t–809t, 813f, 816f, 817t, 818f, 819f, 821f–823f, 824t
management, 863–871, 866f
lipid disorders, 1385
LMD, 1412
male, 881–883, 882f
MBC, 829–855, 833f, 834t–835t, 839t, 841t, 848t, 849f, 852f
AHPCT, 390
TNBC, 853
oncocardiology, 1436
osteoporosis, 1387
PABC, 805, 875–881, 876f, 876t, 877t
pancreatic cancer, 620–621
rehabilitation, 1531
special situations, 875–890, 876f, 876t, 877t, 882f, 885f, 887t, 888t
spinal cord compression, 1407–1408, 1409
targeted therapy, 1327t
TNBC, 803, 805, 817–819, 818f, 819f
LABC and IBC, 865
MBC, 829, 830, 832, 851–854, 852f
MRI, 1597
urinary tract obstruction, 1421
Breast conserving surgery (BCS), 809–810
DCIS, 885, 886
male breast cancer, 882
PABC, 877
Breems, D. A., 37
Breitbart, W., 1567
Brenner tumors, EOC, 904
Brentuximab, doxorubicin, vinblastine, and dacarbazine, HL, 1274
Brentuximab vedotin (BV)
cHL, 312, 314–315
CTCL, 279–280
DLBCL, 215
HL, 291, 1242
PTCLs, 260, 263, 264t
Brentuximab vedotin plus cyclophosphamide, doxorubicin, prednisone (BV-CHP), PTCLs, 253
Bretz, F., 1586
Brexucabtagene autoleucel, 1312
MCL, 236, 244
Briasoulis, E., 1264
Brigatinib, 1337
NSCLC, 538, 539
Bronchiolitis obliterans organizing pneumonia (BOOP), 1462
Bronchiolitis obliterans syndrome (BOS), 1476, 1477t
HSCT, 1473
Bronchoalveolar lavage (BAL)
aspergillosis, 1372, 1373
DAH, 1466
DILI, 1462
EP, 1466
fungal infections, 1364
HP, 1467
Brown, I. N., 449
Bruera, Eduardo, 1523
Bruton tyrosine kinase (BTK)
CLL, 56–57, 60
MALT, 186
MCL, 232, 235–236, 240, 243–244
PCNSL, 1241
WM, 335, 336
BSA. *See* Body surface area
BTD. *See* Bortezomib, thalidomide, and dexamethasone
BTK. *See* Bruton tyrosine kinase
B-type natriuretic peptide (BNP)
cardiomyopathy, 1439
PE, 1478
Budd-Chiari syndrome (BCS)
HCC, 683
PV, 122

VTE, 1503
Buffering, 1530
Buparlisib, 1328
Bupropion, *CYP2D6*, 1558
Burkitt leukemia, 4
Burkitt lymphoma (BL), 11, 193, 202–203, 203f, 213, 215
HIV/AIDS, 1224
MCL, 233
NHL, 1232, 1233, 1234, 1274
Burosumab, TIO, 1389
Busulfan. *See also specific drug combinations*
adrenal insufficiency, 1392
ARDS, 1423
breast cancer, 1398
HP, 1467
hypertension, 1454–1455, 1454t
NSIP, 1466
PV, 124
BV. *See* Brentuximab vedotin
BV-CHP. *See* Brentuximab vedotin plus cyclophosphamide, doxorubicin, prednisone
Byrd, J. C., 56

C

CA19-9
biliary tract cancer, 651
HCC, 685
pancreatic cancer, 625, 631
CA 125. *See* Cancer antigen 125
Cabazitaxel, prostate cancer, 1063, 1065
Cabazitaxel and carboplatin, prostate cancer, 1065
Cabozantinib. *See also specific drug combinations*
mRCC, 1013, 1014–1015
Cabozantinib (Cometriq), 1291t, 1336. *See also specific drug combinations*
HCC, 691, 693
mRCC, 1014, 1018–1019
MTC, 1202
nccRCC, 1019
parathyroid carcinoma, 1204
pRCC, 1019
Cabozantinib, avelumab, axitinib, sunitinib, and pazopanib, mRCC, 1013
Cabozantinib, nivolumab, lenvatinib plus everolimus, and axtinib, RCC, 1005
Cadherin 1 (*CDH1*)
breast cancer, 888
gastric cancer, 580
CAFs. *See* Cancer-associated fibroblasts
CAGE-AID. *See* Cut-down Guilty Annoyed and Eye Opener-Adapted to Include Drugs
Calcineurin inhibitors (CNI)
GVHD, 404
HCC, 688
hypertension, 1454t, 1455
CALR. *See* Chaperone protein calreticulin
Calretinin, NSCLC, 499
Campylobacter jejunii, MALT, 185
Cancer antigen 125 (CA 125)
CUP, 1256
endometrial cancer, 937, 943
EOC, 900, 903, 912, 919
GTD, 990
SCSTs, 925
Cancer-associated fibroblasts (CAFs), 622
Cancer cachexia, NSCLC, 502
Cancer genomics, 1283–1293, 1286f–1288f, 1291t–1292t. *See also* Targeted therapy; *specific genes*
Candidemia, 1367
Candidiasis (*Candida* spp.), 1366–1370, 1366f, 1368, 1368f, 1369t, 1376t
AHSCT, 407
CAO. *See* Central airway obstruction
Capecitabine
appendiceal tumors, 727
arterial ischemia, 1446, 1446t
biliary tract cancer, 655–656
CRC, 744, 745
gastric cancer, 590
gemcitabine, pancreatic cancer, 637
GTD, 997
MBC, 839–840, 841t, 843
pancreatic cancer, 626, 634
TNBC, 818
Capecitabine and 5-fluorouracil, HCC, 694
Capecitabine and ixabepilone, MBC, 841t, 846
Capecitabine and lapatinib, MBC, 850–851
Capecitabine and oxaliplatin (CAPOX)
CRC, 738, 739, 740, 742, 743
gastric cancer, 607
SBA, 713–715
Capecitabine, oxaliplatin, and irinotecan (CAPOXIRI), 713
Capmatinib, 1336–1337
CAPOX. *See* Capecitabine and oxaliplatin
CAPOXIRI. *See* Capecitabine, oxaliplatin, and irinotecan
Caprelsa. *See* Vandetanib
Carbamazepine, seizures, 1413
Carbapenems, seizures, 1412
Carboplatin. *See also specific drug combinations*
anaplastic astrocytoma, 1122
bladder cancer, 1040
EOC, 909
GCTs, 1087
glioma, 1121t
hypocalcemia, 1390
hypomagnesemia, 1390
MBC, 841t, 850–851
NSCLC, 509, 512, 514, 515, 518
osteoporosis, 1387
SCLC, 481, 486
Carboplatin and docetaxel, MBC, 846
Carboplatin and etoposide (CE), 390
Carboplatin and gemcitabine, EOC, 914
Carboplatin and paclitaxel
anal cancer, 774
carcinosarcomas, 944
EOC, 909–910, 911, 914
MBC, 841t, 846
NSCLC, 509, 520–521
Carboplatin and pegylated liposomal doxorubicin, EOC, 914
Carboplatin, gemcitabine and bevacizumab, EOC, 915
Carboplatin, paclitaxel, and bevacizumab, EOS, 910
Carboplatin, paclitaxel, bevacizumab, and atezolizumab, NSCLC, 537
Carboplatin, pemetrexed, and pembrolizumab, NSCLC, 522
Carcinoembryonic antigen (CEA)
biliary tract cancer, 648
CRC, 735, 737, 740, 741, 754
CUP, 1256
MBC, 830
MTC, 1199–1200, 1201
NSCLC, 499
Carcinoid
cervical cancer, 956
CUP, 1263
NETs, 789–790, 795
SBA, 708
Carcinoma in situ (CIS)
bladder cancer, 1035, 1036
cervical SCC, 956
Carcinoma of unknown primary (CUP), 1253–1267, 1255t, 1257t, 1258f, 1264, 1265t
Carcinosarcomas, 934, 943–944
CaRD. *See* Carfilzomib, rituximab, and dexamethasone
CARD11, FL, 170
Cardiac arrhythmia, 1448–1450, 1449f, 1450t
Cardiac tamponade, 1413–1415, 1415f
pericardial effusions, 1453
Cardiomyopathy, 1438–1439, 1439f
CEL/HES, 142
Cardiovascular system. *See also* Oncocardiology
deconditioning, 1539
Carfilzomib
AL, 328
MM, 352
NSIP, 1466
WM, 336
Carfilzomib, rituximab, and dexamethasone (CaRD), 335
Carmustine (BCNU). *See also specific drug combinations*
anaplastic astrocytoma, 1122
DVT and VTE, 1488
extravasation injuries, 1424
HSCT, 1475
male gonadal disorders, 1398
PH, 1469
Carmustine, etoposide, cytarabine, and melphalan (BEAM), 312–313
Carney-Stratakis syndrome, pheochromocytoma, 1206
Carney triad
ACC, 1215t
pheochromocytoma, 1206
CAR-T. *See* Chimeric antigen receptor T-cell
Caspofungin, 1368t
aspergillosis, 1373
candidiasis, 1368, 1369t, 1370
CBT, 437
Castleman disease
HHV8+ DLBCL, 200
KS, 1226
Castration-resistant prostate cancers (CRPCs), 1052, 1060
Catheter thrombosis, 1499
CAV. *See* Cyclophosphamide, anthracycline, and vincristine
Cavenee, Webster, 1284
CBC. *See* Contralateral breast cancer
CBF. *See* Core-binding factor

CBT. *See* Cord blood transplant
CCNU. *See* Lomustine
ccRCC. *See* Clear cell RCC
CCUS. *See* Clonal cytopenia of undetermined significance
CCyR. *See* Complete cytogenetic response
CD4, 1309
  AHSCT, 457
  AITL, 255
  CAR-T, 354
  cervical cancer, 1242
  CTCL-MF, 274
  DLBCL, 198
  fungal infections, 1364
  HL, 1241
  KS, 1126
  melanoma, 1150
  NHL, 193, 1232, 1234, 1235
  PD-1 ICIs, 1298–1299, 1307–1308
  PTCLs, 253
  sarcoid-like reactions, 1467
  SMPLD, 283
CD8, 1309
  bladder cancer, 1043
  CAR-T, 354
  CTCL, 269
  CTCL-MF, 274
  ETP-ALL, 5
  FLHCC, 695
  pancreatic cancer, 639
  PD-1 ICIs, 1298–1299, 1307–1308
  PTCL-NOS, 256
  sarcoid-like reactions, 1467
CD10
  B-ALL, 5
  DLBCL, 196, 197
  ESS, 947
  FL, 165, 166
  HCC, 684
  ISPN, 168
  MALT, 195
  NHL, 199
  SMZL, 187
CD19, 1312
  bispecific antibodies, 1314
  FL, 175
CD20. *See also* Rituximab
  AHPCT, 384
  CAR-T, 364, 1312
  CLL, 50, 52, 56
  DLBCL, 196
  EBV, 1351
  FL, 170, 175
  MALT, 186
  MCL, 231
  NHL, 1235
  NLPHL, 292, 303
  OP, 1465
  PTLD, 1477
  SLL/CLL, 187
  WM, 334, 336
CD20-positive precursor B-cell acute lymphoblastic leukemia, 11–12
CD27, 1309
CD28
  ICANS, 1313
  ICIs, 1298
CD30
  CAR-T, 372–373
  CTCL, 269, 279–280, 282–283
  CTCL-MF, 274
  DLBCL, 196, 198
  HL, 292, 1242
  NHL, 1233
  NLPHL, 292
  PTCLs, 253, 260–261
CD34, HSCT, 1475
CD40
  AHSCT, 458
  CLL, 56
  CTCL-MF, 273
  DCs, 1314
  NHL, 1232
CD47, FL, 176
CD52, hyperthyroidism, 1394
CD55, PNH, 1503
CD59, PNH, 1503
CD68, HCC, 685
CD137, 1309
CDA. *See* Cytidine deaminase
2-CDA. *See* Pentostatin and cladribine
CDC. *See* Collecting duct carcinoma
CDC73, parathyroid carcinoma, 1203, 1204
CDH1. *See* Cadherin 1
CDK4/6. *See* Cyclin-dependent kinase 4/6
CDK12, prostate cancer, 1064
CDKN
  bladder cancer, 1029
  pRCC, 1019
  sRCC, 1019
CDKN2A
  glioblastoma, 1110
  MCL, 228
  melanoma, 1134, 1136
CDKN21, MCL, 230
CDR3s. *See* Complementary determining region
CE. *See* Carboplatin and etoposide
CEA. *See* Carcinoembryonic antigen; Cost-effectiveness analysis
Cedazuridine, MDSs, 107, 109
CED/HES. *See* Chronic eosinophilic disorders/hypereosinophilic syndromes
Ceftazidime, AML, 39
Celecoxib, CRC, 736
Celiac disease, SBA, 708, 709
Cell-cell adhesion molecules, GTD, 985
Cell-free DNA (cfDNA), NSCLC, 535
Cell of origin (COO)
  AITL, 255
  B-NHL, aggressive, 196–197, 209
  DLBCL, 196–197
  PTCL-NOS, 256
CELMoDs, MM, 354
Cemiplimab, PD-1 ICIs, 1299–1311, 1300t–1303t
Central airway obstruction (CAO), 1461
Central hypothyroidism, 1393
Central nervous system (CNS). *See also* Brain; Primary CNS lymphoma; Spinal cord
  ALL, 4
    frontline therapy, 9
  BL, 202–203
  B-NHL, aggressive, 191, 193
  CAR-T, 365
  cryptococcosis, 1374
  FL, 166
  GTD, 988, 996
  IVLBCL, 206
  KS, 1126
  lymphoma, 215
    CAR-T, 372
    fungal infections, 1365
  MCL, 231
    triple-refractory relapsed, 244–245
  PCNSL, 197–198
  pediatric cancer, 1271, 1274–1276
  SCLC, 479
Central venous catheters (CVCs)
  candidemia, 1367
  candidiasis, 1370
  catheter thrombosis, 1499
  disseminated candidiasis, 1367
  fungal infections, 1365
  VTE, 1477, 1493
Centroblasts, DLBCL, 195
Cephalosporin, AML, 39
Cerebrospinal fluid (CSF)
  adenovirus, 1352
  ALL, 9
  brain tumors, 1114
  CNS B-cell lymphoma, 206
  coccidioidomycosis, 1376
  cryptococcosis, 1374
  GTD, 990
  HHV-6, 1351
  ICP, 1409
  LMD, 1412
Ceritinib (Zykadia), 1291t, 1337
  NSCLC, 538, 540
  PTCLs, 263
Cervarix, 767, 1244
Cervical cancer, 955–977, 957t, 958t, 959f, 963t, 967f, 968t, 971f, 1397
  anal cancer, 767
  CUP, 1260–1261
  HIV/AIDS, 1223, 1242–1244, 1242t, 1243f
  invasive, 962–975
  recurrent, 975–976
  urinary tract obstruction, 1421
Cervical intraepithelial neoplasia (CIN), 956, 959, 960–961
Cetuximab (Erbitux), 1291t, 1330–1331. *See also specific combination drugs*
  CRC, 747–748
  CUP, 1261
  HNSCC, 565–566
CEV. *See* Cyclophosphamide, epirubicin, and vincristine
cfDNA. *See* Cell-free DNA
CgA. *See* Chromogranin A
CGH. *See* Comparative genomic hybridization
cGVHD. *See* Chronic graft-versus-host disease
Chai, E., 1514
Chan, J. K., 909
Chang, S., 864
Chaperone protein calreticulin (*CALR*)
  ET, 128, 129, 130, 131
  Ph-MPNs, 1502
  PMF, 135, 136, 138, 139
CHAT. *See* Compassion High Alert Team
cHCC-CC. *See* Combined HCC and cholangiocarcinoma

cHCL. *See* Classical hairy cell leukemia
Checkpoint inhibitors (CPIs). *See* Immune checkpoint inhibitors
Chédiak-Higashi syndrome, B-NHL, aggressive, 192t
CHEK2, prostate cancer, 1052
Chekhov, Anton, 1297
Chemoimmunotherapy (CIT)
  ALL, 3
  CLL, 49, 55
  MCL, 235, 236, 237
  SCLC, 481–483
Chemokine receptor 4 (CXCR4)
  CLL, 56
  SOX11, 230
  WM, 333, 335, 336
Chemoreceptor trigger zone (CTZ), 1563
Chemotherapy. *See also specific cancers, drugs, and drug combinations*
  cardiomyopathy, 1439–1443, 1440f, 1441t, 1442f
  endocrine and metabolic complications, 1381–1400
  pulmonary complications, 1461–1486
  thrombosis, 1502
Chemotherapy-related amenorrhea (CRA), PAB2, 879
Chen, Y. B., 42
Chest X-ray
  anal cancer, 775
  CEL/HES, 142
  cryptococcosis, 1374
  GTD, 988, 989, 993
  MCAO, 1479
  pleural effusions, 1461
Cheyne-Stokes respiration, ICP, 1410
Chickenpox. *See* Varicella zoster virus
Chimeric antigen receptor T-cell (CAR-T), 1297–1298, 1311–1313
  AHSCT, 460–463, 460f, 462t
  ALL, 14, 16–17
  allogeneic cells, 373–374
  CBT, 438
  cHL, 316
  CLL, 58–59, 58t
  DLBCL, 214, 215
  fungal infections, 1365
  HaploSCT, 451t, 452
  ICANS, 1313
  lymphoma, 363–376, 364f, 368t–370t
  MCL, 227, 236, 244
  MM, 354
  novel designs, 374–375
  PTCLs, 263
  sarcoma, 1277
cHL. *See* Classical HL
Chlamydia psittaci, MALT, 185
Chlorambucil
  breast cancer, 1398
  CLL, 56
  male gonadal disorders, 1398
  PV, 124
Chloroacetaldehyde, hemorrhagic cystitis, 1421
Chlorpromazine, delirium, 1568t
CHOEP
  ALK+ LBCL, 212
  PTCLs, 261, 262t
Cholangiocarcinoma. *See also* Biliary tract cancer
  cHCC-CC, 684, 694
  ECC, 649
    proton therapy, 654
  hilar, 653, 669
  ICC, 647–649
    biliary tract cancer, 651
    FGFR, 662
    proton therapy, 654
  perihilar, 653
Chondrosarcoma, 1173, 1175, 1179
CHOP. *See* Cyclophosphamide, Adriamycin, vincristine, and prednisone
CHOP-Bleo, FL, 171
Choriocarcinoma, 1091, 1091f
  brain tumors, 1106
  GTD, 983–984, 986, 988, 989
  ICP, 1410
Choriocarcinoma syndrome, 1092–1093
Chou, W. C., 43
Chow, S. C., 1586
Chromatin regulatory genes, bladder cancer, 1029
Chromogranin A (CgA), NETs, 783, 784
Chromophobe nccRCC, 1005, 1020
Chromosomal translocations
  ALL, 3–4
  BL, 203
  MALT, 185
  PMBL, 199
  SLL/CLL, 188
Chronic eosinophilic disorders/hypereosinophilic syndromes (CED/HES), 119, 141–146, 142t–144, 144f, 145f, 154
Chronic graft-versus-host disease (cGVHD), AHSCT, 413–416, 414t–415t
Chronic infection (CI), DLBCL, 198, 211–212
Chronic lymphocytic leukemia (CLL), 49–63
  AHSCT, 398
  AYA, 60
  clinical features, 50
  cryptococcosis, 1373
  diagnosis, 51–52, 52f, 53f
  differential diagnosis, 52, 53t
  DLBCL, 192
  epidemiology, 49
  fungal infections, 1365
  JC virus, 1357
  laboratory features, 50–51, 51f
  older patients, 60
  patient stratification first-line treatment, 59–60
  prognosis, 55
  SIADH, 1386
  staging, 54, 54t
  transformation, 60–61
  treatment, 55–60, 55t, 58t, 59t
Chronic myeloid leukemia (CML), 67–86
  advanced stage, 84
  AHSCT, 398, 404, 416
  cancer genomics, 1290
  diagnosis, 69–70
  epidemiology, 67–68
  ET, 127
  frontline treatment, 70–78, 73t, 76t, 77t
  MDSs, 94
  molecular biology, 68
  monitoring response, 78–79, 78t
  MPDs, 120
  osteoporosis, 1388
  prognostic tools, 70
  response definition, 70, 71t
  treatment-free remission, 82–84
Chronic myelomonocytic leukemia (CMML)
  MDSs, 93, 94, 101
  MPDs, 120
Chronic neutrophilic leukemia (CNL), 120, 147–148, 147t, 154
Chronic pancreatitis, pancreatic cancer, 620–621, 623
Chronic phase chronic myeloid leukemia (CPML-CP), 67, 68
CI. *See* Chronic infection
Cibula, D., 972
Ciceri, F., 452
Cidofovir, 1346t
  BK virus, 1357
  CMV, 1350
  JC virus, 1357
CIN. *See* Cervical intraepithelial neoplasia
Ciprofloxacin, QT prolongation, 1450t
Circulating tumor DNA (ctDNA)
  appendiceal tumors, 724–725
  B-NHL, aggressive, 218–219
  cancer genomics, 1290
  cHL, 311
  CRC, 740, 748
Cirrhosis, HCC, 678, 679t, 682–683
CIS. *See* Carcinoma in situ
Cisplatin. *See also specific combination drugs*
  anal cancer, 770–772
  arterial ischemia, 1446, 1446t
  bladder cancer, 1039
  brain tumors, 1111–1112
  CUP, 1254, 1264
  EOS, 910
  extravasation injuries, 1424
  glucosuria, 1384
  HNSCC, 565–566
  HSCT, 1475
  hypertension, 1454–1455, 1454t
  hypocalcemia, 1389–1390
  male gonadal disorders, 1398
  MBC, 841t
  NSCLC, 508, 514
  oncocardiology, 1436–1437
  osteomalacia, 1388
  osteoporosis, 1387
  SCLC, 481
  VTE, 1417
Cisplatin and carboplatin, cervical cancer, 974–975
Cisplatin and doxorubicin, adenosarcomas, 949
Cisplatin and 5-fluorouracil (PF)
  anal cancer, 774
  CUP, 1261
  gastric cancer, 588
  HNSCC, 563, 570
Cisplatin and gemcitabine
  CUP, 1264
  pancreatic cancer, 637
Cisplatin and ifosfamide, adenosarcomas, 949
Cisplatin and irinotecan, CUP, 1264

Cisplatin and nab-paclitaxel, biliary tract cancer, 657
Cisplatin and oxaliplatin, gastric cancer, 606
Cisplatin and paclitaxel, cervical cancer, 976
Cisplatin and vinorelbine, NSCLC, 509
Cisplatin, etoposide, bleomycin, and doxorubicin (PEBA), 997
Cisplatin, paclitaxel, and bevacizumab, cervical cancer, 976
Cisplatin, vinblastine, and bleomycin (PVB), 997
Cisplatin, vincristine, and methotrexate, GTD, 997
CIT. *See* Chemoimmunotherapy
Citalopram, depression, 1569
Ciurea, S. O., 449
CK7, CUP, 1258
CK20, CUP, 1258
c-kit
  GCNIS, 1082
  MPDs, 120
  sarcoma, 1167
  targeted therapy, 1331–1332
CK-MB. *See* Creatine kinase myocardial band
Cladribine. *See also specific drug combinations*
  AML, 31
  CEL/HES, 145
  CNL, 120, 148
  EP, 1466
  HCL, 62
  LDAC, AML, 33
  PMF, 139
  SM, 152, 154
Cladribine (5 mg/m^2 IV on days 1-5), IDA (10 mg/m^2 IV on days 1-3), and cytarabine (1 g/m^2 IV on days 1-5) (CLIA)
  AML, 31
  FT3 inhibitors, AML, 33
Clarithromycin, QT prolongation, 1450t
Classical hairy cell leukemia (cHCL), 61–63, 61f, 62f
Classical HL (cHL), 291–295, 293t, 294f, 294t
  GZL, 202
  treatment, 304–312
Claus, E. B., 804
Clear cell carcinoma
  endometrial cancer, 933–934, 934f
  EOC, 904
  melanoma, 1134, 1135t
Clear cell RCC (ccRCC), 1005, 1008
  metastatic, 1011–1019, 1012f, 1013t, 1015t–1018t, 1016f
CLIA. *See* Cladribine (5 mg/m^2 IV on days 1-5), IDA (10 mg/m^2 IV on days 1-3), and cytarabine (1 g/m^2 IV on days 1-5)
Clinical trial statistical designs, 1579–1590
  adaptive group sequential design, 1585
  biomarker-adaptive design, 1585–1586
  phase 1, 1580–1581
  phase 2, 1581–1582
  randomized, 1582–1583
  RAR, 1583–1584
    Bayesian, 1588–1589
    patient heterogeneity, 1586–1587
    seamless phase 2/3 design, 1586
CLL. *See* Chronic lymphocytic leukemia
CLND. *See* Completion lymph node dissection
Clofarabine, AML, 31, 32
Clonal cytopenia of undetermined significance (CCUS), MDSs, 93
Clonazepam, seizures, 1413
Clostridium difficile, 1365
Clostridium spp., typhlitis, 1427
Clustered, regularly interspaced, short palindromic repeat (CRISPR), 374
c-MET. *See MET*
CMF. *See* Cyclophosphamide, methotrexate, and 5-fluorouracil
CML. *See* Chronic myeloid leukemia
CML-CP. *See* Chronic phase chronic myeloid leukemia
CMML. *See* Chronic myelomonocytic leukemia
CMT. *See* Combined modality therapy
CMV. *See* Cytomegalovirus
CN. *See* Cytoreductive nephrectomy
CNI. *See* Calcineurin inhibitors
CNL. *See* Chronic neutrophilic leukemia
CNS. *See* Central nervous system
Coagulopathy. *See also* Disseminated intravascular coagulopathy
  gastrointestinal bleeding, 1426
  HCC, 683
  hemoptysis, 1423
Cobimetinib, 1324–1325
Coccidioidomycosis (*Coccidioides immitis*), 1365, 1376–1377
Codeine, 1158, 1558f
CODOX-M/IVAC, PBL, 212
Colchicine, acute pericarditis, 1453f
Colectomy, CRC, 737
Coleman, R. J., 910
Coley, William, 1297
Collagen staining, PMF, 136
Collecting duct carcinoma (CDC), 1005, 1019–1020
Colonization, MALT, 185
Colonoscopy, CRC, 736, 754
Colony-stimulating factor 1 receptor (CSF1R)
  PNETs, 794
  targeted therapy, 1340
Colorectal cancer (CRC), 733–756, 734f, 734t, 737t, 739f, 741f, 745t–746t, 750t, 751f. *See also* Hereditary nonpolyposis colorectal cancer
  appendiceal epithelial tumors, 721
  appendiceal tumors, 716
  lipid disorders, 1384
  pancreatic cancer, 620–621
  rehabilitation, 1531
  SBA, 708, 709, 716
  targeted therapy, 1327t
Combinational CARs, 374
Combined HCC and cholangiocarcinoma (cHCC-CC), 684, 694
Combined modality therapy (CMT), B-cell lymphoma, 208
Cometriq. *See* Cabozantinib
Communication, 1569, 1570t
Community respiratory viruses (CRVs), 1352–1356, 1354t, 1355f
Comparative genomic hybridization (CGH), biliary tract cancer, 662
Compassion High Alert Team (CHAT), 1525
Complementary determining region (CDR3s), MCL, 228
Complete cytogenetic response (CCyR), 9
Complete hydatidiform moles, 986, 986t, 987
Completion lymph node dissection (CLND), melanoma, 1140, 1142, 1144, 1152
Computed tomography (CT). *See also* CT-guided biopsy; Positron emission tomography/computed tomography
  ACC, 1212
  anal cancer, 768, 775
  ATC, 1202
  biliary tract cancer, 650–651, 669
  bladder cancer, 1034, 1037
  B-NHL, aggressive, 191, 205
  brain tumors, 1108, 1112
  breast cancer, 823
  CEL/HES, 142
  cervical cancer, 968, 972, 975
  cHL, 311
  CRC, 737, 740, 741, 743, 744
  CTCL, 273
  CUP, 1253, 1254, 1256
  DTC, 1195, 1197
  EOC, 906
  EP, 1466
  esophageal cancer, 598, 605
  FL, 168, 171
  fungal infections, 1364
  gastric cancer, 583–585
  GCTs, 1087
  GEP-NETs, 784, 785
  GISTs, 1172
  GTD, 988, 989, 990f, 993, 996
  HCC, 685
  HL, 298, 301, 1274
  HNSCC, 557–558
  hyperleukocytosis, 1417
  ICP, 1410
  KS, 1126
  LABC and IBC, 866, 867
  LMD, 1412
  MALT, 185
  MBC, 830
  MCL, 232
  MM, 341, 344
  MPE, 1482
  NSCLC, 497–498, 504
  OP, 1465, 1465f
  pancreatic cancer, 624, 629, 631
  parathyroid carcinoma, 1203
  PCNSL, 1237–1238
  PE, 1417, 1417f
  penile cancer, 1074, 1075
  pheochromocytoma, 1206, 1210
  pleural effusions, 1461
  RCC, 1006, 1009
  sarcoma, 1161, 1174, 1180, 1277
  SBA, 710
  SCLC, 478f, 479
  SCSTs, 924
  seizures, 1413
  seminoma, 1087
  spinal cord compression, 1408

SVC syndrome, 1415
typhlitis, 1427
urinary tract obstruction, 1421
VC, CRC, 735
WM, 334
Computer Adaptive Test, 1532
Conconi, A., 186
Congestive heart failure, CEL/HES, 142
Constipation
anorexia-cachexia, 1564
opioids, 1556–1557
Continual reassessment method (CRM), 1581
Contralateral breast cancer (CBC), 882
COO. *See* Cell of origin
Cooper, J. S., 561
COP. *See* Cryptogenic organizing pneumonitis
Copanlisib, 1328
COP-Bleo. *See* Cyclophosphamide, vincristine, prednisone, and bleomycin
Copper deficiency, MDSs, 93
Cord blood transplant (CBT), 427–442, 430t, 434t, 435t, 436f, 437, 439t–441t
Core-binding factor (CBF), AML, 34–35
Corticosteroids
acute pericarditis, 1451
ARDS, 1423
aseptic meningitis, 1430
brain tumor seizures, 1126
candidemia, 1367
CAR-T, 367
CTCL, 276
delirium, 1567
DILI, 1462
dyspnea, 1566
fatigue, 1563
gastrointestinal bleeding, 1426
hypercalcemia, 1426
hypertension, 1455
irAEs, 1310
nausea, 1565
osteoporosis, 1387
PMF, 139
primary adrenal insufficiency, 1397
spinal cord compression, 1408
Corticotrophin. *See* Adrenocorticotropic hormone
Cost-effectiveness analysis (CEA), 1604, 1605
Co-stimulatory checkpoints, 1308–1309
Co-twin pregnancy, 998
Courneya, K. S., 1530
COVID-19
MDSs, 105
value-based oncology, 1605
Cowden syndrome, NET, 783
COX-1. *See* Cyclooxygenase 1
COX-2. *See* Cyclooxygenase 2
C-peptide
GTD, 990
PNETs, 788
prostate cancer, 1051
CPK. *See* Creatine phosphokinase
CRA. *See* Chemotherapy-related amenorrhea
CRAB. *See* Hypercalcemia, renal disease, anemia, and bone disease
CRAE, RAS-RAF-MEK pathway inhibitors, 1324
CRC. *See* Colorectal cancer
C-reactive protein (CRP), PTCL-NOS, 259
Creatine kinase myocardial band (CK-MB)
cardiomyopathy, 1439
myocardial ischemia, 1416
Creatine phosphokinase (CPK), myocardial ischemia, 1416
Creatinine
bladder cancer, 1040
CRC, 737
CREBBP, FL, 167, 170
Cremophor EL. *See* Cyclosporine, teniposide, and ixabepilone
CRISPR. *See* Clustered, regularly interspaced, short palindromic repeat
Crizotinib (Xalkori), 215, 1291t, 1338
NSCLC, 538, 540
PTCLs, 263
QT prolongation, 1452t
CRM. *See* Continual reassessment method
Crohn disease
gallbladder carcinoma, 650
SBA, 709
Cromolyn sodium, SM, 152
CRP. *See* C-reactive protein
CRPCs. *See* Castration-resistant prostate cancers
CRS. *See* Cytokine release syndrome; Cytoreductive surgery
CRVs. *See* Community respiratory viruses
Cryoablation
giant cell tumor of bone, 1180
prostate cancer, 1057
RCC, 1009
Cryptococcosis (*Cryptococcus* spp.), 1365, 1373–1375, 1376t
Cryptogenic organizing pneumonitis (COP), 1476–1477
HSCT, 1473
Cryptorchidism, GCTs, 1081–1082
CSF. *See* Cerebrospinal fluid
CSF1R. *See* Colony-stimulating factor 1 receptor
CT. *See* Computed tomography
cTACE. *See* Transcatheter arterial chemoembolization
ctDNA. *See* Circulating tumor DNA
CT-guided biopsy
bladder cancer, 1039
fungal infections, 1364
CTLA-4. *See* Cytotoxic T lymphocyte-associated antigen 4
CTLs. *See* Cytotoxic T lymphocytes
CTZ. *See* Chemoreceptor trigger zone
Cunningham, D., 637
CUP. *See* Carcinoma of unknown primary
Cushing-like syndrome, adrenal insufficiency, 1392
Cushing syndrome
pheochromocytoma, 1205
SCLC, 476, 489
Cutaneous melanoma, 1134, 1135t
Cutaneous T-cell lymphomas (CTCL), 254, 269–285, 271f, 272
CAR-T, 363
Cut-down Guilty Annoyed and Eye Opener-Adapted to Include Drugs (CAGE-AID), 1524, 1525
Cut-through hysterectomy, cervical cancer, 967
CVAD. *See* Cyclophosphamide, vincristine, doxorubicin, and dexamethasone
CVAD/MA. *See* Cyclophosphamide, vincristine, doxorubicin, dexamethasone/methotrexate and cytarabine
CVCs. *See* Central venous catheters
CVD. *See* Cyclophosphamide, vincristine, and dexamethasone
CVP. *See* Cyclophosphamide, vincristine and prednisone
CXCR4. *See* Chemokine receptor 4
CyBorD. *See* Bortezomib, cyclophosphamide, and dexamethasone
Cyclin D1, MCL, 228–230, 232, 233
Cyclin-dependent kinase 4/6 (*CDK4/6*)
glial tumors, 1109
LABC and IBC, 868, 870
male breast cancer, 883
MBC, 830, 831, 833–839, 850–851
MCL, 230
melanoma, 1136
sarcoma, 1175
targeted therapy, 1326t, 1333–1335
Cyclizine, nausea, 1565t
Cyclooxygenase 1 (COX-1), CRC, 736
Cyclooxygenase 2 (COX-2)
CRC, 736
Trousseau syndrome, 1503
Cyclophosphamide. *See also specific combination drugs*
acquired hemophilia, 1431
adenovirus, 1352
ARDS, 1423
bladder cancer, 1028
breast cancer, 1398
cardiac tamponade, 1413
CAR-T, 366
CEL/HES, 145
GVHD, 465
hemorrhagic cystitis, 1421
HSCT, 1475
hypertension, 1455
JC virus, 1357
male gonadal disorders, 1398
MBC, 841t
MDSs, 107–108
NHL, 1237
SCLC, 476
VTE, 1417
Cyclophosphamide, Adriamycin, vincristine, and prednisone (CHOP)
AHPCT, 386
ALK+ LBCL, 212
CTCL, 281
DLBCL, 1235
HHV8, 212
NLPHL, 303
PCNSL, 1125
PEL, 213
POEMS, 357
PTCLs, 253, 261, 262, 262t

Cyclophosphamide and dexamethasone (RCD), CLL, 60
Cyclophosphamide and prednisone, LGLs, 63
Cyclophosphamide, anthracycline, and vincristine (CAV), 481
Cyclophosphamide, doxorubicin, vincristine, methotrexate/ifosfamide, etoposide, high dose cytarabine (R-CODOX-M/IVAC), 213
Cyclophosphamide, epirubicin, and vincristine (CEV), 480
Cyclophosphamide, methotrexate, and 5-fluorouracil (CMF)
  breast cancer, 813
  MBC, 841t, 846
  PABC, 878
Cyclophosphamide, vincristine, and dexamethasone (CVD)
  pheochromocytoma, 1211
  prostate cancer, 1063
Cyclophosphamide, vincristine and prednisone (CVP), 16
Cyclophosphamide, vincristine, doxorubicin, and dexamethasone (CVAD)
  pheochromocytoma, 1211
  PTCLs, 261
Cyclophosphamide, vincristine, doxorubicin, dexamethasone/methotrexate and cytarabine (CVAD/MA), 210
Cyclophosphamide, vincristine, prednisone, and bleomycin (COP-Bleo), 171
Cyclosporine
  aplastic anemia, 1430
  ARDS, 1423
  B-NHL, aggressive, 192
  CEL/HES, 145
  CLL, 60
  hypertension, 1454t, 1455
  LGLs, 63
  PTCLs, 263
Cyclosporine, teniposide, and ixabepilone (Cremophor EL), drug-induced airway disease, 1469
CYP. *See* Cytochrome P450
CYP2D6. *See* Cytochrome oxidase 2D6
CYP21A2, ACC, 1215t
Cyramza. *See* Ramucirumab
Cytarabine. *See also specific combination drugs*
  AML, 31
  ARDS, 1423
  ataxia, 1535
  B-NHL, aggressive, 210
  brain tumors, 1111–1112
  CEL/HES, 145
  hypocalcemia, 1390
  IVDLBCL, 212
  JC virus, 1357
  LMD, 1412
  PCNSL, 1125
Cytidine deaminase (CDA), MDSs, 107
Cytochrome oxidase 2D6 *(CYP2D6)*, 1558
  hydrocodone, 1559, 1559f
  oxymorphone, 1559
Cytochrome P450 (CYP)
  biliary tract cancer, 650
  breast cancer, 815
  glioblastoma, 1124
  hydrocodone, 1559, 1559f
  lipid disorders, 1385
  methadone, 1560
  NHL, 1234
  NSCLC, 497
  primary adrenal insufficiency, 1396
Cytogenetics
  ALL, 3, 5–8, 6t, 7f, 7t
  AML, 24, 26–27, 37
  CEL/HES, 142
  CUP, 1254–1255
  ET, 132
  MDSs, 92, 93, 94–98, 96f–98f, 97t, 99
  PMF, 137
  PV, 122
  SLL/CLL, 188
Cytokeratin, PSTT, 987
Cytokine-based therapies, 1313–1314
Cytokine release syndrome (CRS)
  CAR-T, 363
  fungal infections, 1365
Cytomegalovirus (CMV), 1345, 1349–1350, 1350f
  aplastic anemia, 1430
  brain tumors, 1108
  CBT, 433
  CTCL, 273
  GVHD, 465, 466, 467
  HaploSCT, 452
  HHVs, 1346
  HSCT, 1475
Cytoreductive nephrectomy (CN)
  mRCC, 1010–1011
  RCC, 1005
Cytoreductive surgery (CRS), appendiceal tumors, 715, 726f, 727
Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4)
  bladder cancer, 1042
  HCC, 692
  hyperthyroidism, 1394
  hypothyroidism, 1396
  ICIs, 1298, 1340
    PD-1, 1305–1306
  ipilimumab, 1390
  MBC, 855
  melanoma, 1133, 1142, 1147–1148, 1152
  mRCC, 1034
  nivolumab, biliary tract cancer, 665, 669
  NSCLC, 514
  pancreatic cancer, 639
  primary adrenal insufficiency, 1397
  prostate cancer, 1065
  RRP, 1473
  SCLC, 483
  targeted therapy, 1340
  toxicity, 1427–1431
Cytotoxic T lymphocytes (CTLs)
  adenovirus, 1352
  BK virus, 1357
  CBT, 441
  EBV, 1351
  PTLD, 467–468

D
DA. *See* DNR plus ara-C
DAAs. *See* Direct-acting antivirals
Dabigatran (Pradaxa), 1498t
Dabrafenib (Tafinlar), 1291t, 1324
  melanoma, 1146t, 1149
  sarcoid-like reactions, 1467
Dabrafenib and trametinib (D/T)
  ATC, 1202–1203
  DTC, 1199
  melanoma, 1143t, 1144, 1145, 1146t, 1149
  NSCLC, 1327
DAC. *See* DA plus cladribine; Decitabine
Dacarbazine. *See also specific drug combinations*
  extravasation injuries, 1424
  melanoma, 1146t, 1150–1151
  sarcoma, 1165
Dacomitinib, 1330
  NSCLC, 537
Dactinomycin
  GTD, 994–975, 995t
  hypocalcemia, 1390
Dactinomycin, cisplatin, and etoposide (ACE), 995, 996
Dactolisib, 1328
DA-EPOCH-R. *See* Dose-adjusted etoposide, phosphate, prednisone, Oncovin, cyclophosphamide, hydroxydaunorubicin, and rituximab
DAF. *See* DA plus fludarabine
DAH. *See* Diffuse alveolar hemorrhage
Dalteparin
  DVT, 1418, 1418t
  VTE, 1494
D-AMB. *See* Amphotericin B-deoxycholate
Dameshek, William, 120
D'Amico, A. V., 1056
Damle, R. N., 50
Danazol, PMF, 140
Dang, H. X., 1288
Dantrolene sodium, spasticity, 1536
DA plus cladribine (DAC), AML, 31
DA plus fludarabine (DAF), AML, 31
Daratumumab, MM, 353
DARE. *See* Digital anorectal examination
Darolutamide, prostate cancer, 1049, 1061
Dasatinib (Sprycel), 1291t
  CML, 73–74, 75–76, 80
  parvovirus B19, 1356
  PH, 1478
  pleural effusions, 1467
  QT prolongation, 1452t
Daskalakis, K., 792
Daunorubicin (DNR)
  AML, 28–29, 1273
  KS, 1230
Davelaar, E. M., 963
Dawood, S., 868
dCBT. *See* Double CBT
DCC. *See* Deleted in colon cancer
DCIS. *See* Ductal carcinoma in situ
DCs. *See* Dendritic cells
DDR. *See* DNA damage response
DDT. *See* Dichlorodiphenyltrichloroethane
DeAngelis, L. M., 1125

DEB-TACE. *See* Drug-eluting bead transarterial chemoembolization
Decitabine (DAC)
  AML, 32
  MDSs, 103, 107
Deconditioning, rehabilitation, 1538–1540
Dedifferentiated chondrosarcoma, 1179
Deep learning (DL), 1593, 1594–1595
  mammography, 1597–1598, 1598f
Deep vein thrombosis (DVT), 1417–1419, 1418t, 1419t, 1467–1468, 1477–1478, 1493–1494
  catheter thrombosis, 1499
  deconditioning, 1539
Deferoxamine, MDSs, 105
Deficient mismatch pair (dMMR)
  CRC, 739, 740, 750
  PD-1 ICIs, 1305
Deleted in colon cancer (*DCC*), biliary tract cancer, 650
Delgado-Guay, M. O., 1511
Delirium, 1566–1569, 1567f, 1568f, 1568t
DeLisa, J. A., 1530
Delta-like protein 3 (DLL3), SCLC, 488
Demeclocycline, SIADH, 1386
Demerol. *See* Meperidine
DeMets, D., 1585
Dendritic cells (DCs)
  immunostimulatory agents, 1314
  vaccination, 84
Deng, O., 375
Dennis, J. L., 1258
Denosumab
  bone cancer, MBC, 832
  giant cell tumor of bone, 1180
  hypercalcemia, 1389, 1426
Depression, 1569
  anorexia-cachexia, 1564
  fatigue, 1563
Depsipeptide, QT prolongation, 1450t
Desmoplastic melanoma, 1134, 1135t
De Stefano, V., 1446
Dexamethasone. *See also specific combination drugs*
  brain tumor seizures, 1126
  MCL, 240
  MM, 348
  nausea, 1565
  primary adrenal insufficiency, 1397
Dexrazoxane, 1424
DHAP. *See* Rituximab, cisplatin, dexamethasone, high-dose cytarabine
DHL. *See* Double-hit lymphoma
DHT. *See* Dihydrotestosterone
Diabetes, 1398–1399
  bladder cancer, 1040
  endometrial cancer, 931
  HCC, 681
  pancreatic cancer, 620
  prostate cancer, 1051
  RCC, 1007
Diabetes insipidus, 1386, 1391
Diabetes mellitus, 1382–1384
  ICIs, 1383–1384, 1383t
Diazepam, seizures, 1413
DIC. *See* Disseminated intravascular coagulopathy
Dichlorodiphenyltrichloroethane (DDT)
  ACC, 1215
  lipid disorders, 1384
Dideoxy method, 1284
Dietz, J. H., 1530, 1531
Differentiated thyroid cancer (DTC), 1190–1199, 1190t, 1191f, 1191t, 1192f, 1193t, 1194t, 1195f–1198f
Diffuse alveolar hemorrhage (DAH), 1462, 1466
  HSCT, 1473
Diffuse intrinsic pontine glioma (DIPG), 1275
Diffuse large B-cell lymphoma (DLBCL), 191, 192t, 194f–197f, 194t, 200f, 201t, 202f–205f, 203t, 207t, 208t, 216t, 217t, 218f, 219f, 1309
  AHPCT, 383, 386, 387f
  CAR-T, 214, 215, 363, 365, 366, 374
  CI, 211–212
  ctDNA, 219
  double-expressor, 210
  EBV, 198, 211
  FL, 166, 167, 169
  GCB, HGBL, 201
  GZL, 202
  HHV8, 212
  HIV/AIDS, 193, 1224
  IRF4, 212
  NHL, 1233, 1235
  NLPHL, 304
  NOS, 194–197, 194f–196f
  PCNSL, 197–198
  testes, 211
  treatment, 208–209
Digital anorectal examination (DARE, DRE)
  anal cancer, 768, 775
  prostate cancer, 1056, 1058
Dihydropyridine, hypertension, 1455
Dihydrotestosterone (DHT), prostate cancer, 1066–1067, 1066f
Van Dijk, M. R., 1093
DILI. *See* Drug-induced lung injury
Dimeo, F. C., 1544–1545
Dinutuximab, neuroblastoma, 1276
Dipeptidyl peptidase-4 (DPP4), 1382
  CBT, 438
DIPG. *See* Diffuse intrinsic pontine glioma
Diphenhydramine
  CYP2D6, 1558
  nausea, 1565t
Direct-acting antivirals (DAAs), HCC, 679–680
Direct oral anticoagulants (DOACs), 1419
  atrial fibrillation, 1504
  VTE, 1494, 1499, 1502–1503
Disseminated candidiasis, 1367, 1368f
Disseminated intravascular coagulopathy (DIC)
  AML, 24, 28
  bleeding, 1419–1421
  GTD, 987, 990
  hemorrhagic cystitis, 1421
  TMAs, 1499
  Trousseau syndrome, 1503
Disseminated peritoneal adenomucinosis (DPAM), 721–722
DL. *See* Deep learning
DLBCL. *See* Diffuse large B-cell lymphoma
DLI. *See* Donor lymphocyte infusion
DLL3. *See* Delta-like protein 3
DLT. *See* Dose limiting toxicity
DME. *See* Durable medical equipment
dMMR. *See* Deficient mismatch pair
DNA damage response (DDR)
  PD-1 ICIs, 1307
  prostate cancer, 1049, 1052, 1064
DNA methylation
  epigenetics, 965
  MDSs, 96
DNR. *See* Daunorubicin; Do Not Resuscitate
DNR plus ara-C (DA), 31
DOACs. *See* Direct oral anticoagulants
do Camo, T. M., 1521
Docetaxel. *See also specific drug combinations*
  cervical cancer, 976
  gastric cancer, 606
  gemcitabine doublet, pancreatic cancer, 636
  HNSCC, 570
  MBC, 841, 842–843
  NSCLC, 509, 514
  prostate cancer, 1062, 1063
  TMAs, 1501
Docetaxel, EOC, 911
Docetaxel and capecitabine, MBC, 841t, 845
Docetaxel and carboplatin
  CUP, 1264
  prostate cancer, 1065
Docetaxel and cyclophosphamide (TC), breast cancer, 813
Docetaxel, cisplatin, and 5-fluorouracil (TPF), HNSCC, 559, 563
Docetaxel, doxorubicin, and cyclophosphamide (TAC), 868
Docetaxel, oxaliplatin, and S-1 (DOS), 590
Docetaxel, platinum, cetuximab (TPEx), 570
Donor lymphocyte infusion (DLI)
  AHSCT, 459–460
  HaploSCT, 451–452, 451t
Do Not Resuscitate (DNR), 1512, 1513
Dopamine
  bradyarrhythmias, 1449
  CTZ, 1563
DOS. *See* Docetaxel, oxaliplatin, and S-1
Dose-adjusted etoposide, phosphate, prednisone, Oncovin, cyclophosphamide, hydroxydaunorubicin, and rituximab (DA-EPOCH-R)
  ALL, 11
  B-cell lymphoma, 208
  BL, 213
  double-expressor DLBCL, 210
  HGBL, 213
  LYG, 212
  NHL, 1235, 1237
  PMBL, 212
Dose limiting toxicity (DLT), 1581
Dostarlimab, endometrial cancer, 941–942
Double CBT (dCBT), 431, 436, 441

Double-expressor, DLBCL, 210
Double-hit lymphoma (DHL), 201–202, 201t, 202f
  CAR-T, 365
Double-hit myeloma, 346
Down syndrome (trisomy 21)
  ALL, 4
  AML, 24, 25t
  MDSs, 92
  PABC, 878
Doxazosin
  pheochromocytoma, 1207
  urinary tract obstruction, 1421
Doxorubicin. *See also* Liposomal doxorubicin
  adenosarcomas, 949
  bladder cancer, 1040
  breast cancer, 1398
  DVT and VTE, 1488
  extravasation injuries, 1424
  hypocalcemia, 1390
  liposarcoma, 1169
  male gonadal disorders, 1398
  MBC, 841t, 842
  sarcoma, 1163–1165, 1166–1167, 1168
  TNBC, 853
Doxorubicin and carboplatin, TNBC, 817
Doxorubicin and cisplatin, osteosarcoma, 1177–1178
Doxorubicin and cyclophosphamide (AC)
  breast cancer, 810, 813, 814
  MBC, 841t, 845
  TNBC, 818
Doxorubicin and dacarbazine (ADIC)
  LMS, 1169
  sarcoma, 1165
Doxorubicin and ifosfamide
  LMS, 1169
  osteosarcoma, 1178
  sarcoma, 1168
Doxorubicin, bleomycin, and vinblastine (ABV)
  cHL, 304, 305
  KS, 1230
Doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD)
  cHL, 304–305, 307–309, 311
  HL, 291, 1241, 1242
  NLPHL, 303
DPAM. *See* Disseminated peritoneal adenomucinosis
DPP4. *See* Dipeptidyl peptidase-4
DRE. *See* Digital anorectal examination
DRESS. *See* Drug reaction with eosinophilia and systemic symptoms
Van Driel, W. J., 910
Drolet, M., 957
Drug development, 1579–1580
Drug-eluting bead transarterial chemoembolization (DEB-TACE), NETs, 793
Drug formularies, 1611
Drug-induced airway disease, 1469
Drug-induced lung injury (DILI), 1462–1465, 1463t–1465
Drug pricing, 1611
Drug reaction with eosinophilia and systemic symptoms (DRESS), 1427, 1428
Druker, B. J., 1290
D/T. *See* Dabrafenib and trametinib
DTC. *See* Differentiated thyroid cancer
Ductal cancer, prostate cancer, 1054
Ductal carcinoma in situ (DCIS), 804–805, 804t, 884–888, 885f, 887t
Dunleavy, K., 212
Durable medical equipment (DME), 1530, 1545, 1545t
Durham, S., 1584
Durvalumab
  biliary tract cancer, 669
  endometrial cancer, 941–942
  NSCLC, 512
  SCLC, 483
Duvelisib, 1328
  ALL, 175–176
  CLL, 49, 58
  PTCLs, 263
DVT. *See* Deep vein thrombosis
Dysphagia
  anorexia-cachexia, 1564
  spinal cord injury, 1535
Dyspnea, 1566

E

EACA. *See* Epsilon-aminocaproic acid
Early T-cell precursor lymphoblastic leukemia (ETP-ALL), 5
  AHSCT, 14
EATL. *See* Enteropathy-associated T-cell lymphoma
E/B. *See* Encorafenib and binimetinib
EBRT. *See* External-beam radiation therapy
EBUS. *See* Endobronchial ultrasound
EBV. *See* Epstein-Barr virus
E-cadherin, LABC and IBC, 868
ECC. *See* Extrahepatic cholangiocarcinoma
ECE. *See* Extracapsular extension
ECF. *See* Epirubicin, cisplatin, and infusional 5-fluorouracil
ECG. *See* Electrocardiogram
Echinocandins
  AHSCT, 407
  aspergillosis, 1373
  candidiasis, 1368, 1369t
Echocardiogram
  cardiac tamponade, 1415, 1415f
  cardiomyopathy, 1439, 1439f
  CEL/HES, 142
  pericardial effusions, 1452, 1453, 1453f, 1454
  PH, 1478
Ectopic pregnancy, GTD, 988
Eculizumab, HUS, 1430
ECX. *See* Epirubicin, cisplatin, and capecitabine
Eczema, brain tumors, 1108
Edmonton Classification System for Cancer, 1555, 1555f
Edmonton Symptom Assessment Scale (ESAS), 1520, 1522, 1555, 1556f
Edmonton Symptom Assessment Scale-Financial and Spiritual (ESAS-FS), 1524
Edoxaban, VTE, 1478, 1499
EDP. *See* Etoposide, doxorubicin, cisplatin
EDRT. *See* Escalated-dose radiotherapy
EFRT. *See* Extended-field radiation therapy
EFT. *See* Ewing family of tumors
EGD. *See* Esophagogastroduodenoscopy
Egerm-cell tumors. *See* Extragonadal germ cell tumors
EGFR. *See* Epidermal growth factor receptor
EHE. *See* Epithelioid hemangioendothelioma
Eick, S. G., 1585
eIF4E. *See* Eukaryotic translation initiation factor 4e
Einhorn, L. H., 1089, 1096
Electrocardiogram (ECG)
  acute pericarditis, 1451
  cardiac tamponade, 1415
  cardiomyopathy, 1439
  CEL/HES, 142
  myocardial toxicity, 1442
ELF, MIBC, 1030
ELISA. *See* Enzyme-linked immunoassay
Ellenberg, 1586
Elotuzumab, MM, 353
EMA-CO. *See* Etoposide, methotrexate, and dactinomycin alternating weekly with cyclophosphamide and vincristine
EMA-EP. *See* Etoposide, methotrexate, dactinomycin, and cisplatin
Embryonal carcinoma, 1089–1090, 1089f
EMCU. *See* Epstein-Barr virus-positive mucocutaneous ulcer
EMH. *See* Extramedullary hematopoiesis
EMR. *See* Endoscopic mucosal resection
Enasidenib
  AML, 34, 35
  MDSs, 110
Encorafenib, 1324
Encorafenib and binimetinib (E/B), melanoma, 326, 1146t, 1150
Encorafenib and cetuximab, CRC, 733
Endobronchial ultrasound (EBUS), NSCLC, 503, 504
Endocrine therapy (ET)
  endometrial cancer, 941–942
  PABC, 878, 879
Endodermal sinus tumors, 1090–1091
End-of-life, rehabilitation, 1546–1548
Endometrial cancer, 931–949, 933f–937f, 933t–934t, 936t, 938t, 939f–941f, 943f–945f, 946t, 947f
  DCIS, 887
Endometrial hyperplasia, 932, 933t
Endometrial stromal sarcoma (ESS), 934, 946–948, 947f
Endometrioid adenocarcinoma, 932, 933f
  EOC, 904
Endoscopic mucosal resection (EMR), esophageal cancer, 600
Endoscopic ultrasonography (EUS)
  CRC, 737, 743
  esophageal cancer, 598, 605
  gastric cancer, 583–585
  pancreatic cancer, 624
  PNETs, 785
Endoscopy
  MALT, 185
  NETs, 784–785
  SBA, 710

Endothelial factor VIII, KS, 1227
Enfortumab vedotin, bladder cancer, 1027
Enhanced Recovery After Surgery (ERAS), 1613
ENKL. *See* Extranodal natural-killer/T-cell lymphoma
Enoxaparin
  DVT, 1418, 1418t
  thrombosis, 1502
  VTE, 1494
Entecavir (Baraclude), 1356
Enterocolitis, irAEs, 1311
Enteropathy-associated T-cell lymphoma (EATL), 254
Entrectinib (Rozlytrek), 1338, 1340t
  cervical cancer, 976
  NSCLC, 545
  pancreatic cancer, 638
Enzalutamide, 131
  prostate cancer, 1049, 1061, 1062, 1063
Enzyme-linked immunoassay (ELISA)
  HIV/AIDS, 1225
  KS, 1226
  phantom human chorionic gonadotropin syndrome, 991
EOC. *See* Epithelial ovarian cancer
Eosinophilic pneumonia (EP), 1466
EP. *See* Etoposide and cisplatin
EP300, FL, 167, 170
EP-EMA. *See* Etoposide and dactinomycin alternating weekly with etoposide and cisplatin
Ependymoma, 1105, 1107
  pediatric cancer, 1275–1276
EPHOSS. *See* Extra physiologic oxygen shock/stress
Epidermal growth factor receptor (*EGFR*), 1286. *See also* Human epidermal growth factor receptor 2
  ACC, 1217
  appendiceal tumors, 723, 724
  ARDS, 1423
  brain tumors, 1118
  cancer genomics, 1290
  CRC, 733, 748, 749
  gastric cancer, 607
  glioblastoma, 1110, 1111
  GTD, 985
  HNSCC, 556, 565
  hypomagnesemia, 1390
  NSCLC, 54t, 499, 514, 518–519, 520, 535, 536–538
  OP, 1465
  PD-1 ICIs, 1308
  RAS-RAF-MEK pathway inhibitors, 1324
  RRP, 1473
  SBA, 716
  SCLC, 476
  targeted therapy, 1325t, 1329–1331
Epinephrine
  bradyarrhythmias, 1449
  hemoptysis, 1423
Epirubicin. *See also specific drug combinations*
  breast cancer, 1398
  MBC, 842
Epirubicin, cisplatin, and capecitabine (ECX), 601
Epirubicin, cisplatin, and infusional 5-fluorouracil (ECF), 588, 589
Episcleritis, 1431
Episode-based payment models, value-based oncology RT, 1612–1613
Epithelial membrane antigen, HCC, 685
Epithelial ovarian cancer (EOC), 897–921, 899f, 899t, 901t, 902t, 903f, 904f, 905t, 907f–908f, 913t
Epithelioid hemangioendothelioma (EHE)
  HCC, 685
  sarcoma, 1167–1168
Epithelioid trophoblastic tumor (ETT), 983, 987
  GTD, 988, 989, 990, 994, 998
Epo. *See* Erythropoietin
EPOCH. *See* Etoposide phosphate, prednisone, Oncovin, cyclophosphamide, and hydroxydaunorubicin
EPOCH-R
  HIV/AIDS, 1223
  NHL, 1274
Epsilon-aminocaproic acid (EACA), 1421
Epstein-Barr virus (EBV), 1345, 1351
  aGVHD, 464
  AHSCT, 457
  AITL, 256
  BL, 202
  B-NHL, aggressive, 192–193, 192t
  brain tumors, 1108
  CTCL, 273
  DLBCL, 198, 211
  gastric cancer, 580–581
  GVHD, 466, 467
  HHVs, 1346
  HIV/AIDS, 1224
  HL, 293, 1241
  HNSCC, 557
  LYG, 198
  NHL, 1232, 1234
  PCNSL, 198, 1238
  primary cutaneous B-cell lymphomas, 284
  PTCL-NOS, 256
  PTCLs, 254, 259
Epstein-Barr virus-positive mucocutaneous ulcer (EMCU), 198, 212
ER. *See* Estrogen receptor
ERAS. *See* Enhanced Recovery After Surgery
ERBB2
  biliary tract cancer, 662
  bladder cancer, 1029
  lung cancer, 544, 546
  myocardial toxicity, 1442
  NRGs, 545
  oncocardiology, 1436, 1438
Erbitux. *See* Cetuximab
ERCC2
  lung cancer, 497
  MIBC, 1030–1031
Erdafitinib, 1339
  bladder cancer, 1039, 1041, 1043
Eribulin
  MBC, 839–840, 844
  sarcoma, 1165–1166
Erivedge. *See* Vismodegib
ERK. *See* Extracellular signal-regulated kinase
Erlotinib (Tarceva), 1291t, 1329. *See also specific drug combinations*
  gemcitabine doublet, pancreatic cancer, 636
  hypomagnesemia, 1390
  RRP, 1473
Erythroid-stimulating agents (ESAs), PMF, 139–140
Erythromelalgia, PV, 122
Erythromycin, QT prolongation, 1450t
Erythropoietin (Epo)
  hypertension, 1454, 1454t, 1455
  MDSs, 93, 103, 105, 106
  PMF, 140
  PV, 121
ESAs. *See* Erythroid-stimulating agents
ESAS. *See* Edmonton Symptom Assessment Scale
ESAS-FS. *See* Edmonton Symptom Assessment Scale-Financial and Spiritual
Escalated-dose radiotherapy (EDRT), biliary tract cancer, 654
Escitalopram, depression, 1569
Esophageal cancer, 593–612, 595t–597t, 598f, 599f, 600f, 602t
Esophagitis, 1366
Esophagogastroduodenoscopy (EGD)
  esophageal cancer, 598, 605
  gastric cancer, 582
ESS. *See* Endometrial stromal sarcoma
Essential thrombocytopenia (ET), 119, 127–134, 129f, 129t, 130, 130t–132t, 134t, 154
  arterial ischemia, 1445–1446
  ET, 128
  Ph-MPNs, 1502, 1503
  PMF, 134, 135, 136, 138t, 139
  PV, 125, 126
Estradiol, male breast cancer, 883
Estramustine, osteomalacia, 1389
Estrogen
  endometrial cancer, 931
  MBC, 838–839
Estrogen receptor (ER)
  breast cancer, 805, 807, 808, 814, 829
  DCIS, 884, 886
  ESS, 948
  PABC, 876
ET. *See* Endocrine therapy; Essential thrombocytopenia
Ether-a-go-go-related gene (hERG), oncocardiology, 1438
Etoposide. *See also specific combination drugs*
  anaplastic astrocytoma, 1122
  brain tumors, 1111–1112
  drug-induced airway disease, 1469
  EOC, 917
  extravasation injuries, 1424
  NSCLC, 509
Etoposide and cisplatin (EP)
  SCLC, 480, 481
  seminoma, 1087
Etoposide and dactinomycin alternating weekly with etoposide and cisplatin (EP-EMA), GTD, 996, 997t

Etoposide, doxorubicin, cisplatin (EDP), 1215–1216
Etoposide, ifosfamide, and cisplatin, GTD, 996
Etoposide, methotrexate, and dactinomycin alternating weekly with cyclophosphamide and vincristine (EMA-CO)
  GTD, 995, 996
  PSTT, 998
Etoposide, methotrexate, dactinomycin, and cisplatin (EMA-EP), 995
Etoposide, methylprednisolone, cytarabine, and cisplatin (R-ESHAP), 21, 1237
Etoposide phosphate, prednisone, Oncovin, cyclophosphamide, and hydroxydaunorubicin (EPOCH)
  ALK+ LBCL, 212
  ALL, 11
  B-cell lymphoma, 208
  DLBCL, HHV8, 212
  NHL, 1235
  PEL, 213
  PTCLs, 261
ETP-ALL. *See* Early T-cell precursor lymphoblastic leukemia
ETT. *See* Epithelioid trophoblastic tumor
EUA. *See* Examination under anesthesia
Eukaryotic translation initiation factor 4e (eIF4E), appendiceal tumors, 724
EUS. *See* Endoscopic ultrasonography
Everolimus (Afinitor), 1291t. *See also specific drug combinations*
  hyperglycemia, 1385
  nccRCC, 1019
  parathyroid carcinoma, 1204
Everolimus and exemestane, MBC, 839–840
Everolimus and fulvestrant, MBC, 839–840
Ewing family of tumors (EFT), 1172, 1175
Ewing sarcoma, 1179–1180
  CUP, 1258
Examination under anesthesia (EUA), bladder cancer, 1034, 1037
Exemestane
  breast cancer, 815
  everolimus, MBC, 839–840
Exenteration, cervical cancer, 968t, 975–976
Exercise
  fatigue, 1563
  rehabilitation, 1540–1541, 1542f
Extended-field radiation therapy (EFRT)
  cHL, 304
  HL, 292
  NLPHL, 302
External-beam radiation therapy (EBRT)
  cervical cancer, 972, 973, 974, 975
  DTC, 1196, 1198
  hemoptysis, 1423
  MTC, 1201
  pheochromocytoma, 1211
  sarcoma, 1162, 1163
Extracapsular extension (ECE), melanoma, 1141
Extracellular signal-regulated kinase (ERK), 1323–1324
Extracorporeal photopheresis, CTCL, 282
Extragonadal germ cell tumors (Egerm-cell tumors), 1098–1099
  CUP, 1263
Extrahepatic cholangiocarcinoma (ECC), 649
  proton therapy, 654
Extramedullary hematopoiesis (EMH), PMF, 134, 135, 141
Extranodal disease, B-NHL, aggressive, 193
Extranodal natural-killer/T-cell lymphoma (ENKL), 254
Extra physiologic oxygen shock/stress (EPHOSS), CBT, 437
Extravasation injuries, 1423–1424, 1425t
EZH2
  FL, 167, 170, 176
  ISPN, 168

F

FAC. *See* 5-fluorouracil, doxorubicin, and cyclophosphamide
FACIT-F. *See* Functional Assessment of Chronic Illness-Fatigue
FACIT-Sp. *See* Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being Scale
FACT-G. *See* Functional Assessment of Cancer Therapy-General
Fader, A. N., 920
FAM. *See* 5-fluorouracil, doxorubicin, and mitomycin C
Famciclovir, 1346t
  HSV, 1346
  VZV, 1348
Familial adenomatous polyposis (FAP)
  CRC, 736, 740
  SBA, 708, 709
Familial atypical multiple mole and melanoma syndrome (FAMMM), 1134
Familial recurrent hydatidiform mole syndrome, 985
FAMMM. *See* Familial atypical multiple mole and melanoma syndrome
Fam-trastuzumab deruxtecan-Xki, 1333
Fanconi anemia
  AHSCT, 398
  ALL, 4
  AML, 24
  HCC, 678
  MDSs, 92
FAP. *See* Familial adenomatous polyposis
FAS. *See* 5-fluorouracil, doxorubicin, and streptozocin
Fatigue, 1562–1563, 1563f
FCI. *See* Flow cytometric immunophenotyping
FDG-PET. *See* Fluorodeoxyglucose positron emission tomography
FDG-PET/CT. *See* Fluorodeoxyglucose positron emission tomography/computed tomography
Fedratinib, PMF, 140–141
Feldman, D. R., 390
Fentanyl, 1559–1560
Ferrant, A., 38
Ferriss, J. S., 910
Fertility-sparing surgery, cervical cancer, 969–971
Fetal occult blood testing (FOBT), CRC, 735
a-fetoprotein (AFP)
  CUP, 1256
  GCTs, 1081, 1082, 1083, 1086
  HCC, 682
  NSGCT, 1095
  yolk sac tumors, 1090–1091
FFPE. *See* Formalin-fixation and paraffin-embedding
FGFR. *See* Fibroblast growth factor receptor
FGR1, CEL/HES, 142, 143t
FH, RCC, 1006
Fibroblast growth factor receptor (*FGFR*)
  biliary tract cancer, 647, 662–663, 1029
  bladder cancer, 1028, 1031, 1037, 1041, 1043
  CEL/HES, 146
  LABC and IBC, 868, 870
  MIBC, 1030
  mRCC, 1014
  PNETs, 794
  targeted therapy, 1339
Fibrolamellar HCC (FLHCC), 677, 684–685, 694–695
Filgrastim
  CBT, 437
  NHL, 1237
FIM. *See* Functional Independence Measure
Finasteride, urinary tract obstruction, 1421
Fine-needle aspiration (FNA)
  ACC, 1214
  ATC, 1202
  DTC, 1197
  HNSCC, 557
  MTC, 1199
  penile cancer, 1073, 1075
  sarcoma, 1161
  thyroid cancer, 1190
Fischer, K., 56
FISH. *See* Fluorescence in situ hybridization
Fisher, I., 1581
5q-syndrome, MDSs, 96
Fixed allocation randomization, 1583
FL. *See* Follicular lymphoma
FLAG-IDA. *See* Fludarabine, high-dose cytarabine, and IDA
FLAIR. *See* Fluid-attenuated inversion recovery
Flavopiridol, 1333
FLCN, RCC, 1006
Fleming, T. R., 1582, 1585
FLHCC. *See* Fibrolamellar HCC
Flow cytometric immunophenotyping (FCI), 4
Flow cytometry
  breast cancer, 808
  MDSs, 98
  MPE, 1482
  SLL/CLL, 188
  WM, 334
FLP. *See* Platinum and 5-fluorouracil
FLT3. *See* Fms-like tyrosine kinase 3
FLT3-mutated, AML, 33
Fluconazole, 1368t
  AHSCT, 407
  candidiasis, 1368, 1369, 1369t

coccidioidomycosis, 1377
cryptococcosis, 1374
Flucytosine
candidiasis, 1369t
cryptococcosis, 1374
Fludarabine. *See also specific drug combinations*
EP, 1466
granulomatous pneumonitis, 1467
HaploSCT, 449
HBV, 1356
JC virus, 1357
MDSs, 107–108
Fludarabine and rituximab, WM, 335
Fludarabine, cyclophosphamide, and rituximab (PCR), 55–56, 57, 60
Fludarabine, high-dose cytarabine, and IDA (FLAG-IDA), 31
Fludrocortisone
primary adrenal insufficiency, 1397
SIADH, 1386
Fluid-attenuated inversion recovery (FLAIR), brain tumors, 1114
Fluorescence in situ hybridization (FISH)
AL, 324
ALL, 7
breast cancer, 808
CLL, 50
CML, 68, 69, 78
CUP, 1258
HGBL, 201
MCL, 229, 234
MDSs, 98
MM, 345, 346
nodal marginal zone lymphoma, 186
SLL/CLL, 188
Fluorodeoxyglucose positron emission tomography (FDG-PET)
ACC, 1212
ATC, 1202
brain tumors, 1114
cHL, 311
CUP, 1256
DTC, 1197
esophageal cancer, 598–601
FL, 168–169
gastric cancer, 585
GEP_NETs, 785
HNSCC, 558
MTC, 1201
NSCLC, 504
pancreatic cancer, 625
penile cancer, 1075
pheochromocytoma, 1210
sarcoma, 1174
Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT)
B-NHL, aggressive, 204–205, 204f, 217–218, 218f, 219t
HL, 298
PTCLs, 259
Fluoropyrimidine, CRC, 739, 742, 743
Fluoroquinolone, MDSs, 105
5-fluorouracil (5-FU). *See also specific combination drugs*
appendiceal tumors, 727
arterial ischemia, 1446, 1446t
ataxia, 1535
biliary tract cancer, 655, 656
breast cancer, 1397
cervical cancer, 976
CRC, 754
gastric cancer, 589
myocardial ischemia, 1416
NETs, 784
oncocardiology, 1436–1437
pancreatic cancer, 634
SBA, 713
VTE, 1417
5-fluorouracil and cisplatin
cHCC-CC, 694
penile cancer, 1076–1077
5-fluorouracil and gemcitabine doublet, pancreatic cancer, 636
5-fluorouracil and IFN-α, FLHCC, 694–695
5-fluorouracil and leucovorin
CRC, 738, 744
pancreatic cancer, 638
SBA, 713
5-fluorouracil, cisplatin, and paclitaxel (FPT)
esophageal cancer, 605
gastric cancer, 590
5-fluorouracil, doxorubicin, and cyclophosphamide (FAC)
breast cancer, 810, 814
PABC, 878
5-fluorouracil, doxorubicin, and mitomycin C (FAM), SBA, 713
5-fluorouracil, doxorubicin, and streptozocin (FAS)
NETs, 794
PNETs, 781
5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX)
biliary tract cancer, 655
CRC, 742, 743
pancreatic cancer, 540, 622, 632, 634–635, 637, 639
Fluoxetine
CYP2D6, 1558
depression, 1569
Fms-like tyrosine kinase 3 (FLT3))
AHSCT, 416
AML, 23, 35, 38
MDSs, 110
PMF, 140, 141
FNA. *See* Fine-needle aspiration
FNH. *See* Focal nodular hyperplasia
FOBT. *See* Fetal occult blood testing
Focal nodular hyperplasia (FNH), HCC, 685
FOLFIRINOX. *See* 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin
Folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX)
appendiceal tumors, 727
biliary tract cancer, 670
CRC, 738, 739, 740, 742, 743, 744
esophageal cancer, 600
SBA, 715, 716
Follicle-stimulating hormone (FSH), 1397
Follicular carcinoma, 192, 192f
Follicular lymphoma (FL), 165–177, 167f, 169f, 170t, 172t–175t
AHPCT, 386–387
AHSCT, 459
CAR-T, 363, 365
DLBCL, 192
MCL, 233
nodal marginal zone lymphoma, 186
transformed, 215
Formalin-fixation and paraffin-embedding (FFPE), 1289
Foscarnet, 1346t
CMV, 1350
HSV, 1346
Fosphenytoin, seizures, 1413
FOX01, FL, 170
FPT. *See* 5-fluorouracil, cisplatin, and paclitaxel
Franc, E. L., 965
Freidlin, B., 1589
Freireich, E. J., 27
FSH. *See* Follicle-stimulating hormone
5-FU. *See* 5-fluorouracil
Fulvestrant. *See also specific drug combinations*
male breast cancer, 883
MBC, 836, 838
Functional Assessment of Cancer Therapy-General (FACT-G), 1520–1521
Functional Assessment of Chronic Illness-Fatigue (FACIT-F), 1562, 1562t
Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being Scale (FACIT-Sp), 1520
Functional Independence Measure (FIM), 1532, 1533f
Fung, Y. K., 1284
Fungal infections, 1363–1378, 1365f, 1366f, 1368f, 1368t, 1369t, 1371f, 1372t, 1375f, 1376t
Furosemide, hypercalcemia, 1426
Fusariosis (*Fusarium* spp.), 1375, 1375f, 1376t
Futibatinib, biliary tract cancers, 662–663

G

Gabapentin
pain management, 1561, 1561t
seizures, 1413
Ga-DOTANOC, NETs, 785
Ga-DOTATATE
GEP-NETs, 782
NETs, 785
Ga-DOTATOC, NETs, 785
Galactomannan, aspergillosis, 1372
Gallbladder carcinoma, 648–650
incidental, 656
radical cholecystectomy, 651
Gallstones
gallbladder carcinoma, 650
pancreatic cancer, 623
GALT. *See* Gut-associated lymphoid tissue
Ganciclovir, 1346t
CMV, 1350
HHV-6, 1351
HSV, 1346
JC virus, 1357
Gardasil, 767, 957, 1242
Gardin, C., 29
Gardner syndrome
biliary tract cancer, 647
gallbladder carcinoma, 650

sarcoma, 1160
Gastournioti, A., 1598
Gastric cancer, 579–612, 581t, 583t–585t, 585, 586f, 591t, 607, 610t, 611t
Gastric NETs, 786
Gastrinoma, PNETs, 789
Gastroenteropancreatic NETs (GEP-NETs), 781–785
Gastroesophageal junction (GEJ) cancer, 593–612, 593f, 595t–597t
Gastrointestinal bleeding, 1426–1427
ACS, 1504
Gastrointestinal stromal tumors (GISTs), 1171–1172, 1172t
c-kit, 1331
sarcoma, 1162, 1167
Gastroparesis, pancreatic cancer, 639
GBS. *See* Guillain-Barré syndrome
GC. *See* Gemcitabine and carboplatin; Germinal center
GCB. *See* Germinal center B-cell subtype
GCI. *See* Gemcitabine, carboplatin, and iniparib
G-CSF. *See* Granulocyte colony-stimulating factor
GCT. *See* Goblet cell tumor
GCTs. *See* Germ-cell tumors
GDTCL. *See* gd T-cell lymphoma
Gefitinib (Iressa), 1291t, 1329
Gehan, E. A., 1582
GEJ. *See* Gastroesophageal junction cancer
Gemcitabine. *See also specific drug combinations*
ARDS, 1423
arterial ischemia, 1446–1447, 1446t
biliary tract cancer, 655, 657
bladder cancer, 1040
cervical cancer, 976
CTCL, 281
CUP, 1266
EOC, 917
GTD, 997
HP, 1467
LMS, 1169
MBC, 839–840, 841t, 843–844
pancreatic cancer, 626–627, 631, 632–633, 634–635, 636–637
sarcoma, 1165
SBA, 713
TMAs, 1501
Gemcitabine and bevacizumab, cHCC-CC, 694
Gemcitabine and capecitabine
biliary tract cancer, 656
MBC, 841t, 846
Gemcitabine and carboplatin (GC)
MBC, 841t
TNBC, 853
Gemcitabine and cisplatin
biliary tract cancer, 654–655, 656, 657
durvalumab, biliary tract cancer, 669
nivolumab, biliary tract cancer, 665, 669
Gemcitabine and docetaxel
LMS, 1169
sarcoma, 1168
Gemcitabine and paclitaxel (GT), MBC, 841t, 845
Gemcitabine and platinum, cHCC-CC, 694
Gemcitabine, carboplatin, and iniparib (GCI), 853
Gemcitabine, dexamethasone, and cisplatin (R-GDP), 214
Gemcitabine, nab-paclitaxel, and cisplatin, pancreatic cancer, 637–638
Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), 312
Gemtuzumab ozogamicin (GO)
AML, 23, 30, 43–43
APL, 42
Van Genderen, P. J., 133
Gene expression profiling (GEP)
DCIS, 886
DLBCL, 197
MM, 342, 343, 345
PTCLs, 255
sALCL, 256
Genome-wide association studies (GWAS), NSCLC, 497
GEP. *See* Gene expression profiling
GEP-NETs. *See* Gastroenteropancreatic NETs
Gerlinger, M., 171, 1297
Germ cell neoplasia in situ (GGNIS), 1082
Germ-cell tumors (GCTs), 1081–1099, 1088f–1092f, 1094f, 1097f
AHPCT, 389–391
CUP, 1263
pediatric cancer, 1271
phantom human chorionic gonadotropin syndrome, 991
SCSTs, 923–925
seminomas, 1081, 1083–1089, 1084t–1086t, 1085f, 1086f, 1088f
spinal cord compression, 1409
Germinal center (GC)
B-cells, MM, 342
HL, 292
ISPN, 168
Germinal center B-cell subtype (GCB)
DLBCL, 191, 197, 209
BL, 203
HGBL, 201
Gershenson, D. M., 920
Gestational trophoblastic disease (GTD), 983–999, 985t, 986t, 988t, 989f, 990f, 991t, 992f, 992t, 994t, 995t, 996f, 997t
Gestational trophoblastic neoplasia (GTN), 983, 985, 989
Gestational trophoblastic tumor (GTT), 983
GGNIS. *See* Germ cell neoplasia in situ
GH. *See* Growth hormone
Ghobadi, A., 459
Ghorashian, S., 375
Giant cell tumor of bone, 1180
Gilotrif. *See* Afatinib
GISTs. *See* Gastrointestinal stromal tumors
GITR. *See* Glucocorticoid-induced TNFR
Giuliano, A. R., 767
Gleevec. *See* Imatinib
Glial tumors, 1110–1111
Glioblastoma, 1105, 1110–1111, 1112f, 1117, 1117f, 1122–1124
Glioma, 1105, 1107, 1110, 1112f
HGGs, pediatric cancer, 1275
LGGs, 1118–1120, 1119t
malignant, 1120–1122, 1121t
Glucagonoma, PNETs, 789
Glucocorticoid-induced TNFR (GITR), 1309
primary adrenal insufficiency, 1397
Glucocorticoids
ACC, 1215
CEL/HES, 145, 146
diabetes mellitus, 1382
TBG, 1396
Glucosuria, 1384
Glutamate, mRCC, 1017
Glutamine, mRCC, 1017
Glutathione-*S*-transferase (GST)
AHSCT, 401
MDSs, 92
NSCLC, 497
Glutathione-*S*-transferase Mu 1 (GSTM1), bladder cancer, 1029
Glycogen storage disease (GSD), HCC, 678, 682
Glypican-3 (GPC3), FLHCC, 684
GM-CSF. *See* Granulocyte-macrophage colony-stimulating factor
GNA11, melanoma, 1137
GNAQ, melanoma, 1137
GNAS, appendiceal tumors, 723, 725
GnRH. *See* Gonadotropin-releasing hormone
GnRHa. *See* Gonadotropin-releasing hormone analogue
GO. *See* Gemtuzumab ozogamicin
Goblet cell tumor (GCT)
appendiceal carcinoid tumors, 720
appendiceal tumors, 719
Goff, B. A., 946
Gonadal disorders
female, 1397–1398
male, 1398, 1399f
Gonadotropin-releasing hormone (GnRH)
male gonadal disorders, 1398
osteoporosis, 1387
ovarian cancer, 1397
Gonadotropin-releasing hormone analogue (GnRHa)
male breast cancer, 882, 883
PAB2, 879
Gordon, A. N., 917
Gorlin syndrome, 1275
GPC3. *See* Glypican-3
Graft-versus-host disease (GVHD). *See also* Acute graft-versus-host disease; Chronic graft-versus-host disease
adenovirus, 1351, 1352
AHSCT, 404–406, 457–460, 458f, 464–468
CBT, 427, 431, 433
CMV, 1349
CRVs, 1353
fungal infections, 1365
HaploSCT, 448, 449, 451, 453
HCV, 1356
HSCT, 1473–1475, 1476–1477
JC virus, 1357
RSV, 1354
VZV, 1348

De Gramont, A., 745
Granulocyte colony-stimulating factor (G-CSF)
  AHPCT, 384
  AHSCT, 402–403
  AML, 39
  CNL, 147
  CUP, 1264
  fungal infections, 1377
  HNSCC, 570
  KS, 1230
  MDSs, 94, 105
  NHL, 1235
Granulocyte-macrophage colony-stimulating factor (GM-CSF)
  melanoma, 1150
  mucormycosis, 1375
  TVEC, 1314
  vaccines, 1313
Granulomatous pneumonitis, 1467
Graves disease, 1394, 1428
Grey-zone lymphoma (GZL), 202
Gribben, J. G., 170
Groenvold, M., 1521
Growth hormone (GH), 1392–1393, 1392f
  adrenal insufficiency, 1392
  deficiency, 1391
    AHSCT, 417
  diabetes mellitus, 1382
GSD. *See* Glycogen storage disease
GSIs. *See* g-secretase inhibitors
GST. *See* Glutathione-*S*-transferase
GSTM1. *See* Glutathione-*S*-transferase Mu 1
GT. *See* Gemcitabine and paclitaxel
GTD. *See* Gestational trophoblastic disease
GTN. *See* Gestational trophoblastic neoplasia
GTT. *See* Gestational trophoblastic tumor
Gu, X., 1586
Guadecitabine, MDSs, 107
Guillain-Barré syndrome (GBS), 1429
Gut-associated lymphoid tissue (GALT), HIV/AIDS, 1225
Guzzetti, A., 1449
GVD. *See* Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin
GVHD. *See* Graft-versus-host disease
GWAS. *See* Genome-wide association studies
Gynandroblastomas, SCSTs, 924
GZL. *See* Grey-zone lymphoma

H

HAART. *See* Highly active antiretroviral therapy
HAE. *See* Hepatic artery embolization
Hainsworth, J. D., 1263, 1266
Hairy cell leukemia (HCL), 52, 61–63, 61f, 62f
  MCL, 233
Haloperidol
  delirium, 1567, 1568t
  nausea, 1565t
Hamilton Rating Scale for Depression (HAM-D), 1569
HAMN. *See* High-grade appendiceal mucinous neoplasm
Hans, C. P., 197
Haploidentical hematopoietic stem cell transplantation (HaploSCT), 447–453, 448t, 450t, 451t
Harris, A. C., 411
Hasford, J., 77
HAT. *See* Histone acetyltransferase
Hay fever, brain tumors, 1108
HBeAg. *See* HBV *e*-antigen
HBOC. *See* Hereditary breast and ovarian cancer
HBV. *See* Hepatitis B virus
HBV *e*-antigen (HBeAg), HCC, 678
HCC. *See* Hepatocellular carcinoma
hCG. *See* Human chorionic gonadotropin
HCL. *See* Hairy cell leukemia
HCoV. *See* Human coronavirus
Hct. *See* Hematocrit
HCT. *See* Hematopoietic stem cell transplantation
HCV. *See* Hepatitis C virus
HCVAD. *See* Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone
HDAC. *See* High-dose ara-C; Histone deacetylase
HDCT. *See* High-dose chemotherapy
HDI. *See* High-dose interferon
HDIL-2. *See* High-dose interleukin-2
HDL. *See* High-density lipoprotein
HD-MTX. *See* High-dose methotrexate
HDT-ASCT. *See* High-dose therapy with autologous stem cell transplantation
Head and neck cancer (HNSCC), 555–571, 557f, 558, 559t, 560t, 561f–563f, 564t, 567t–569t
  ICIs, 1382
  lipid disorders, 1384
  MPE, 1482
  PD-1 ICIs, 1305
Health economics and outcomes research (HEOR), 1604
Heart failure (HF), 1438, 1438t
  coagulopathy, 1439
  congestive, CEL/HES, 142
Hedgehog inhibitors, pancreatic cancer, 638–639
Helicobacter pylori
  gastric cancer, 481–582
  MALT, 184, 185
  pancreatic cancer, 623
  primary cutaneous B-cell lymphomas, 284
Hemangiomas, HCC, 685
Hematochezia, CRC, 737
Hematocrit (Hct), PV, 124–125, 154
Hematopoietic growth factors, MDSs, 105
Hematopoietic stem cell transplantation (HCT, HSCT), 1345
  adenovirus, 1351, 1352
  CMV, 1349, 1350
  complications, 1473–1477, 1474t–1477t
  CRVs, 1353
  fungal infections, 1363
  HBV, 1356
  HCoV, 1355–1356
  HCV, 1356
  HHV-6, 1351
  hMPV, 1355
  HSV, 1346
  rhinovirus, 1355
  RSV, 1354
  TMAs, 1501
  VZV, 1348
Hemispatial neglect, spinal cord injury, 1535
Hemochromatosis, HCC, 682
Hemolytic uremic syndrome (HUS), 1430
Hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), 369–370
Hemoptysis, 1423
Hemorrhagic cystitis, 1421
HEOR. *See* Health economics and outcomes research
Hepatic adenoma, HCC, 685
Hepatic artery embolization (HAE)
  appendiceal carcinoid tumors, 720
  HCC, 688, 689
  NETs, 793
Hepatitis
  AHSCT, 407
  anal cancer, 766
  MCL, 231
Hepatitis B virus (HBV), 1345, 1356
  biliary tract cancer, 647
  HCC, 677–678, 681t
Hepatitis C virus (HCV), 1345, 1356, 1357f
  anal cancer, 768
  biliary tract cancer, 647
  B-NHL, aggressive, 192t, 204
  HCC, 677, 678–680, 681t, 682, 688
  primary cutaneous B-cell lymphomas, 284
  SMZL, 187
Hepatoblastoma, HCC, 685
Hepatocellular carcinoma (HCC), 648, 677–696, 679t–681t, 681–682, 683f, 684, 684f, 685, 687t, 688, 696f
  CUP, 1258
Hepatocyte growth factor (HGF), 1336
Hepatocyte paraffin 1 (HepPar1), FLHCC, 684
Hepatomegaly
  CLL, 50
  FL, 168
  MM, 343
Hepatosplenomegaly
  ALL, 4
  histoplasmosis, 1376
  MDSs, 93
HepPar1. *See* Hepatocyte paraffin 1
HER2. *See* Human epidermal growth factor receptor 2
Herceptin. *See* Trastuzumab
Hereditary breast and ovarian cancer (HBOC), prostate cancer, 1049
Hereditary leiomyomatosis, pRCC, 1019
Hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome)
  ACC, 1214, 1215t
  endometrial cancer, 932
  SBA, 709
Hereditary papillary renal cancer, RCC, 1006
Hereditary tyrosinemia, HCC, 678

hERG. *See* Ether-a-go-go-related gene
Herpes simplex virus (HSV), 1345, 1346–1347, 1346t
  anal cancer, 766
  brain tumors, 1108
  CMV, 1349
  HHVs, 1346
  TVEC, 1314
HES/CEL, 14
HF. *See* Heart failure
2-HG. *See* 2-hydroxyglutarate
HGAL
  FL, 166
  ISPN, 168
HGBL. *See* High-grade B-cell lymphoma
HGF. *See* Hepatocyte growth factor
HGGs. *See* High-grade gliomas
HGSCs. *See* High-grade serous carcinomas
HHV-6. *See* Human herpesvirus 6
HHV-8. *See* Human herpesvirus 8
HHVs. *See* Human herpesviruses
HIF. *See* Hypoxia-inducible factor
High-density lipoprotein (HDL), 1384–1385
High-dose ara-C (HDAC), AML, 29–30, 30t
High-dose chemotherapy (HDCT)
  B-NHL, aggressive, 214
  breast cancer, 888
  cHL, 310, 312–315
High-dose corticosteroids, CAR-T, 367
High-dose cytarabine, MDSs, 107–108
High-dose dexamethasone, MM, 348
High-dose ifosfamide, carboplatin, and etoposide (ICE)
  cHL, 312, 315
  GTD, 997
  HL, 1242
High-dose interferon (HDI), melanoma, 1141–1142
High-dose interleukin-2 (HDIL-2), mRCC, 1011, 1033
High-dose melphalan, POEMS, 357
High-dose methotrexate (HD-MTX), DLBCL, 210
High-dose therapy with autologous stem cell transplantation (HDT-ASCT), AL, 327, 328
High-grade appendiceal mucinous neoplasm (HAMN), 718
High-grade B-cell lymphoma (HGBL), 201–202, 201t, 202f
  NOS, 202, 213
High-grade gliomas (HGGs), pediatric cancer, 1275
High-grade serous carcinomas (HGSCs), EOC, 898, 900, 903
High-grade squamous intraepithelial lesion (HSIL), 960
  anal cancer, 1244
  cervical cancer, 1242
  CIN, 961
Highly active antiretroviral therapy (HAART)
  anal cancer, 1244
  cervical cancer, 1242
  HIV/AIDS, 1107, 1223, 1224
  HL, 1241
  IRIS, 1246
  KS, 1126, 1226, 1229, 1230–1231
  NHL, 1232, 1233, 1234
  PCNSL, 1238, 1240–1241
High-risk primary breast cancer (HRPBC), AHPCT, 390
Hilar cholangiocarcinoma, 653, 669
Hilgard, P., 689
HIPEC. *See* Hyperthermic intraperitoneal chemotherapy
Hippocrates, 983
Histone acetyltransferase (HAT), SCLC, 478
Histone deacetylase (HDAC)
  CTCL, 280, 281
  diabetes mellitus, 1383t
  MDSs, 107
  MM, 353
  sarcoma, 1277
Histoplasmosis, 1365, 1375
HIV/AIDS. *See* Human immunodeficiency virus/acquired immunodeficiency syndrome
HL. *See* Hodgkin lymphoma
HLA. *See* Human leukocyte antigen
HLA-DR
  MDSs, 108
  NHL, 1233
HLH/MAS. *See* Hemophagocytic lymphohistiocytosis/macrophage activation syndrome
HMAs. *See* Hypomethylating agents
hMPV. *See* Human metapneumovirus; Metapneumovirus
HNPCC. *See* Hereditary nonpolyposis colorectal cancer
HNSCC. *See* Head and neck cancer; Squamous cell carcinoma of the head and neck
Hochster, H. S., 749
Hodgkin, Thomas, 291
Hodgkin and Reed-Sternberg cells (HRS), 196, 198, 202, 292
Hodgkin lymphoma (HL), 291–317, 293f, 294f, 296f–300f, 299t, 301t, 302t, 305t, 306t, 308t, 312t, 313t, 1309
  AHPCT, 387–388, 388f
  AHSCT, 459
  CAR-T, 363, 373
  CLL, 61
  DLBCL, 192
  FL, 169
  HIV/AIDS, 1223, 1241–1242
  JC virus, 1357
  PD-1 ICIs, 1305
  pediatric cancer, 1271, 1273–1274
  SIADH, 1386
  spinal cord compression, 1409
Holowiecki, J., 31
Homologous-recombination deficiency (HRD), EOS, 910
Homologous recombination repair (HRR), prostate cancer, 1064
Hong, J. H., 963
Hormone replacement therapy (HRT)
  breast cancer, 805, 884
  endometrial cancer, 943
Horner syndrome, NSCLC, 502
Hospice, PSCU, 1512
HOXB13, prostate cancer, 1052
HP. *See* Hypersensitivity pneumonitis
HPO. *See* Hypertropic pulmonary osteoarthropathy
HPV. *See* Human papillomavirus
HRAS, 1284
  RAS-RAF-MEK pathway inhibitors, 1324
HRD. *See* Homologous-recombination deficiency
HRPBC. *See* High-risk primary breast cancer
HRR. *See* Homologous recombination repair
HRS. *See* Hodgkin and Reed-Sternberg cells
HRT. *See* Hormone replacement therapy
HSCT. *See* Hematopoietic stem cell transplantation
HSIL. *See* High-grade squamous intraepithelial lesion
HSV. *See* Herpes simplex virus
HTLV1. *See* Human T-lymphotropic virus 1
HU. *See* Hydroxyurea
Hu, F., 1584
Huang, H. J., 1284
Huang, X., 1585, 1587
Hudis, Clifford A., 1606
Human chorionic gonadotropin (hCG)
  bladder cancer, 1035, 1038
  choriocarcinoma, 1091
  GCTs, 1081, 1082–1083, 1086
  GTD, 983, 986, 987, 988–989, 990
  NSGCT, 1095
β-human chorionic gonadotropin, CUP, 1256
Human coronavirus (HCoV), 1345, 1355–1356
Human epidermal growth factor receptor 2 (*HER2*)
  appendiceal tumors, 727
  biliary tract cancer, 647, 664
  breast cancer, 803–825, 829
    male, 881
  CRC, 733, 752–753
  CUP, 1255
  DCIS, 884–885
  esophageal cancer, 603
  gastric cancer, 579, 607, 609
  GEJ cancer, 607
  LABC and IBC, 865, 868, 870
  male breast cancer, 883
  MBC, 829–855
  NSCLC, 514, 535, 544
  oncocardiology, 1436
  OP, 1465
  PABC, 876
  targeted therapy, 1323, 1325t, 1332–1333
Human herpesvirus 6 (HHV-6), 466, 468, 1350–1351
Human herpesvirus 8 (HHV-8)
  B-NHL, aggressive, 192t, 193
  DLBCL, 200, 212
  HIV/AIDS, 1223
  KS, 1226–1227, 1229, 1230
  NHL, 1235
  PEL, 200
  vaccination, 1230
Human herpesviruses (HHVs), 1345–1346
Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), 1223–1248, 1227f,

1228t, 1231f, 1233t–1236t, 1237f, 1238f, 1239t, 1240f, 1242t, 1243f, 1244t, 1245f, 1246t–1247t
anal cancer, 766–768
BL, 202–203
B-NHL, aggressive, 192t, 193, 204
cervical cancer, 956
cHL, 309, 312
CMV, 1349
cryptococcosis, 1373, 1374
CTCL, 273
DLBCL, HHV8, 212
fungal infections, 1364–1365
HAART, 1107, 1223, 1224
HBV, 1356
HHV-6, 1351
JC virus, 1357
MDSs, 93
PBL, 212
PCNSL, 198, 1107
VZV, 1347–1348
Human leukocyte antigen (HLA)
AHSCT, 397–398, 399–400, 457
bleeding, 1420
CAR-T, 1312
CBT, 427–431, 436–437
GTD, 984
HaploSCT, 447, 449, 451
HSCT, 1475
PSTT, 987
PTLD, 1477
Human metapneumovirus (hMPV), 1345
Human papillomavirus (HPV)
anal cancer, 766, 1244
cervical cancer, 957–977, 1242–1244
HIV/AIDS, 1224
HNSCC, 555–556, 558, 561–562, 571
penile cancer, 1071–1073, 1078
testing, 958, 958t
vaccination, 571, 765, 767, 776, 955, 957, 1078, 1244
Human T-lymphotropic virus 1 (HTLV1), 254
CTCL, 273
PTCLs, 259
Hürthle cell carcinoma, 192
HUS. *See* Hemolytic uremic syndrome
Hyaluronic acid, pancreatic cancer, 622
Hydatidiform moles, GTD, 983–999, 985t, 986t, 988t, 989f, 990f, 991t, 992f, 992t, 994t, 995t, 996f, 997t
Hydrocodone, 1558–1559, 1559f
Hydrocortisone, primary adrenal insufficiency, 1397
Hydromorphone, 1559, 1560f
2-hydroxyglutarate (2-HG), AML, 34
Hydroxyurea (HU)
CED/HES, 119
CEL/HES, 145
CNL, 120, 148, 153
ET, 133–134, 134t, 154
PMF, 139
PV, 119, 124, 126–127, 154
TLS, 1426
Hydroxyzine, SM, 152
Hyoscine, nausea, 1565t
Hypercalcemia, 1389, 1426
altered mental status, 1413
bone cancer, MBC, 832
delirium, 1567
MM, 343
NSCLC, 502
Hypercalcemia, renal disease, anemia, and bone disease (CRAB), 341, 343, 345, 345t, 355
Hypercoagulability, 1444–1445
Hyper-CVAD. *See* Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone
Hyperemesis gravidarum, GTD, 987
Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD, HCVAD)
ALK+ LBCL, 212
ALL, 3, 8–9, 10, 12, 13, 14, 17–18
B-NHL, aggressive, 216t
MCL, 237
PBL, 212
T-ALL, 12
Hyperglycemia
diabetes mellitus, 1382–1384, 1383t
everolimus, 1385
GEP-NETs, 792
SIADH, 1424
Hyperleukocytosis, 1417
bleeding, 1420
Hyperlipidemia, 1384–1385
SIADH, 1424
Hypernatremia
diabetes insipidus, 1386
SIADH, 1424
Hyperparathyroidism
hypercalcemia, 1389
osteomalacia, 1389
Hypersensitivity pneumonitis (HP), 1467
DILI, 1462
Hypertension, 1454–1455, 1454t. *See also* Pulmonary hypertension
bladder cancer, 1040
GTD, 987
oncocardiology, 1435
pheochromocytoma, 1207
RCC, 1007
Hyperthermic intraperitoneal chemotherapy (HIPEC)
appendiceal epithelial tumors, 721, 725–726
EOC, 910
Hyperthyroidism, 1394
GTD, 987, 991
Hypertropic pulmonary osteoarthropathy (HPO), NSCLC, 502–503, 502f
Hyperviscosity syndrome, 1416–1417, 1416f
Hypoalbuminemia
HCC, 683
rhinovirus, 1355
Hypocalcemia, 1389–1390
osteomalacia, 1388, 1389
Hypodiploidy, ALL, 3
Hypofractionated radiation therapy, HCC, 689
Hypogammaglobulinemia, CLL, 60
Hypoglycemia
altered mental status, 1413
GEP-NETs, 792
Hypogonadism
AHSCT, 417
osteoporosis, 1387
Hypogonadotropic hypogonadism, 1393, 1393f
Hypokalemia, SCLC, 489
Hypomagnesemia, 1390
Hypomethylating agents (HMAs)
AHSCT, 459
AML, 23, 32, 33, 37
MDSs, 91, 92, 106–107, 109
failure, 110
Hyponatremia
altered mental status, 1413
primary adrenal insufficiency, 1428
SCLC, 489
SIADH, 1385–1386, 1424, 1425
Hypopharynx, HNSCC, 562–563, 563f
Hypophosphatemia, osteomalacia, 1388
Hypophysitis, 1428–1429
Hypopigmentation, CTCL, 272, 272f
Hypotension, pericardial effusions, 1454
Hypothalamic disorders, 1390–1393, 1391f–1393f, 1392t
Hypothalamic-pituitary axis, central hypothyroidism, 1393
Hypothyroidism, 1394–1396, 1395f, 1395t
AHSCT, 417
prostate cancer, 1062
Hypoxia-inducible factor (HIF)
ccRCC, 1008
mRCC, 1017–1018
Hysterectomy
cervical cancer, 966, 967, 967f, 968t, 971, 973, 975
GTD, 983, 989, 994
molar pregnancy, 992
PSTT, 998

I

IBC. *See* Inflammatory breast cancer
IBD. *See* Inflammatory bowel disease
IBE. *See* Ipsilateral breast events
Iberdomide, MM, 354
Ibrutinib (Imbruvica), 1291t
atrial fibrillation, 1504
CLL, 56
cryptococcosis, 1373
DLBCL, 209
FL, 175
MCL, 231, 234, 235–236, 241–242
triple-refractory relapsed, 244–245
oncocardiology, 1436
WM, 335
Ibrutinib and rituximab (IR)
CLL, 57
MCL, 239, 240–241
smoldering, 236
Ibrutinib with venetoclax, MCL, 241
Ibuprofen
acute pericarditis, 1453f
hydrocodone, 1558–1559
ICANS. *See* Immune effector cell-associated neurotoxicity syndrome
iCARs. *See* Inhibitor CARs
ICC. *See* Intrahepatic cholangiocarcinoma
ICE. *See* High-dose ifosfamide, carboplatin, and etoposide
ICER. *See* Incremental cost-effectiveness ratio
ICIs. *See* Immune checkpoint inhibitors

Iclusig. *See* Ponatinib
ICOS. *See* Inducible T-cell co-stimulatory
ICP. *See* Intracranial pressure
ICR. *See* Intermediate cluster region
ICUS. *See* Idiopathic cytopenia of undetermined significance
Idarubicin (IDA)
  AML, 28–29, 31
  APL, 40
  myocardial toxicity, 1440
Idelalisib (Zydelig), 1291t, 1328
Idelalisib and rituximab, CLL, 58
IDH. *See* Isocitrate dehydrogenase
Idiopathic cytopenia of undetermined significance (ICUS), MDSs, 93
Idiopathic pneumonia syndrome (IPS), HSCT, 1473
IECs. *See* Immune effector cells
IFN. *See* Interferon
IFN-g. *See* Interferon-g
IFN-α. *See* Interferon-α
IFN-β. *See* Interferon-β
Ifosfamide. *See also specific combination drugs*
  bladder cancer, 1028
  cardiac tamponade, 1413
  glucosuria, 1384
  hemorrhagic cystitis, 1421
  osteomalacia, 1388–1389
  osteosarcoma, 1178
  sarcoma, 1163–1165, 1166–1167
Ifosfamide, carboplatin, and etoposide (R-ICE)
  BL, 215
  B-NHL, aggressive, 214, 216t
  cervical cancer, 976
  MCL, 241
Ifosfamide, gemcitabine, vinorelbine (IGEV), 312
IFRT. *See* Involved-field radiation therapy
Ig. *See* Immunoglobulin
IgA. *See* Immunoglobulin A
IGEV. *See* Ifosfamide, gemcitabine, vinorelbine
IGF-1. *See* Insulin-like growth factor 1
IgG. *See* Immunoglobulin G
IGH. *See* Ig heavy-chain locus
Ig heavy-chain locus (*IGH*)
  FL, 166–167
  ISPN, 168
  MALT, 195
  MM, 342
IGHV. *See* Immunoglobulin heavy-chain variable gene
IgM. *See* Immunoglobulin M
IHC. *See* Immunohistochemistry
IL-1. *See* Interleukin-1
IL-2. *See* Interleukin-2
IL-6. *See* Interleukin-6
IL-10. *See* Interleukin-10
IL-12. *See* Interleukin-12
ILD. *See* Interstitial lung disease
Imatinib (Gleevec), 1291t
  cancer genomics, 1290
  CML, 71–73, 73t
  GISTs, 1171, 1172
  pleural effusions, 1467
  sarcoma, 1167
  SM, 152
Imbruvica. *See* Ibrutinib
IMiDs. *See* Immunomodulatory drugs
Imipenem, AML, 39
Imiquimod, CTCL, 277
Immune checkpoint inhibitors (ICIs), 1297, 1298–1311, 1299f, 1299t–1303t, 1310f
  anal cancer, 774
  ARDS, 1423
  biliary tract cancer, 665, 666t–668t, 669
  bladder cancer, 1028, 1037, 1039, 1040–1041
  co-stimulatory, 1308–1309
  diabetes mellitus, 1382–1384, 1383t
  DILI, 1464t–1465t
  EOC, 919
  fungal infections, 1365
  granulomatous pneumonitis, 1467
  GTD, 997
  hypothyroidism, 1396
  MBC, 831, 855
  mRCC, 1012, 1014, 1015, 1017, 1018, 1034
  myocardial toxicity, 1443–1444
  NSCLC, 514–516, 515t, 517t
  oncocardiology, 1438
  OP, 1465
  penile cancer, 1078
  pneumonitis, 1469–1471, 1470f, 1470t, 1472t
  primary adrenal insufficiency, 1396–1397
  prostate cancer, 1049
  RCC, 1010
  sarcoid-like reactions, 1467
  targeted therapy, 1306–1307, 1340, 1341f
Immune editing, 1298
Immune effector cell-associated neurotoxicity syndrome (ICANS), 367–369, 1313
Immune effector cells (IECs), CAR-T, 363
Immune reconstitution inflammatory syndrome (IRIS), 1244–1246
Immune-related adverse events (irAEs), 1297–1298, 1461
  ICIs, 1309–1311, 1310f, 1382, 1469
  mRCC, 1017
  toxicity, 1427–1431
Immune surveillance, 1298
Immune thrombocytopenia (ITP), 1430–1431
  CLL, 50, 57, 60
Immune tolerance, 1298
Immunoblasts
  DLBCL, 195–196
  PEL, 200
Immunoglobulin (Ig). *See also* Intravenous immunoglobulin
  CTLA-4, 1298
  MALT, 185
Immunoglobulin A (IgA)
  hyperviscosity syndrome, 1416
  MM, 344
  PABC, 878
Immunoglobulin G (IgG)
  HCC, 691–692
  hyperviscosity syndrome, 1416
  MM, 344
Immunoglobulin heavy-chain variable gene (*IGHV*)
  CLL, 50, 55, 59–60
  MCL, 228, 232, 235
Immunoglobulin M (IgM)
  HHV8+ DLBCL, 200
  hyperviscosity syndrome, 1416
  MM, 344, 345
  SLL/CLL, 188
  SMZL, 186
  WM, 333–334
Immunohistochemistry (IHC)
  brain tumors, 1118
  breast cancer, 808
  CMV, 1349
  CRC, 735, 736
  CUP, 1253, 1254, 1255, 1257, 1258f, 1259, 1261, 1262, 1264, 1266
  EOC, 902
  FLHCC, 684
  meningiomas, 1111
  NETs, 783, 783t
  NSCLC, 499
  PSTT, 987
Immunomodulatory drugs (IMiDs)
  AHSCT, 416
  FL, 176
  MALT, 186
  MM, 341–342, 348, 351–352
  PMF, 139–140
Immunophenotype
  DLBCL, 196
  PEL, 200
Immunotherapy, 1297–1315, 1299f, 1299t–1303t, 1310f, 1312f
  FL, 166, 175
  MDSs, 109
  toxicity, 1427–1431
IMPT. *See* Intensity-modulated proton therapy
IMRT. *See* Intensity-modulated radiation therapy
Incremental cost-effectiveness ratio (ICER), 1605
Indolent NHL (iNHL), 371–372
Indolent SM (ISM), 148
Indomethacin, acute pericarditis, 1453f
Inducible T-cell co-stimulatory (ICOS), 1309
Indwelling pleural catheter (IPC), 184–185, 1485f
Inferior vena cava (IVC) filter, VTE, 1494, 1499
Infigratinib, biliary tract cancers, 662–663
Inflammatory bowel disease (IBD)
  biliary tract cancer, 647
  gallbladder carcinoma, 650
  SBA, 709
Inflammatory breast cancer (IBC), 863–871, 866f
Influenza, 1353–1354
  aspergillosis, 1370
Inhibin A, SCSTs, 924, 925
Inhibin B, 1397
  SCSTs, 924, 925
Inhibitor CARs (iCARs), 375
iNHL. *See* Indolent NHL
Inlyta. *See* Axitinib
Inotuzumab ozogamicin, ALL, 12–14, 17
INRT. *See* Involved-node radiotherapy
In situ follicular neoplasia (ISFN), 167–168
In situ mantle cell neoplasia, 233

Insomnia, 1461, 1485
Insulin-like growth factor 1 (IGF-1)
AKT, 1329
prostate cancer, 1051
Insulinoma, PNETs, 788–789
Intensity-modulated proton therapy (IMPT)
biliary tract cancers, 653–654
HNSCC, 560
sarcoma, 1163
value-based oncology, 1612
Intensity-modulated radiation therapy (IMRT)
cervical cancer, 973, 974
HNSCC, 560, 567
Interferon (IFN)
AHSCT, 459
ARDS, 1423
CED/HES, 119
CNL, 120, 153
CTCL, 278–279, 281
DCs, 1314
ET, 154
HCC, 679–680
HDI, melanoma, 1141–1142
hyperthyroidism, 1394
hypothyroidism, 1394
KS, 1227
melanoma, 1141–1142
PD-1 ICIs, 1307
PH, 1469
primary cutaneous B-cell lymphomas, 284
PV, 119
SS, 383
TMAs, 1501
Interferon-g (IFN-g)
bladder cancer, 1031
ICANS, 1313
KS, 1229
mucormycosis, 1375
PD-1 ICIs, 1308
Interferon-α (IFN-α)
anaplastic astrocytoma, 1122
CEL/HES, 145
CNL, 148
diabetes mellitus, 1382
EP, 1466
ET, 133–134
5-fluorouracil, FLHCC, 694–695
granulomatous pneumonitis, 1467
HCL, 62
JC virus, 1357
KS, 1229
mRCC, 1011, 1014, 1033
OP, 1465
pleural effusions, 1467
PMF, 140
PV, 126–127
SM, 152
Interferon-β (IFN-β), PH, 1469
Interleukin-1 (IL-1)
GTD, 985
KS, 1126, 1227
Interleukin-2 (IL-2)
AHSCT, 458
ARDS, 1423
bladder cancer, 1031
HDIL-2, mRCC, 1011, 1033
JC virus, 1357
melanoma, 1145, 1146t
mRCC, 1018
osteoporosis, 1387
PTCLs, 263
Interleukin-6 (IL-6)
AHSCT, 458
anorexia-cachexia, 1564
biliary tract cancer, 650
CAR-T, 367
EOC, 902
ICANS, 1313
KS, 1126, 1226–1227, 1231
MM, 343
Interleukin-10 (IL-10)
EOC, 902
MCL, 228
Interleukin-12 (IL-12)
AHSCT, 459
CAR-T, 364
Intermediate cluster region (ICR), FL, 167
Internal tandem duplication (ITD)
AHSCT, 416
AML, 33
Interstitial lung disease (ILD)
MBC, 836
NSCLC, 537
Intraclonal heterogeneity, MM, 343
Intracranial hemorrhage, CNL, 148
Intracranial pressure (ICP), 1409–1412, 1410f–1412f
seizures, 1413
SVC syndrome, 1415
Intraepithelial lesion or malignancy (NILM), 959
Intrahepatic cholangiocarcinoma (ICC), 647–649
biliary tract cancer, 651
FGFR, 662
proton therapy, 654
Intraocular lymphoma (IOL), PCNSL, 211
Intraparenchymal hemorrhage, brain tumors, 1106
Intrathecal (IT) chemotherapy, ALL, 9
Intravascular large B-cell lymphoma (IVLBCL), 199, 206, 212
Intravenous immunoglobulin (IVIG)
aseptic meningitis, 1430
CLL, 60
coagulopathy, 1439
irAEs, 1428
ITP, 1431
JC virus, 1357
parvovirus B19, 1356
PIV, 1355
RSV, 1354
Invasive fungal infections (IFIs). *See* Fungal infections
Invasive hydatidiform moles, 986
Involved-field radiation therapy (IFRT)
B-NHL, aggressive, 209
cHL, 304, 305–306, 307, 309, 312
FL, 171
HL, 292
NLPHL, 302, 304
Involved-node radiotherapy (INRT), cHL, 305
Iobenguane, pheochromocytoma, 1211
IOL. *See* Intraocular lymphoma
IPC. *See* Indwelling pleural catheter
Ipilimumab. *See also specific drug combinations*
CTLA-4, 1298, 1390
diabetes mellitus, 1382
melanoma, 1133, 1142, 1143t, 1145–1147, 1146t
mRCC, 1017
NSCLC, 519
primary adrenal insufficiency, 1397
prostate cancer, 1065
SCLC, 483, 485
IPS. *See* Idiopathic pneumonia syndrome
Ipsilateral adrenalectomy, RCC, 1010
Ipsilateral breast events (IBE), 886, 887
IR. *See* Ibrutinib and rituximab
irAEs. *See* Immune-related adverse events
IRE. *See* Irreversible electroporation
Iressa. *See* Gefitinib
IRF4
DLBCL, 198, 212
FL, 165
Irinotecan. *See also specific drug combinations*
anaplastic astrocytoma, 1122
appendiceal tumors, 727
cervical cancer, 976
CRC, 739, 745
gemcitabine doublet, pancreatic cancer, 636
NSIP, 1466
pancreatic cancer, 638
SBA, 715
IRIS. *See* Immune reconstitution inflammatory syndrome
Iritis, 1431
Iron chelation, MDSs, 103, 105
Iron deficiency anemia
CRC, 737
esophageal cancer, 594
GTD, 987
Irreversible electroporation (IRE), HCC, 689
Isatuximab, MM, 353
Isavuconazole, 1368t, 1369t
candidiasis, 1369–1370
mucormycosis, 1375–1376
Isbam, H., 1034
ISFN. *See* In situ follicular neoplasia
ISM. *See* Indolent SM
Isocitrate dehydrogenase (*IDH*), 1105, 1286
AML, 34, 35
biliary tract cancer, 647, 662, 664
brain tumors, 1114
chondrosarcoma, 1179
glioblastoma, 1110–1111
glioma, 1120
Isolated tumor cells (ITCs), cervical cancer, 972
IT. *See* Intrathecal chemotherapy
ITCs. *See* Isolated tumor cells
ITD. *See* Internal tandem duplication
ITP. *See* Immune thrombocytopenia
Itraconazole, 1368t, 1369t
AHSCT, 407
coccidioidomycosis, 1377
histoplasmosis, 1376
IVC. *See* Inferior vena cava
IVIG. *See* Intravenous immunoglobulin
IVLBCL. *See* Intravascular large B-cell lymphoma

Ivosidenib
AML, 35
biliary tract cancer, 664
Ixabepilone, MBC, 841t, 844–845
Ixazomib
AL, 328
RMC, 1020

J
Jacobson, C. A., 367
JAK. *See* Janus kinase
JAK2, 1288–1289
PVT, 1502
Jakafi. *See* Ruxolitinib
JAK-STAT. *See* Janus kinase/signal transducers, and activators of transcription
Janus kinase (*JAK*)
CEL/HES, 142, 146
CNL, 120, 147, 148
ET, 128, 129, 130–132, 133
GZL, 202
HL, 1241
NLPHL, 295
PMBL, 199
PMF, 135, 139, 140–141
PTCLs, 255
PV, 121–122, 126
Janus kinase/signal transducers, and activators of transcription (JAK-STAT)
biliary tract cancers, 662–663
FGFR, 663
HCC, 678
El-Jawahri, A., 1511
JC virus, 1357
GVHD, 467–468
Jiao, Y., 782
JMML. *See* Juvenile myelomonocytic leukemia
John, M. J., 769
Joint contractures, rehabilitation, 1539
Jones, R. J., 409
Juvenile myelomonocytic leukemia (JMML), MPDs, 120

K
Kabbani, W., 723–725
Kadcyla. *See* Ado-trastuzumab-emtansine
Kantarjian, H. M., 32
Kaposi, Moritz, 1228
Kaposi sarcoma (KS)
HHV8+ DLBCL, 200
HIV/AIDS, 1224, 1226–1231, 1227f, 1228t, 1231f
NHL, 1232
Karnofsky Performance Scale (KPS), 1532
Kattan, M. W., 1057
KAVE. *See* Ketoconazole and doxorubicin alternating with vinblastine and estramustine
Kebriaei, P., 462
Keefe, D. M., 407
Kelsey, C. R., 713
Ketoconazole and doxorubicin alternating with vinblastine and estramustine (KAVE), prostate cancer, 1063
Keys, H. M., 974
Keytruda. *See* Pembrolizumab
aKG. *See* Alpha-ketoglutarate
Khorana, A. A., 1502
Ki-67
ACC, 1212–1214
breast cancer, 808
EOC, 898
LABC and IBC, 868, 870
MCL, 234, 244
smoldering, 236
Killer cell immunotype receptor (KIR)
AHSCT, 464
CBT, 437
HaploSCT, 452–453
Kinesin-spindle protein (KSP), MM, 355
KIR. *See* Killer cell immunotype receptor
KIT. *See also c-kit*
AML, 34–35
CEL/HES, 145
GCTs, 1082
GISTs, 1171–1172
melanoma, 1136, 1150
mRCC, 1014
RAS-RAF-MEK pathway inhibitors, 1324
sarcoma, 1159, 1167
SM, 148, 151, 152, 153
Klatskin tumor, 653
biliary tract cancer, 669
Klinefelter (XXY) syndrome
ALL, 4
AML, 24
KMT2A
ALL, 3
rearranged ALL, 14
KMT2D, MCL, 228
Knudson, Alfred, 1284
Kolstad, A., 235
Konopleva, M., 42
Koreth, J., 38
Kostmann syndrome, AML, 24
Kothari, S., 460
KPS. *See* Karnofsky Performance Scale
KRAS, 1286
appendiceal tumors, 723
biliary tract cancer, 662
CRC, 733, 749
EOC, 899, 900
LGSC, 920
pancreatic cancer, 620–621
SBA, 709
Krivak, T. C., 949
KS. *See* Kaposi sarcoma
KSP. *See* Kinesin-spindle protein
Kumar, A., 236
Kurman, R. J., 932

L
Lactate dehydrogenase (LDH)
BCL, 206
BL, 213
B-NHL, aggressive, 204
CLL, 51, 61
CTCL, 273
FL, 166, 168, 169
GCTs, 1082, 1083
MCL, 231, 234
smoldering, 236
triple-refractory relapsed, 244
melanoma, 1137
MM, 344, 346
PTCLs, 259, 260
SCLC, 476
Laengsri, V., 966
LAG-3. *See* Lymphocyte activation gene 3
Lambert-Eaton myasthenic syndrome (LEMS), SCLC, 476, 478, 489
Lamm, D. L., 1035
LAMN. *See* Low-grade appendiceal mucinous neoplasm
Lamotrigine, seizures, 1413
Lan, K., 1585
LANA, KS, 1231
Landolfi, R., 126
Lanreotide, NETs, 792
Laparoscopic colectomy, CRC, 737
Lapatinib (Tykerb), 1291t, 1332
breast cancer, 821
gastric cancer, 607
GEJ cancer, 608
PABC, 878
QT prolongation, 1450t, 1452t
Large cell carcinoma, NSCLC, 501, 501f
Large granular lymphocytic leukemia (LGLs), 63
Larotrectinib (Vitrakvi), 1323, 1338, 1340t
biliary tract cancer, 665
cervical cancer, 976
CUP, 1266
DTC, 1199
NSCLC, 545
L-asparaginase
arterial ischemia, 1446, 1446t
diabetes mellitus, 1382
drug-induced airway disease, 1469
TBG, 1396
thrombosis, 1502
Latent membrane protein-1 (LMP-1), NHL, 1232
Lawrence, M. S., 1285
LCIS. *See* Lobular carcinoma in situ
LCT. *See* Local consolidative therapy
LD. *See* Lymphodepleting chemotherapy
LDAC. *See* Low-dose ara-C
LDH. *See* Lactate dehydrogenase
LDHL. *See* Lymphocyte-depleted Hodgkin lymphoma
LDL. *See* Low-density lipoprotein
Lectin-reactive isoenzyme of AFP (AFP-L3), HCC, 684
Lee, D. W., 365, 366, 1284
Lee, J. M., 918
Lefebvre, J. L., 566
Lehmann, Justus, 1530
Leijte, J. A., 1075
Leiomyosarcoma (LMS), 945f, 946t, 955–946, 1168–1169
GISTs, 1171
LEMS. *See* Lambert-Eaton myasthenic syndrome
Lenalidomide
DLBCL, 209, 215
FL, 174
MCL, 236, 240
MDSs, 103, 106
MM, 354
PCNSL, 1240
PMF, 140
PTCLs, 263
thrombosis, 1502
VTE, 1478
Lenalidomide and rituximab (LR), MCL, 239t, 241

Lenalidomide plus high-dose dexamethasone (Len/Dex), MM, 348
Lentigo maligna, 1134, 1135t
Lenvatinib (Lenvima), 1291t. *See also specific drug combinations*
  ACC, 1217
  DTC, 1199
  HCC, 691
  mRCC, 1014, 1015
Lenvatinib and everolimus, mRCC, 1015
Leonine facies, CTCL, 271, 271f
Leptin, prostate cancer, 1051
Leptomeningeal disease (LMD), 1412, 1532
  hyperleukocytosis, 1417
  seizures, 1413
Lerner, K. G., 411
Letermovir, 1346t, 1350
Letrozole
  breast cancer, 815
  endometrial cancer, 941–942
  ESS, 948
  MBC, 833, 836, 838
Leucovorin (LV)
  gastric cancer, 589
  PCNSL, 1240
Leucovorin and oxaliplatin, CRC, 738
Leukemia. *See also specific types*
  arterial ischemia, 1445, 1446
  cardiac tamponade, 1413
  CMV, 1349
  LMD, 1412
  MPE, 1482
  pericardial effusions, 1454
  VZV, 1348
Leukocytosis
  AML, 28
  CNL, 148
  PMF, 135
  PV, 119, 122, 124
  SM, 120, 151
Leukopenia, PMF, 135
Leukostasis, AML, 24, 28
Levofloxacin, CBT, 437
Levothyroxine, central hypothyroidism, 1393
LGGs. *See* Low-grade gliomas
LGLs. *See* Large granular lymphocytic leukemia
LGSCs. *See* Low-grade serous carcinomas
LHRH. *See* Luteinizing hormone-releasing hormone
Li, A. J., 947
Li, J., 213
Libourel, E. J., 1447
Li-Fraumeni syndrome
  ACC, 1214, 1215t
  brain tumors, 1108
  sarcoma, 1159
Lim, M. C., 910
Lipid disorders, 1384–1385
Lipophilin B, CUP, 1258
Liposarcoma, 1169
Liposomal doxorubicin
  EOC, 917
  LGSC, 920
  TNBC, 853
Lisocabtagene maraleucel, MCL, 244
Lithium, SIADH, 1386
Liu, S., 1585
Liver
  cancer
    bladder cancer, 1033, 1038
    CUP, 1262
    GTD, 988
    penile cancer, 1073
  transplantation
    FLHCC, 694–695
    HCC, 687–688
    NETs, 792
LMD. *See* Leptomeningeal disease
LMO2
  FL, 166
  ISPN, 168
LMP-1. *See* Latent membrane protein-1
LMS. *See* Leiomyosarcoma
LMWH. *See* Low-molecular weight heparin
Lobular carcinoma in situ (LCIS), 804–805, 804t
  DCIS, 887
Local consolidative therapy (LCT), NSCLC, 529
Locally advanced breast cancer (LABC), 803–825, 804t, 806t–809t, 813f, 816f, 817t, 818f, 819f, 821f–823f, 824t
  management, 863–871, 866f
Locke, H., 371
Lo-Coco, F., 40
Loghavi, S., 27
Lomustine (CCNU). *See also* Procarbazine, CCNU, and vincristine
  glioblastoma, 1124
  glioma, 1119, 1121t
  male gonadal disorders, 1398
Loop of Henle
  hypomagnesemia, 1390
  MM, 343
Lorazepam
  delirium, 1567, 1568t
  seizures, 1413
Lordick, F., 599
Lorlatinib, 1337
  NSCLC, 539, 540
Low-density lipoprotein (LDL), 381
Low-dose ara-C (LDAC), AML, 32, 33
Low-dose dexamethasone, MM, 348
Lowenberg, B., 30
Low-grade appendiceal mucinous neoplasm (LAMN), 718
Low-grade gliomas (LGGs), 1118–1120, 1119t
  pediatric cancer, 1275
Low-grade serous carcinomas (LGSCs), 920–921
  EOC, 898, 903–903
Low-grade squamous intraepithelial lesion (LSIL), 956, 960
  CIN, 960–961
Low-molecular weight heparin (LMWH), 1418, 1431
  bleeding, 1499
  thrombocytopenia, 1499
  Trousseau syndrome, 1503
  VTE, 1478, 1494, 1499, 1502–1503
LOXO-305, MCL, 243
LR. *See* Lenalidomide and rituximab
LRHL. *See* Lymphocyte-rich classical Hodgkin lymphoma
LSIL. *See* Low-grade squamous intraepithelial lesion
Lu-DOTATATE
  NETs, 794
  pheochromocytoma, 1211
Lung cancer. *See also* Non-small cell lung cancer; Small cell lung cancer
  adenocarcinoma, brain tumors, 1114f
  bladder cancer, 1033, 1038
  cardiac tamponade, 1413
  CNS tumors, 1105
  CUP, 1258
  DTC, 1197
  GTD, 988, 993, 996
  ICIs, 1382
  LMD, 1412
  MPE, 1482
  PD-1 ICIs, 1304
  penile cancer, 1073
  sarcoma, 1159
  spinal cord compression, 1407–1408
  targeted therapy, 1585
Luspatercept
  MDS, 105–106
  MDSs, 103
Luteinizing hormone
  male breast cancer, 883
  oral contraceptives, 993
Luteinizing hormone-releasing hormone (LHRH), MBC, 827
LV. *See* Leucovorin
LVSI. *See* Lymphovascular space invasion
LYG. *See* Lymphomatoid granulomatosis
Lymphadenectomy
  cervical cancer, 972
  penile cancer, 1074, 1075–1076
  PSTT, 998
  urinary tract obstruction, 1421
Lymphadenopathy
  ALL, 4
  B-NHL, aggressive, 193
  CLL, 50
  EOC, 905
  FL, 166
  HHV8+ DLBCL, 200
  MCL, 231
  MM, 343
  nodal marginal zone lymphoma, 186
  penile cancer, 1071
  SMZL, 186
Lymphedema, rehabilitation, 1542–1544
Lymphoblastic lymphoma
  MCL, 233
  spinal cord compression, 1408
Lymphocyte activation gene 3 (LAG-3), 1308
Lymphocyte-depleted Hodgkin lymphoma (LDHL), 298, 298f
Lymphocyte-rich classical Hodgkin lymphoma (LRHL), 295, 296f
Lymphodepleting chemotherapy (LD), CAR-T, 365, 366
Lymphoma. *See also specific types*
  cardiac tamponade, 1413
  CAR-T, 363–376, 364f, 368t–370t
  CNS, fungal infections, 1365
  CUP, 1258, 1263
  MPE, 1482
  VZV, 1348

Lymphomatoid granulomatosis (LYG), 198, 212
Lymphomatoid papulosis (LyP), 282–283
Lymphopenia, 1430
Lymphovascular space invasion (LVSI)
  bladder cancer, 1034, 1035
  cervical cancer, 933, 936, 939, 966, 971, 973
  penile cancer, 1073, 1074
Lynch syndrome. *See* Hereditary nonpolyposis colorectal cancer
Lynparza. *See* Olaparib
LyP. *See* Lymphomatoid papulosis

M
mABs. *See* Monoclonal antibodies
MAC. *See* Myeloablative conditioning
Machine learning, 1593–1594
  case studies, 1595–1598, 1596f, 1598f
  error versus test error, 1595
MACOP-B, PTCLs, 262t
Macrophage inflammatory protein (MIP), MM, 343
MADRS. *See* Montgomery Asberg Depression Rating Scale
Mafeld, S., 695
Mafodotin, MM, 353
MAG. *See* Myelin-associated glycoprotein
Magnetic resonance imaging (MRI)
  ACC, 1212
  AL, 325
  anal cancer, 768
  biliary tract cancer, 650–651, 669
  bladder cancer, 1034
  B-NHL, aggressive, 191, 205
  brain tumors, 1106–1107, 1112
  cervical cancer, 972, 975
  CRC, 737, 740, 744, 754
  CUP, 1256, 1261
  DTC, 1197
  GCTs, 1087
  GEP-NETs, 784, 785
  glioma, 1190
  GTD, 989, 990, 993, 996
  HCC, 685
  HNSCC, 558
  hyperleukocytosis, 1417
  ICP, 1410, 1410f–412f
  LABC and IBC, 866, 867
  LMD, 1412
  MM, 341, 344, 345
  MPE, 1482
  NHL, 1234
  NSCLC, 504, 529
  PABC, 876, 877
  PCNSL, 1237–1238
  penile cancer, 1074, 1075
  pheochromocytoma, 1206, 1210
  prostate cancer, 1055, 1057
  sarcoma, 1161, 1174
  SBA, 710
  SCLC, 479
  spinal cord compression, 1408
  SVC syndrome, 1415
  TNBC, 1597
  typhlitis, 1427
  urinary tract obstruction, 1421
MAID. *See* Mesna, doxorubicin, ifosfamide, and dacarbazine
Major histocompatibility complex (MHC), 1297
  KS, 1227
  LAG-3, 1308
Male breast cancer, 881–883, 882f
Malignant central airway obstruction (MCAO), 1479–1480, 1480t, 1481f
Malignant mixed Müllerian tumors (MMMTs), 934
Malignant ovarian germ cell tumors (MOgerm-cell tumors), 921–923, 921t–923t
Malignant pleural effusions (MPE), 1480–1485, 1482f–1485f
Malignant pleural mesothelioma (MPM), 1482
Mallory-Weiss tears, 1426
Malpica, A., 903
MALT. *See* Mucosa-associated lymphoid tissue
Malthaner, R. A., 604
Maltoni, M., 1521
Mammalian target of rapamycin (mTOR)
  AKT, 1329
  diabetes mellitus, 1382
  HCC, 688
  hypertension, 1454t, 1455
  lipid disorders, 1385
  male breast cancer, 883
  MBC, 839–840
  meningiomas, 1111
  mRCC, 1033
  NSIP, 1466
  PNETs, 782
  targeted therapy, 1325t, 1327–1329
  TMAs, 1501
MammaPrint, breast cancer, 812, 813
Mammography
  DL, 1597–1598, 1598f
  LABC and IBC, 866, 866f
  PABC, 876, 877
Mannitol, ICP, 1411
Mantle cell lymphoma (MCL), 227–245, 230t, 232f, 233f, 234t, 237, 238t–239t
  atypical, 233
  CAR-T, 373, 1312
  hyper-CVAD, 216
  smoldering, 236–237
  triple-refractory relapsed, 244–245
Mantle cell lymphoma international prognostic score (MIPI), 234
MAP. *See* Methotrexate, doxorubicin, and cisplatin
MAPIE. *See* Methotrexate, doxorubicin, cisplatin, ifosfamide, and etoposide
MAPK. *See* Mitogen-activated protein kinase
MAPK/extracellular signal-regulated kinase (*MEK*), 1323–1327, 1326f, 1326t, 1327t
  biliary tract cancer, 664
  LGSC, 920
  melanoma, 1133, 1144, 1149–1150
  OP, 1465
  targeted therapy, 1324–1325, 1325t
Marginal zone lymphoma (MZL), 52, 183–187, 186f, 187f
  CAR-T, 363
  DLBCL, 192
  MALT, 183–186, 184f, 195t
  MCL, 233
  WM, 334
Martin, P. J., 413
Masitinib, SM, 153
Masked PV (mPV), 124
  ET, 129
Mast cell disease, 148–153, 149t, 150t, 151f
Mastectomy
  BPMs, 889–890
  breast cancer, 810
  DCIS, 885
  LABC and IBC, 867
  male breast cancer, 882
MAT. *See* Multifocal atrial tachycardia
Mathur, S. P., 964
Matrix metalloproteinases, GTD, 985
Mature B-cell acute lymphoblastic leukemia, 11
Maude, S. I., 452
Maurer, W., 1586
Maximal tolerated dose (MTD), 1580, 1581
  CVP, 16
Mayumi, H., 449
MBC. *See* Metastatic breast cancer
MCAO. *See* Malignant central airway obstruction
McCarthy, John, 1593
MCD. *See* Multicentric Castleman disease
MCDA. *See* Multicriteria decision analysis
MCHL. *See* Mixed-cellularity Hodgkin lymphoma
McKinney, S. M., 1594
MCL. *See* Mantle cell lymphoma
mCRPC. *See* Metastatic castration-resistant prostate cancer
MDex. *See* Melphalan and dexamethasone
MDM2. *See* Murine double minute 2
MDR, HCC, 691
MDS. *See* Myeloid dysplasia syndrome
MDS-associated fibrosis, 109
MDS-EB. *See* MDS with excess blasts
MDSs. *See* Myelodysplastic syndromes
MDS, unclassified (MDS-U), 99
MDS with excess blasts (MDS-EB), 99
Measurable residual disease (MRD)
  AHSCT, 460
  ALL, 3, 8, 9, 11
  AML, 23, 28, 31, 42–44, 43t
  HCL, 62
  MCL, 232, 235, 240
  MM, 341, 347
Meat
  pancreatic cancer, 620–621
  SBA, 708
Mechlorethamine, vincristine, procarbazine, prednisone (MOPP)
  breast cancer, 1398
  cHL, 304
Mediastinal GZL (MGZL), 202
Medroxyprogesterone acetate, ESS, 948
Medullary thyroid carcinoma (MTC), 1199–1202, 1200f
Medulloblastoma, pediatric cancer, 1275

MEF-2B, FL, 167, 170
Megestrol acetate
  adrenal insufficiency, 1392
  nausea, 1565
MEK. *See* MAPK/extracellular signal-regulated kinase
Mekinist. *See* Trametinib
Melanoma, 1133–1152, 1134t, 1135t, 1137, 1137t–1140t, 1140, 1143t, 1146t, 1149
  cardiac tamponade, 1413
  ICP, 1410
  LAG-3, 1308
  LMD, 1412
  pancreatic cancer, 620–621
  PD-1 ICIs, 1303, 1308
  RAS-RAF-MEK pathway inhibitors, 1324
  spinal cord compression, 1408
  targeted therapy, 1327t
  TVEC, 1150, 1314
Melatonin, ovarian cancer, 1397
Melflufen, MM, 354–355
Melphalan. *See also specific combination drugs*
  AHPCT, 383
  breast cancer, 1398
  HaploSCT, 449
  male gonadal disorders, 1398
  MM, 347
Melphalan and dexamethasone (MDex), AL, 328
Melphalan and prednisone (MP), MM, 349
Melphalan, prednisone, and bortezomib (MPB), 349
Memorial Delirium Assessment Scale, 1567
MEN1. *See* Multiple endocrine neoplasia type 1
MEN2. *See* Multiple endocrine neoplasia type 2
Men having sex with men (MSM), anal cancer, 766
Meningiomas, 1107, 1111, 1113f, 1118, 1118f, 1124–1125
Meperidine (Demerol), 1559
  seizures, 1412
Mepolizumab, CEL/HES, 146
Mercaptopurine
  glucosuria, 1384
  HP, 1467
MERS-CoV. *See* Middle Eastern respiratory syndrome coronavirus
Mesenchymal chondrosarcoma, 1179
Mesenchymal-epithelial transition (*MET*)
  ASPS, 1170
  HCC, 693
  mRCC, 1013, 1015
  NSCLC, 514, 542–543, 543t
  pRCC, 1019
  RCC, 1006
  targeted therapy, 1336–1337
  Trousseau syndrome, 1503
Mesenchymal stromal cells (MSCs), CBT, 437
Mesna
  hemorrhagic cystitis, 1421
Mesna, doxorubicin, ifosfamide, and dacarbazine (MAID), 1165
Mesothelioma
  MPE, 1482
  NSCLC, 499
MET. *See* Mesenchymal-epithelial transition
Metaiodobenzylguanidine (MIBG)
  NETs, 785
  pheochromocytoma, 1206, 1210, 1211
Metapneumovirus (hMPV), 1355
Metastatic breast cancer (MBC), 829–855, 833f, 834t–835t, 839t, 841t, 848t, 849f, 852f
  AHPCT, 390
  TNBC, 853
Metastatic castration-resistant prostate cancer (mCRPC), 1051, 1062, 1064
Metastatic RCC (mRCC), 1007–1008, 1007t, 1008t
  ccRCC, 1011–1019, 1012f, 1013t, 1015t–1018t, 1016f
Methadone, 1560
  oncocardiology, 1435
  QT prolongation, 1450t
Methotrexate (MTX). *See also specific drug combinations*
  ARDS, 1423
  B-NHL, aggressive, 210
  brain tumors, 1112
  CEL/HES, 145
  CTCL, 281
  DLBCL, testes, 211
  EP, 1466
  glucosuria, 1384
  GTD, 994, 995t
  IVDLBCL, 212
  JC virus, 1357
  LGLs, 63
  LMD, 1412
  NSIP, 1466
  PCNSL, 1125
  pleural effusions, 1467
  sarcoid-like reactions, 1467
  VTE, 1417
Methotrexate and folinic acid, GTD, 994, 995t
Methotrexate and vincristine, PCNSL, 1240
Methotrexate-ara-C, MCL, 237, 238t, 239
Methotrexate, doxorubicin, and cisplatin (MAP), 1177, 1178, 1179
Methotrexate, doxorubicin, cisplatin, ifosfamide, and etoposide (MAPIE), 1178
Methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), 1037, 1039
O6-methylguanine-DNA methyltransferase (*MGMT*), 1105
  glioma, 1110
Methylphenidate
  depression, 1569
  fatigue, 1563
Methylprednisolone, aseptic meningitis, 1430
Metoclopramide, nausea, 1565, 1565t
MF. *See* Mycosis fungoides; Myelofibrosis
MFC. *See* Multiparameter flow cytometry
mFOLFIRINOX. *See* Modified 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin
mFOLFOX. *See* Modified folinic acid, 5-FU, and oxaliplatin
MG. *See* Myasthenia gravis
MGMT. *See* O6-methylguanine-DNA methyltransferase
MGUS. *See* Monoclonal gammopathy of undetermined significance
MGZL. *See* Mediastinal GZL
MHC. *See* Major histocompatibility complex
MIBCs. *See* Muscle-invasive bladder cancers
MIBG. *See* Metaiodobenzylguanidine
Micafungin, 1368t
  aspergillosis, 1373
Microangiopathic hemolytic anemia, GTD, 987
b2-microglobulin (b2M), FL, 171
Microsatellite instability (MSI)
  CRC, 739
  endometrial cancer, 941–942
  ICIs, 1340
  prostate cancer, 1064
  SBA, 708, 716
Microtubule inhibitors, MBC, 844–845
Microwave ablation (MWA), HCC, 689
Midazolam
  delirium, 1568–1569
  seizures, 1413
Middle Eastern respiratory syndrome coronavirus (MERS-CoV), 1355
Midostaurin, SM, 120, 152, 153
MiHAs. *See* Minor histocompatibility antigens
Miller, 1586
Mini Mental Status Exam, 1567
Minor histocompatibility antigens (MiHAs), AHSCT, 458, 459
MIP. *See* Macrophage inflammatory protein
MIPI. *See* Mantle cell lymphoma international prognostic score
Mirtazapine, depression, 1569
Mitogen-activated protein kinase (MAPK)
  brain tumors, 1108
  DTC, 1190, 1192, 1199
  EOC, 900
  melanoma, 1149
  NRG1 fusions, 545–546
  NRTK fusions, 544
  RAS-RAF-MEK pathway, 1323–1324
Mitomycin C (MMC)
  anal cancer, 769
  ARDS, 1423
  cervical cancer, 976
  NSIP, 1466
  TMAs, 1501
Mitomycin C and 5-FU
  anal cancer, 770–772
  biliary tract cancer, 655
Mitotane
  ACC, 1215
  lipid disorders, 1384
Mitoxantrone (MTZ), AML, 28–29
Mitsuhashi, A., 965
Mixed-cell endometrial cancers, 934
Mixed-cellularity Hodgkin lymphoma (MCHL), 296–298, 297f
Mixed phenotype acute leukemia (MPAL), 25t

MLH
breast cancer, 804
CRC, 736
endometrial cancer, 932
EOC, 899–900
MLN-Eo. *See* Myeloid/lymphoid neoplasms with eosinophilia
MM. *See* Multiple myeloma
MMAE. *See* Monomethyl auristatin E
MMC. *See* Mitomycin C
MMMF. *See* Mycophenolate mofetil
MMMTs. *See* Malignant mixed Müllerian tumors
Model-assisted design, 1581
Modified 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (mFOLFIRINOX), pancreatic cancer, 626, 630, 631
Modified folinic acid, 5-FU, and oxaliplatin (mFOLFOX)
biliary tract cancer, 657, 664
CRC, 749
SBA, 713
Moertel, C. G., 794
Mogamulizumab
CTCL, 280
PTCLs, 263
MOGCTs. *See* Malignant ovarian germ cell tumors
Molar pregnancy, GTD, 985, 988, 992–993, 992f
Molecular analysis
ALL, 3, 5–8, 6t, 7f, 7t
AML, 24, 26–27
biliary tract cancer, 657–653, 669
CEL/HES, 142
CUP, 1266
GISTs, 1171
MDSs, 94–98, 96f–98f, 97t
SM, 151–152
Monoclonal antibodies (mABs). *See also specific types*
CMV, 1349
CRC, 747–749
FL, 170, 175
GTD, 997
JC virus, 1357
MM, 352–353
NOTCH, 1339
oncocardiology, 1436–1437
TIO, 1389
TNBC, 852
Monoclonal gammopathy of undetermined significance (MGUS), 343
AL, 324
MM, 341, 342, 355
Monoclonal protein (M-protein), MM, 344, 346–347
Monomethyl auristatin E (MMAE), 314
HL, 1241–1242
Montgomery Asberg Depression Rating Scale (MADRS), 1569
MOPP. *See* Mechlorethamine, vincristine, procarbazine, prednisone
Morphine, 1559, 1559f
Morphologic analysis, MDSs, 93–94, 93f, 95f
Morris, M., 974
Mortensen, M. S., 1087
Moskowitz, C., 312
Motzer, R. J., 1007, 1254
Mount, Balfour, 1512
Moxetumomab pasudotox, HCL, 62
Moxifloxacin, QT prolongation, 1450t
MP. *See* Melphalan and prednisone
MPAL. *See* Mixed phenotype acute leukemia
MPB. *See* Melphalan, prednisone, and bortezomib
MPDs. *See* Myeloproliferative disorders
MPE. *See* Malignant pleural effusions
MPL, Ph-MPNs, 1502
MPM. *See* Malignant pleural mesothelioma
MPN. *See* Myeloproliferative neoplasm
MPO. *See* Myeloperoxidase
M-protein. *See* Monoclonal protein
mPV. *See* Masked PV
mRCC. *See* Metastatic RCC
MRD. *See* Measurable residual disease
MRI. *See* Magnetic resonance imaging
MSCs. *See* Mesenchymal stromal cells
MSH
endometrial cancer, 932
EOC, 899–900
MSI. *See* Microsatellite instability
MSM. *See* Men having sex with men
MTC. *See* Medullary thyroid carcinoma
MTD. *See* Maximal tolerated dose
mTOR. *See* Mammalian target of rapamycin
MTX. *See* Methotrexate
MTZ. *See* Mitoxantrone
Mucinous appendiceal adenocarcinoma, 722–723
Mucinous carcinoma, EOC, 904, 904f
Mucoepidermoid carcinoma, esophageal cancer, 594
Mucormycosis (*Mucorales* spp.), 1375–1376, 1376t
Mucosa-associated lymphoid tissue (MALT), 183–186, 184f, 195t
NHL, 1232
Mucosal melanoma, 1134, 1135t, 1151
Muller, E. A., 1539
Multicentric Castleman disease (MCD), 1226
Multicriteria decision analysis (MCDA), 1605–1606, 1607t
Multifocal atrial tachycardia (MAT), 1449
Multiparameter flow cytometry (MFC), ALL, 3
Multiple endocrine neoplasia type 1 (*MEN1*), 782–783, 790–791
ACC, 1214, 1215t
parathyroid carcinoma, 1204
Multiple endocrine neoplasia type 2 (*MEN2*)
MTC, 1199, 1201
pheochromocytoma, 1206
Multiple myeloma (MM), 341–358, 343f, 344f, 345t–347t, 348, 349, 355t, 357t
AHPCT, 388–389, 390f
AL, 323, 324, 327
CAR-T, 461
MPE, 1482
osteoporosis, 1387, 1388
SIADH, 1386
spinal cord compression, 1408
Multistage design, 1582
Murine double minute 2 (*MDM2*)
PV, 127
sarcoma, 1161, 1175
targeted therapy, 1339
Muscle atrophy, rehabilitation, 1539
Muscle-invasive bladder cancers (MIBCs), 1029, 1030
MUTYH-associated polyposis, CRC, 735, 736
MVAC. *See* Methotrexate, vinblastine, doxorubicin, and cisplatin
MWA. *See* Microwave ablation
Myasthenia gravis (MG), 1429
MYC
B-cell lymphomas, 206
BL, 203
CAR-T, 365
DLBCL, 195–196
GTD, 985
GZL, 202
HGBL, 201, 202
LABC and IBC, 868, 870
MCL, 227, 230, 235
MM, 342
NHL, 1274
prostate cancer, 1051
sarcoma, 1175
MYCN, prostate cancer, 1067
Mycophenolate mofetil (MMMF)
CBT, 437
hypertension, 1454, 1454t
JC virus, 1357
Mycosis fungoides (MF), CTCL, 269, 271f, 273–282, 275t, 279t
MYD88. *See* Myeloid differentiation primary response 88
Myelin-associated glycoprotein (MAG), WM, 333, 334
Myeloablative conditioning (MAC)
AHSCT, 400f, 401
CBT, 431–432, 434t, 437
HaploSCT, 450t
Myelodysplastic syndromes (MDSs), 91–111, 120, 1438
AML, 24
Myelofibrosis (MF), 154
ET, 119, 128–129
PMF, 135
PV, 119, 122–123
Myeloid differentiation primary response 88 (*MYD88*)
CLL, 50
WM, 333
Myeloid dysplasia syndrome (MDS), 91, 97–98
AHSCT, 398, 416, 459, 460
AML, 25t
clinical features, 93
diagnosis, 99
epidemiology and etiology, 92–93
ET, 127
MPDs, 120
prognosis, 99–102, 100t–103t
specific clinical situations, 110–111
therapy, 103–110, 104f
Myeloid/lymphoid neoplasms with eosinophilia (MLN-Eo), 120

Myeloperoxidase (MPO), 4
AML, 26
Myeloproliferative disorders (MPDs), 1444
Myeloproliferative neoplasm (MPN)
AHSCT, 398
AML, 24, 25t
MDSs, 93
Philadelphia chromosome-negative, 119–154
Myocardial ischemia, 1415–1416
Myocarditis, irAEs, 1311
Myxoid liposarcoma, 1169
MZL. *See* Marginal zone lymphoma

N
Nabholtz, J. M., 845
Nab-paclitaxel
gemcitabine, pancreatic cancer, 637
MBC, 841, 843
pancreatic cancer, 634–635
TNBC, 852–853
N-acetyltransferase 2 (NAT2), bladder cancer, 1029
NADCs. *See* Non-AIDS-defining cancer
NAFLD. *See* Nonalcoholic fatty liver disease
NAIs. *See* Neuraminidase inhibitors
NASH. *See* Nonalcoholic steatohepatitis
Nasopharyngeal cancer (NPC), 556
HNSCC, 558–560
NAST. *See* Neoadjuvant systemic therapy
Nastoupil, L. J., 367
NAT2. *See* N-acetyltransferase 2
Natalizumab, JC virus, 1357
National Comprehensive Cancer Network Evidence Blocks (NEB), 1606–1607, 1608f
Natural killer cell acute lymphoblastic leukemia (NK-ALL), 3, 4, 5
Natural killer cells (NK)
AHSCT, 457, 464
B-NHL, aggressive, 193
CAR-T, 363, 374, 1312
CBT, 428, 438, 441
CTCL, 282
HaploSCT, 452–453
LAG-3, 1308
LGLs, 63
nausea, 1563
NHL, 1232
PTCLs, 253
Nausea, 1563–1566, 1564f, 1565f, 1565t
Navitoclax, CLL, 57
nccRCC. *See* Non-clear cell RCC
NCPE. *See* Noncardiogenic pulmonary edema
NEB. *See* National Comprehensive Cancer Network Evidence Blocks
NECs. *See* Neuroendocrine carcinomas
Nelarabine, T-ALL, 12
Neoadjuvant systemic therapy (NAST), 1597
Neratinib, 1333
breast cancer, 821–822
LABC and IBC, 868
MBC, 850–851
Net Health Benefit (NHB), 1606
NETs. *See* Neuroendocrine tumors
Neuraminidase inhibitors (NAIs), 1354
Neuroblastoma, pediatric cancer, 1276
Neuroendocrine carcinomas (NECs), 782
bladder cancer, 1031
CUP, 1257, 1262–1263
Neuroendocrine tumors (NETs), 781–796, 782t, 783f, 783t, 785, 786f, 787t, 788t, 791f, 795t
SCLC, 477, 489–490, 490t
Neurofibromatosis type 1 (*NF1*)
brain tumors, 1108–1109
EOC, 900
melanoma, 1133
NET, 783
parathyroid carcinoma, 1203
sarcoma, 1159
Neurofibromatosis type 2 (*NF2*)
brain tumors, 1108, 1109
meningiomas, 1111
sRCC, 1019
Neuroregulins (NRGs), 545
Neurotrophic tropomyosin-related kinase gene fusions (*NTRK* fusions)
biliary tract cancer, 664–665
cervical cancer, 976
CRC, 733, 753
CUP, 1266
DTC, 1199
HGGs, 1275
NSCLC, 544–545
pancreatic cancer, 638
sarcoma, 1161
targeted therapy, 1323, 1337–1338
Neutral protamine Hagedorn insulin (NPH), 1382
Neutropenia
aspergillosis, 1373
candidemia, 1367
CRVs, 1353
FLHCC, 695
fungal infections, 1365–1366
MBC, 839–840
MDSs, 93, 105
New-onset diabetes (NOD), pancreatic cancer, 620
Nexavar. *See* Sorafenib
Next generation sequencing (NGS), 1284–1290
AML, 24, 26, 26t
NSCLC, 513–514
NF1. *See* Neurofibromatosis type 1
NF2. *See* Neurofibromatosis type 2
NF-kB. *See* Nuclear factor kB
Ngan, H. Y., 964
NGS. *See* Next generation sequencing
NHB. *See* Net Health Benefit
NHL. *See* Non-Hodgkin lymphoma
Nicotinamide, carcinoid, 795
Nigro, N. D., 768, 769
NILM. *See* Intraepithelial lesion or malignancy
Nilotinib (Tasigna), 1291t
CML, 74–76, 80
diabetes mellitus, 1382
PH, 1469
QT prolongation, 1450t, 1452t
Ning, J., 1585
Niraparib, 1336
EOS, 915–916
Nirogacestat, 1339
Nivolumab
ALK+LBCL, 215
biliary tract cancer, 665, 669
cHL, 315
EOC, 919
gastric cancer, 609–610
HCC, 691, 692
HL, 1274
HNSCC, 570
LAG-3, 1308
MDSs, 109
melanoma, 1142, 1143t, 1146t, 1147
mRCC, 1017
nccRCC, 1019
NSCLC, 516, 519
PD-1 ICIs, 1299–1311, 1300t–1303t
RCC, 1010
sarcoma, 1277
SCLC, 485
Nivolumab and atezolizumab, bladder cancer, 1041
Nivolumab and everolimus, mRCC, 1014
Nivolumab and ipilimumab
HCC, 691, 692–693
melanoma, 1144–1145, 1146t, 1147–1148
mRCC, 1012, 1013, 1014–1015
sRCC, 1019
Nivolumab and sunitinib, mRCC, 1012
Nivolumab, cabozantinib, lenvatinib, everolimus, and axitinib, mRCC, 1014
Nivolumab, ipilimumab and pembrolizumab, mRCC, 1034
NK. *See* Natural killer cells
NK-ALL. *See* Natural killer cell acute lymphoblastic leukemia
NLPHL. *See* Nodular lymphocyte-predominant HL
NMGZL. *See* Nonmediastinal GZL
NMIBCs. *See* Non-muscle-invasive bladder cancers
NNSTs. *See* Non-neural solid tumors
NOD. *See* New-onset diabetes
Nodal marginal zone lymphoma, 186, 186f
Nodular lymphocyte-predominant HL (NLPHL), 291, 292–295, 293t, 294f, 294t
treatment, 302–304
Nodular melanoma, 1134, 1135t
Nodular sclerosis (NS), 293, 295
Non-AIDS-defining cancer (NADCs), 1224
Nonalcoholic fatty liver disease (NAFLD), HCC, 677, 680, 681–682
Nonalcoholic steatohepatitis (NASH)
biliary tract cancer, 647
HCC, 681–682
Noncardiogenic pulmonary edema (NCPE), 1466
Non-clear cell RCC (nccRCC), 1005, 1019–1020
Nonfunctional PNETs, 789

Non-Hodgkin lymphoma (NHL). *See also* B-cell non-Hodgkin lymphoma; Cutaneous T-cell lymphomas; Peripheral T-cell lymphomas
AHPCT, 386
ARDS, 1466
B-cell, 191–220, 192t, 194f–197f, 194t, 200f, 201t, 202f–205f, 203t, 207t, 208t, 216t, 217t, 218f, 219f
CAR-T, 363
COO, 196–197, 209
CUP, 1258
FL, 165
HIV/AIDS, 1224, 1231–1241, 1233t–1236t, 1237f, 1238f, 1239t, 1240f
LMD, 1412
PD-1 ICIs, 1305
pediatric cancer, 1271, 1274
primary refractory, 214
SIADH, 1386
spinal cord compression, 1409
Noninvasive papillary urothelial carcinoma
high grade, 1031–1032
low grade, 1031
Nonmediastinal GZL (NMGZL), 202
Nonmucinous appendiceal adenocarcinoma, 723
Non-muscle-invasive bladder cancers (NMIBCs), 1029
Nonmyeloablative allogeneic transplantation, MDSs, 108
Non-neural solid tumors (NNSTs), 1276–1277
Nonseminoma germ cell tumors (NSGCTs), 1081, 1089–1098, 1089f–1092f, 1094f, 1097f
Non-small cell lung cancer (NSCLC)
BRAF, 1326–1327
localized disease, 495–529, 496t–501t, 500f–502f, 503t, 504f, 505t, 506t, 507f–514f, 510t, 511t, 513t, 515t, 517t, 519f, 521t–528t
PD-1 ICIs, 1304
pneumonitis, 1469
ramucirumab, 693
RET, 1340
SCLC, 475
targeted therapy, 535–546, 536t, 538t, 543t, 1327t
vaccination, 514
Nonspecific interstitial pneumonitis (NSIP), 1465–1466, 1466f
Nonsteroidal antiinflammatory drugs (NSAIDs)
acute pericarditis, 1451, 1453f
CRC, 736
SM, 152
Nortriptyline, depression, 1569
NOS. *See* Not otherwise specified
NOTCH
CLL, 50
HNSCC, 556
MCL, 230, 234, 235
SCLC, 477
targeted therapy, 1338–1339
Not otherwise specified (NOS)
DLBCL, 194–197, 194f–196f
HGBL, 202, 213
NPC. *See* Nasopharyngeal cancer
NPH. *See* Neutral protamine Hagedorn insulin
NPM1. *See* Nucleophosmin
NRAS
melanoma, 1133, 1136
RAS-RAF-MEK pathway inhibitors, 1324
NRG1, 1437
NSCLC, 545–546
NRGs. *See* Neuroregulins
NS. *See* Nodular sclerosis
NSAIDs. *See* Nonsteroidal antiinflammatory drugs
NSCLC. *See* Non-small cell lung cancer
NSGCTs. *See* Nonseminoma germ cell tumors
NSIP. *See* Nonspecific interstitial pneumonitis
N-terminal pro b-type natriuretic peptide (NT-BNP), 325, 326
PE, 1478
NTRK fusions. *See* Neurotrophic tropomyosin-related kinase gene fusions
Nuclear export inhibitor, MM, 353
Nuclear factor kB (NF-kB)
CTCL, 273
DLBCL, 209
ependymoma, 1276
glial tumors, 1109
HL, 1241
KS, 1230
MALT, 185
MCL, 230
NLPHL, 295
PMBL, 199
PTCLs, 260
Nuclear grade, breast cancer, 808
Nucleophosmin (NPM1), 257

O

Obesity. *See also* Body mass index
breast cancer, 805
endometrial cancer, 931–932
LABC and IBC, 864
NETs, 782
prostate cancer, 1051
RCC, 1007
Obinutuzumab
CLL, 56
FL, 176
SLL/CLL, 188
O'Brien, P. C., 1585
Obstructive sleep apnea, 1485
Occupational therapy (OT), 1531
ataxia, 1535
pressure ulcers, 1544
RFS, 1538
Octreotide, NETs, 792
O'Donnell, P. V., 406
Ofatumumab, ALL, 11–12
Olanzapine, delirium, 1568t
Olaparib (Lynparza), 1291t, 1335–1336
EOS, 910, 915
prostate cancer, 1049, 1064
Olaparib and bevacizumab, EO4, 911
Older patients
AITL, 259
ALL, 12–13
AML, 31–34
B-NHL, aggressive, 213–214
cHL, 310
CLL, 60
CML, 76
CRC, 754
ET, 131
HCC, 678
MCL, 227–228, 237, 240, 241
NETs, 781
NSCLC, 528
PMF, 135
prostate cancer, 1050
SCLC, 487–488
Oligodendroglioma, 1105, 1107
anaplastic, 1115–1116, 1116f, 1120–1121
Oligometastatic disease, NSCLC, 528–529
Olverembatinib, CML, 81
Omalizumab, SM, 152
Oncocardiology, 1435–1457, 1436t, 1437f–1440f, 1438t, 1441t, 1442f, 1445f, 1445t–1447t, 1446f, 1448f, 1450f, 1450t, 1451f, 1452t, 1453f, 1454t, 1456f
Oncocytoma nccRCC, 1005
Oncolytic viruses, TVEC, 1314
Oncotype DX
breast cancer, 812, 813
DCIS, 886
Ondansetron, nausea, 1565t
On-switch CARs, 375
Oocyte cryopreservation, 1397
OP. *See* Organizing pneumonia
OPC. *See* Oropharyngeal cancer
OPG. *See* Osteoprotegerin
Opioids
GH deficiency, 1393
pain management, 1553–1561, 1554f–1559f, 1558t, 1561t
rotation, 1557
safety, 1560–1561
O'Quigley, J., 1581
Oral cavity
candidiasis, 1366, 1366f
HNSCC, 561
Oral contraceptives
breast cancer, 805
cervical cancer, 956
GTD, 993
HCC, 685
Orchiectomy, DLBCL, testes, 211
Orchiopexy, GCTs, 1081–1082
Organizing pneumonia (OP), 1462–1465, 1465f
RRP, 1473
"OR"-gate CARs, 374
Oropharyngeal cancer (OPC), 555, 561–562
cervical cancer, 975
HNSCC, 558, 559t, 560t
Oropharyngeal mucositis, AHPCT, 383
Oseltamivir (Tamiflu), 1346t, 1354
Osimertinib, 1330
NSCLC, 537
Osteomalacia, 1388–1889
Osteoporosis, 1386–1388, 1387f
Osteoprotegerin (OPG), MM, 343

Osteosarcoma, 1174–1175, 1177–1179
pediatric cancer, 1277
OT. *See* Occupational therapy
Ovarian ablation
breast cancer, 816–817
CUP, 1263
MBC, 827, 837–838
Ovarian cancer, 1397
CUP, 1258, 1262
EOC, 897–921, 899f, 899t, 901t, 902t, 903f, 904f, 905t, 907f–908f, 913t
HBOC, prostate cancer, 1049
MOGCTs, 897, 921–923, 921t–923t
MPE, 1482
pancreatic cancer, 620–621
SCSTs, 923–925, 924t
targeted therapy, 1327t
urinary tract obstruction, 1421
OX40, 1309
Oxaliplatin. *See also specific drug combinations*
appendiceal tumors, 727
CRC, 740, 745–747
extravasation injuries, 1424
gastric cancer, 589, 590
HP, 1467
hypomagnesemia, 1390
NSIP, 1466
SBA, 715
TMAs, 1501
Oxaliplatin and 5-fluorouracil, esophageal cancer, 603
Oxaliplatin and gemcitabine doublet, pancreatic cancer, 636
Oxycodone, 1559
Oxymorphone, 1559
Oxytocin, molar pregnancy, 992

P

P13K. *See* Phosphatidylinositol 3-kinase
P13K-AKT-mTOR pathway
ROS1 fusions, 539
SCC, 499, 502t
P13K-AKT pathway
NRG1 fusions, 545–546
NRTK fusions, 544
P16INK4a, penile cancer, 1072
p53
brain tumors, 1109, 1118
CTCL, 273
CUP, 1255
GTD, 985
MM, 346
prostate cancer, 1054
targeted therapy, 1339
PABC. *See* Pregnancy-associated breast cancer
Paclitaxel. *See also* Nab-paclitaxel; *specific combination drugs*
EOC, 917
GEJ cancer, 608
LGSC, 920
MBC, 841t, 842
NSCLC, 509, 512, 518
TNBC, 817
Paclitaxel, trastuzumab, and pertuzumab, MBC, 846, 849
Paclitaxel and bevacizumab
EOC, 910
MBC, 846
Paclitaxel and carboplatin, cervical cancer, 973
Paclitaxel and cisplatin, EOC, 910
Paclitaxel and etoposide alternating weekly with paclitaxel and cisplatin (TE/TP)
GTD, 996
PSTT, 998
Paclitaxel and trastuzumab, breast cancer, 823
Paclitaxel, carboplatin, and etoposide, CUP, 1264
Paclitaxel, doxorubicin, and cisplatin (TAP), 941–942
Paclitaxel, estramustine, and carboplatin (TEC), 1063
Paclitaxel, estramustine, and etoposide (TEE), 1063
Paclitaxel, ifosfamide, and cisplatin (TIP), 389–390
MOGCTs, 923
penile cancer, 1071, 1076, 1077
Paclitaxel, topotecan, and rituximab (TTR), 21
Pagetoid reticulosis, 282
PAH. *See* Pulmonary arterial hypertension
Pain management, 1553–1561, 1554f–1559f, 1558t
seizures, 1412
Palbociclib, 1333–1334
MBC, 836
Palbociclib and letrozole, MBC, 833, 836
Palivizumab, RSV, 1354–1355
Palliative and supportive care unit (PSCU), 1509–1514, 1510f, 1512t, 1513f
Palliative care
delirium, 1566–1569, 1567f, 1568–1569, 1568f, 1568t
depression, 1569
dyspnea, 1566
end-of-life, 1546–1548
fatigue, 1562–1563, 1563f
FL, 176–177
inpatients, 1509–1514, 1510f, 1512t, 1513f
nausea, 1563–1566, 1564f, 1565f, 1565t
outpatients, 1519–1525, 1522t, 1524f
pain management, 1553–1572, 1554f–1559f, 1558t, 1561t, 1562f, 1562t, 1564f, 1565f, 1565t, 1567f, 1568f, 1570t
rehabilitation, 1529–1548, 1531f, 1533f, 1539t, 1543f, 1544t, 1545t, 1547t
Pancoast syndrome, NSCLC, 502, 513, 513f
Pancreatic cancer, 619–640, 620t, 623f, 623t, 625f, 626t, 627f, 628f, 629t, 630t, 632–633, 633f–635f, 639
MPE, 1482
SIADH, 1424
stoma, 622
Pancreatic neuroendocrine tumors (PNETs), 781, 782–796
Pancreaticoduodenectomy (PD), 653
SBA, 710
Pancreatic polypeptide (PP), PNETs, 784, 789
Pancreatitis, pancreatic cancer, 620–621, 623
Pandya, C., 350
Panitumumab, 1331
CRC, 748
Panitumumab (Vectibix), 1291t
Panobinostat, MM, 353
Pantou, D., 1254, 1258
Panuveitis, 1431
Papillary ncc RTCC, 1005
Papillary renal cell carcinoma (pRCC), 1019
Papillary thyroid carcinoma (PTC), DTC, 1190
Papillary urothelial neoplasm of low malignant potential (PUNLMP), 1031
Pap smear, cervical cancer, 957, 975
Paraganglioma, 1205–1211, 1206t, 1207f
Parainfluenza (PIV), 1355
Paraneoplastic syndromes (PNSs), SCLC, 476, 488–489
Paraneoplastic thrombotic microangiopathy, 1501
Paraortic nodes, cervical cancer, 974
Parathyroid carcinoma, 1203–1204, 1203t, 1204f
Parathyroid hormone (PTH)
hypercalcemia, 1389
hypocalcemia, 1390
osteoporosis, 1387, 1388
Pareja, R., 967, 970
Park, J. Y., 969
Paroxetine
CYP2D6, 1558
depression, 1569
Paroxysmal nocturnal hemoglobinuria (PNH), 1503
PARP inhibitors. *See* Poly(ADP-ribose) polymerase inhibitors
Partial hydatidiform moles, 986, 986t, 987–988
Parvovirus B19, 1356
Passamonti, F., 122, 139
Patau syndrome, AML, 24
Patient Scheduling Coordinators (PSCs), 1513
Pautas, C., 29
Pazopanib (Votrient), 1292t
DVT and VTE, 1488
hypertension, 1454, 1454t
LMS, 1170
mRCC, 1011, 1013–1014, 1033
QT prolongation, 1450t, 1452t
RCC, 1010
sarcoma, 1167
PBC. *See* Primary biliary cholangitis
PBL. *See* Plasmablastic lymphoma
PBPCs. *See* Peripheral blood progenitor cells
PBRM, ccRCC, 1008
pCEA. *See* Polyclonal carcinoembryonic antigen
pcFCL. *See* Primary cutaneous follicle center lymphoma
pcGDL. *See* Primary cutaneous gd T-cell lymphoma
PCI. *See* Prophylactic cranial irradiation
PCLBCL-LT. *See* Primary cutaneous diffuse large B-cell lymphoma, leg type
pcMZL. *See* Primary cutaneous marginal zone lymphoma

PCNSL. *See* Primary CNS lymphoma
PCR. *See* Fludarabine, cyclophosphamide, and rituximab; Polymerase chain reaction
PCS. *See* Primary cytoreductive surgery
PCV. *See* Procarbazine, CCNU, and vincristine
PD. *See* Pancreaticoduodenectomy
PD-1. *See* Programmed death-1
PDAC. *See* Poorly differentiated adenocarcinoma
PDC. *See* Poorly differentiated carcinoma
PDGF. *See* Platelet-derived growth factor
PDGFR. *See* Platelet-derived growth factor receptor
PDGFRA
  GISTs, 1171–1172
  sarcoma, 1159, 1167
PE. *See* Pulmonary embolism
Peacock, J. G., 695
PEBA. *See* Cisplatin, etoposide, bleomycin, and doxorubicin
Pediatric cancers, 1271–1279, 1272f, 1278t
Pegylated hyaluronidase (PEGPH20), pancreatic cancer, 639
Pegylated liposomal doxorubicin, CTCL, 281
PEL. *See* Primary effusion lymphoma
Pelger-Huet anomaly, MDSs, 96
Pelvic cancer, GTD, 988, 993
Pembrolizumab (Keytruda), 1323, 1340t. *See also specific drug combinations*
  ACC, 1217
  bladder cancer, 1037, 1041–1042
  cervical cancer, 976
  cHL, 315
  CRC, 750
  CUP, 1266
  gastric cancer, 609
  GEJ cancer, 607
  HCC, 691, 692
  HNSCC, 567–570
  MBC, 855
  MDSs, 109
  melanoma, 1133, 1142–1144, 1143t, 1146t, 1147
  mRCC, 1017, 1034
  NSCLC, 515, 518, 522
  PD-1 ICIs, 1299–1311, 1300t–1303t
  pheochromocytoma, 1211
  PNETs, 795
  prostate cancer, 1064
Pembrolizumab and axitinib
  mRCC, 1012–1015
  sRCC, 1019
Pembrolizumab and ipilimumab, melanoma, 1148
Pemetrexed. *See also specific combination drugs*
  cervical cancer, 976
  NSCLC, 514, 515, 522
Pemigatinib, 1339
  biliary tract cancers, 662–663
  CEL/HES, 146
Penile cancer, 1071–1078, 1071t, 1074t, 1076t
Penile intraepithelial neoplasia (PIeN), 1072
Pentostatin
  PLL, 63
  TMAs, 1501
Pentostatin and cladribine (2-CDA), HCL, 62
Pepe, M., 1581
Peptic ulcer disease, SBA, 708
Peptide receptor radionuclide therapy (PRRT), NETs, 781
Peramivir (Rapivab), 1346t, 1354
PERDS. *See* Peri-engraftment respiratory distress syndrome
Pericardial disease, 1450–1454, 1452t, 1453f
Pericardial effusions, 1451–1454, 1453f
  oncocardiology, 1435
Peri-engraftment respiratory distress syndrome (PERDS), HSCT, 1473–1475
Perihilar cholangiocarcinoma, 653
Peripheral blood progenitor cells (PBPCs), AHPCT, 384
Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), 256, 259
Peripheral T-cell lymphomas (PTCLs), nodal, 253–265, 254t, 255f, 257f–258f, 258t, 261f, 262f, 262t, 264t
Peritoneal mucinous carcinomatosis (PMCA), 722
Perjeta. *See* Pertuzumab
Peroxisome proliferation-activated receptor (PPAR)
  CBT, 438
  DTC, 1191–1192
Pertuzumab (Perjeta), 1292t, 1333
  LABC and IBC, 868
  MBC, 834, 846–847
  PABC, 878
Pertuzumab, trastuzumab, and docetaxel (THP), MBC, 846, 849
Pertuzumab and docetaxel, breast cancer, 820–821
Pertuzumab and trastuzumab, breast cancer, 820
PET-CT. *See* Positron emission tomography/computed tomography
Peutz-Jeghers syndrome (PJS)
  biliary tract cancer, 647
  gallbladder carcinoma, 650
  pancreatic cancer, 620–621
  SBA, 709
  SCSTs, 924
Pexidartinib, 1340
  TGCT, 1170
PF. *See* Cisplatin and 5-fluorouracil
PFT. *See* Pulmonary function tests
P-glycoprotein, PABC, 878
Ph. *See* Philadelphia chromosome
PH. *See* Pulmonary hypertension
Phantom human chorionic gonadotropin syndrome, 991, 994
Phase 1 clinical trials, 1580–1581
Phase 2 clinical trials, 1581–1582
Phenacetin, bladder cancer, 1028–1029
Phenobarbital, seizures, 1413
Phenoxybenzamine, pheochromocytoma, 1207
Phenytoin
  brain tumor seizures, 1126
  seizures, 1413
Pheochromocytoma, 1205–1211, 1205f, 1205t, 1206f, 1207, 1207t, 1208t, 1209f, 1210f
  MTC, 1199–1200
Philadelphia chromosome (Ph)
  bispecific antibodies, 1314
  CML, 67, 69, 70
Philadelphia chromosome-like acute lymphoblastic leukemia, 10–11
Philadelphia chromosome-negative myeloproliferative neoplasms (Ph-MPNs), 119–154, 1502–1503
Philadelphia chromosome-positive acute lymphoblastic leukemia, 9–10
Phlebotomy, PV, 125, 126
Ph-MPNs. *See* Philadelphia chromosome-negative myeloproliferative neoplasms
Phosphatase and tensin homolog (PTEN), 1286
  bladder cancer, 1029
  breast cancer, 804
    male, 881
  ccRCC, 1008
  DTC, 1191t
  EOC, 902
  glioblastoma, 1110
  HNSCC, 556
  melanoma, 1136
  parathyroid carcinoma, 1203
  prostate cancer, 1049, 1054, 1055
  SBA, 709
  SCLC, 477
Phosphatidylinositol 3-kinase (PI3K)
  diabetes mellitus, 1382, 1383t
  EOC, 900
  FGFR, 663
  FL, 175–176
  glial tumors, 1109
  HGGs, 1275
  MBC, 839–840
  MCL, 230
  melanoma, 1136
  meningiomas, 1111
  oncocardiology, 1436
  OP, 1465
  osteoporosis, 1388
  parathyroid carcinoma, 1203
  targeted therapy, 1325t, 1328
Photon therapy, HCC, 689
Phototherapy, CTCL, 277
PHQ-9, 1569
Physical therapy (PT), 1531
  ataxia, 1535
  pressure ulcers, 1544
  RFS, 1538
Physician Orders for Life-Sustaining Treatment (POLST), 1571
PI3K. *See* Phosphatidylinositol 3-kinase
PIA. *See* Proliferative inflammatory atrophy
Piantodosi, S., 1581
Pictilisib, 1328
PIeN. *See* Penile intraepithelial neoplasia
PIGA, PNH, 1503
PIGF1. *See* Placenta growth factor 1
PIK3CA
  bladder cancer, 1029
  breast cancer, male, 881
  EOC, 900–902
  LABC and IBC, 868, 870

male breast cancer, 883
MBC, 831, 833f, 838, 839, 840
PIN. *See* Prostate intraepithelial neoplasia
Pinnix, C. C., 371
Pipobroman, PV, 124
PIs. *See* Proteasome inhibitors
Pituitary disorders, 1390–1393, 1391f–1393f, 1392t, 1399–1400
PIV. *See* Parainfluenza
PJP. *See Pneumocystis jirovecii* pneumonia
PJS. *See* Peutz-Jeghers syndrome
Placenta growth factor 1 (*PIGF1*)
EOC, 902
GTD, 985
Placental alkaline phosphatase (PLAP), GCTs, 1083
Placental site trophoblastic tumor (PSTT), 983, 987
GTD, 988, 989, 990, 993, 994, 997–998
Plasmablastic lymphoma (PBL), 200, 212
Plasmacytoid urothelial cancer, 1032
Platelet-derived growth factor (*PDGF*)
brain tumors, 1111
glial tumors, 1109
osteoporosis, 1388
PMF, 135
Platelet-derived growth factor receptor (*PDGFR*)
CEL/HES, 142–144, 143t, 145, 146
CNL, 148
HCC, 693
mRCC, 1014
SM, 152
Platelet transfusion
BK virus, 1357
bleeding, 1420
MDSs, 105
Platinum
EO4, 911
EOC, 914
EOS, 917–918
FLHCC, 695
prostate cancer, 1065
refractory disease, HNSCC, 570
RMC, 1020
TNBC, 817
Platinum and 5-fluorouracil (FLP)
esophageal cancer, 599–600
SBA, 715
Pleural effusions, 1461, 1467
CUP, 1262
GTD, 988
MPE, 1480–1485, 1482f–1485f
RRP, 1473
PLK1, prostate cancer, 1067
PLL. *See* Prolymphocytic leukemia
PLNs. *See* Positive lymph nodes
PMBL. *See* Primary mediastinal (thymic) B-cell lymphoma
PMCA. *See* Peritoneal mucinous carcinomatosis
PMF. *See* Primary myelofibrosis
PML. *See* Progressive multifocal leukoencephalopathy; Promyelocytic leukemia protein
PMP. *See* Pseudomyxoma peritonei
PMRT. *See* Postmastectomy radiation therapy
PMS. *See* Postmeiotic segregation
PNETs. *See* Pancreatic neuroendocrine tumors
Pneumocystis jirovecii pneumonia (PJP), 1365
aplastic anemia, 1430
CBT, 437
Pneumonia
aspergillosis, 1371
BOOP, 1462
cryptococcosis, 1374
eosinophilic, 1466
OP, 1462–1465, 1465f
RRP, 1473
PJP, 1365
aplastic anemia, 1430
CBT, 437
Pneumonitis
COP, 1476–1477
HSCT, 1473
granulomatous, 1467
HP, 1467
DILI, 1462
ICIs, 1469–1471, 1470f, 1470t, 1472t
RRP, 1473
PNH. *See* Paroxysmal nocturnal hemoglobinuria
PNSs. *See* Paraneoplastic syndromes
Podophyllotoxin, anal cancer, 1244
POEMS. *See* Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin change
POF. *See* Premature ovarian failure
Polatuzumab-vedotin-BR, 215
POLE
CRC, 753–754
PD-1 ICIs, 1307
POLST. *See* Physician Orders for Life-Sustaining Treatment
Poly(ADP-ribose) polymerase inhibitors (PARP inhibitors), 1335–1336
EOC, 915–917
EOS, 910
gastric cancer, 609
LGSC, 921
MBC, 839–840
pancreatic cancer, 620–621, 622, 638
prostate cancer, 1049, 1052, 1064, 1065
SCLC, 488
TNBC, 853–854
Polychromasia, MDSs, 94
Polyclonal carcinoembryonic antigen (pCEA), FLHCC, 684
Polycythemia vera (PV), 119, 121–127, 123t, 124t, 125f, 126, 127t, 154
arterial ischemia, 1445–1446
ET, 127
Ph-MPNs, 1502
PMF, 134, 136
Polymerase chain reaction (PCR). *See also* Real-time PCR
adenovirus, 1352
ALL, 8
AML, 26, 43
APL, 40
aseptic meningitis, 1430
aspergillosis, 1372
cancer genomics, 1284, 1289
candidiasis, 1368
CMV, 1349
CRC, 736
FL, 168, 170–171
fungal infections, 1363–1364
HBV, 1356
HHVs, 1346
HIV/AIDS, 1225
HSV, 1346
NHL, 1234
PCNSL, 1238
penile cancer, 1072
PTCLs, 259
sarcoma, 1161
VZV, 1348
Polymorphic ventricular tachycardia, 1449–1450, 1450t
Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin change (POEMS), MM, 341, 356–357, 357t
Polyoma hominis. *See* BK virus
Polyomavirus, 1356–1357
hemorrhagic cystitis, 1421
Pomalidomide
MM, 351–352, 354
PCNSL, 1240
POMP. *See* Purinethol, Oncovin, methotrexate, and prednisone
Ponatinib (Iclusig), 1292t
ALL, 10, 17–18
arterial ischemia, 1446t, 1447
CML, 80–81, 82
PH, 1469
Poorly differentiated adenocarcinoma (PDAC), CUP, 1263
Poorly differentiated carcinoma (PDC), CUP, 1257, 1260, 1261, 1263
Porcelain gallbladder, 650
Portal vein embolization (PVE), HCC, 687
Portal vein thrombosis (PVT), 1502, 1503
Portal venous tumor thrombus (PVTT), HCC, 689
Porter, M. E., 1604
Posaconazole, 1368t, 1369t
AHSCT, 407
aspergillosis, 1372–1373
CBT, 437
fusariosis, 1375
Posch, M., 1586
Positive lymph nodes (PLNs), SBA, 710
Positron emission tomography (PET). *See also* Fluorodeoxyglucose positron emission tomography
B-NHL, aggressive, 191, 204, 204f, 217
brain tumors, 1112
breast cancer, 823
cHL, 305–306, 307, 311
CUP, 1254
esophageal cancer, 600
GEP-NETs, 784
GISTs, 1172
HL, 291, 301–302, 1274
NETs, 785
NHL, 1237
pancreatic cancer, 624–625
pheochromocytoma, 1206, 1210
PMBL, 212
PTCLs, 259
sarcoma, 1161
SCLC, 482f, 484f
seminoma, 1088

Positron emission tomography/computed tomography (PET-CT)
appendiceal carcinoid tumors, 720
biliary tract cancer, 651
B-NHL, aggressive, 217
cervical cancer, 968, 972, 975
CRC, 744, 754
CUP, 1256–1257
EOC, 919
FL, 165, 169, 170, 171
gastric cancer, 585
GTD, 996, 997
HL, 298, 301
LABC and IBC, 867
MBC, 830
MCL, 232
MM, 341, 344
MPE, 1482
MTC, 1201
NHL, 1234
NSCLC, 504, 529
penile cancer, 1074, 1075
sarcoma, 1174, 1180
SCLC, 479, 481
WM, 334
Postmastectomy radiation therapy (PMRT), male breast cancer, 883
Postmeiotic segregation (*PMS*)
endometrial cancer, 932
EOC, 899–900
Posttransplant cyclophosphamide (PTCy), HaploSCT, 449, 451, 453
Posttransplant lymphoproliferative disorder (PTLD), 1477
aGVHD, 464, 467
EBV, 1351
HSCT, 1473
Pouliquen, X., 604
PP. *See* Pancreatic polypeptide
PPAR. *See* Peroxisome proliferation-activated receptor
PR. *See* Progesterone receptor
Pracinostat, MDSs, 107
Pradaxa. *See* Dabigatran
Pralatrexate, PTCLs, 263, 264t
Pralsetinib, NSCLC, 544
Pravastatin, lipid disorders, 1385
Prazosin
pheochromocytoma, 1207
urinary tract obstruction, 1421
PRCA. *See* Pure red cell aplasia
pRCC. *See* Papillary renal cell carcinoma
Prednisolone
acquired hemophilia, 1431
IVDLBCL, 212
Prednisone. *See also specific combination drugs*
acute pericarditis, 1451, 1453f
aseptic meningitis, 1430
B-NHL, aggressive, 192
DILI, 1462
irAEs, 1310
ITP, 1430–1431
PMF, 140
SM, 152
Preeclampsia
co-twin pregnancy, 998
GTD, 987
Prefibrotic primary myelofibrosis (pre-PMF), 119, 154
ET, 129
Pregabalin, 1561
Pregnancy
B-NHL, aggressive, 204
cervical cancer, 970
ET, 134
GTD, 983–999, 985t, 986t, 988t, 989f, 990f, 991t, 992f, 992t, 994t, 995t, 996f, 997t
LABC and IBC, 865
Pregnancy-associated breast cancer (PABC), 805, 875–881, 876f, 876t, 877t
Prehabilitation, 1541–1542, 1543f
Premature ovarian failure (POF), PAB2, 879
Pre-PMF. *See* Prefibrotic primary myelofibrosis
Pressure ulcers, rehabilitation, 1544, 1544t, 1545t
Primary adrenal deficiency, 1396–1397, 1428
Primary biliary cholangitis (PBC), HCC, 682–683
Primary brain tumors, 1107–1108
Primary CNS lymphoma (PCNSL), 372, 1113f, 1115, 1125
HIV/AIDS, 1107
NHL, 1232, 1237–1241
Primary cutaneous CD8+ cytotoxic aggressive epidermotropic T-cell lymphoma, 283
Primary cutaneous diffuse large B-cell lymphoma, leg type (PCLBCL-LT), 198, 211, 284
Primary cutaneous follicle center lymphoma (pcFCL), 284
Primary cutaneous gd T-cell lymphoma (pcGDL), 269
Primary cutaneous marginal zone lymphoma (pcMZL), 284
Primary cytoreductive surgery (PCS), EOC, 906
Primary diffuse large B-cell lymphoma of the central nervous system (PCNSL), 211
Primary DLBCL of the central nervous system (PCNSL), 197–198
Primary effusion lymphoma (PEL), 193, 213
HHV8, 201
KS, 1226, 1231
NHL, 1233–1234
Primary lymphoma, esophageal cancer, 594
Primary mediastinal (thymic) B-cell lymphoma (PMBL), 199, 212, 215
Primary myelofibrosis (PMF), 119, 134–141, 136f–138f, 136t, 138t, 139t, 140
ET, 129
Ph-MPNs, 1502
Primary refractory, B-NHL, aggressive, 214
Primary sclerosing cholangitis (PSC), biliary tract cancer, 647, 650
Primidone, seizures, 1413
Procarbazine. *See also specific drug combinations*
central hypothyroidism, 1393
granulomatous pneumonitis, 1467
HP, 1467
male gonadal disorders, 1398
Procarbazine, CCNU, and vincristine (PCV)
glioblastoma, 1124
glioma, 1120, 1121t
Prochlorperazine, nausea, 1565t
Progesterone receptor (PR)
breast cancer, 805, 808, 814, 829
ESS, 948
PABC, 876
Progestins
endometrial cancer, 941–942
MBC, 838–839
Programmed death-1 (PD-1)/programmed death ligand 1 (PD-L1)), 1438
ACC, 1217
AHSCT, 459, 464
anal cancer, 774–775
ASPS, 1170
biliary tract cancer, 647, 665
bladder cancer, 1028, 1031, 1037, 1040, 1041, 1042–1043
CAR-T, 370–371
ccRCC, 1008
cervical cancer, 976
cHL, 315
chondrosarcoma, 1179
CRC, 750
EOC, 897, 918
FL, 176
gastric cancer, 579, 582, 609
GEJ cancer, 607–608
GTD, 997
HCC, 691–692
HL, 291, 1241
HNSCC, 567
hypocalcemia, 1390
hypothyroidism, 1396
ICIs, 1297, 1298–1305, 1340, 1384
CTLA-4, 1305–1306
KS, 1230
MBC, 831
MDSs, 109
melanoma, 1133, 1142–1144, 1147–1148, 1152
mRCC, 1012, 1013, 1014, 1018
NSCLC, 512, 514–520, 537, 541
pancreatic cancer, 639
RRP, 1473
SBA, 716
SCLC, 483
targeted therapy, 1340, 1341f
TNBC, 818, 852, 853
toxicity, 1427–1431
Progressive multifocal leukoencephalopathy (PML), 1357
Proliferation centers (pseudofollicles), SLL/CLL, 188
Proliferative inflammatory atrophy (PIA), 1055
Prolymphocytic leukemia (PLL), 52, 63
Promethazine
nausea, 1565t
QT prolongation, 1450t
Promyelocytic leukemia protein (PML)
APL, 39
lipid disorders, 1384
Prophylactic cranial irradiation (PCI), SCLC, 486–487

Propylthiouracil (PTU), 1428
Prostate cancer, 1049–1067, 1051f, 1053f, 1056t–1060t, 1060f, 1063t, 1065t, 1066f
  CUP, 1258
  osteoporosis, 1388
  spinal cord compression, 1407–1408
  targeted therapy, 1327t
  urinary tract obstruction, 1421
  vaccines, 1313
Prostate intraepithelial neoplasia (PIN), 1055
Prostate-specific antigen (PSA), 1050, 1055, 1058, 1061
  CUP, 1253, 1257
PROSTVAC, 1313
Proteasome inhibitors (PIs)
  AL, 328
  MM, 341, 352
  NSIP, 1466
  RMC, 1020
Proton pump inhibitors, carcinoid, 795
Proton therapy
  biliary tract cancers, 654
  HCC, 689
  HNSCC, 560, 562
  NSCLC, 512
  prostate cancer, 1057
PRRT. *See* Peptide receptor radionuclide therapy
Pruritus
  CEL/HES, 142
  CTCL, 284–285
PSA. *See* Prostate-specific antigen
PSA-TRICOM, 1313
PSC. *See* Primary sclerosing cholangitis
PSCs. *See* Patient Scheduling Coordinators
PSCU. *See* Palliative and supportive care unit
Pseudofollicles (proliferation centers), SLL/CLL, 188
Pseudomyxoma peritonei (PMP)
  appendiceal epithelial tumors, 721–722
  appendiceal tumors, 716
Pseudo-Pelger-Huet anomaly, MDSs, 94
PSTT. *See* Placental site trophoblastic tumor
PT. *See* Physical therapy
PTC. *See* Papillary thyroid carcinoma
PTCH
  brain tumors, 1109
  medulloblastoma, 1275
  meningiomas, 1111
PTCL-NOS. *See* Peripheral T-cell lymphoma not otherwise specified
PTCLs. *See* Peripheral T-cell lymphomas
PTCy. *See* Posttransplant cyclophosphamide
PTEN. *See* Phosphatase and tensin homolog
PTH. *See* Parathyroid hormone
PTLD. *See* Posttransplant lymphoproliferative disorder
PTU. *See* Propylthiouracil
Pulmonary arterial hypertension (PAH), 1469, 1479t
Pulmonary embolism (PE), 1415, 1417–1419, 1417f, 1419t, 1477–1478
  deconditioning, 1539
  hyperleukocytosis, 1417
  myocardial ischemia, 1416
  VTE, 1494
Pulmonary function tests (PFT)
  CEL/HES, 142
  MCAO, 1479
Pulmonary hypertension (PH), 1467, 1469, 1478–1479, 1479t
  GTD, 988, 996
  HSCT, 1475
Pulmonary veno-occlusive disease (PVOD)
  HSCT, 1475
  PH, 1469, 1478
PUNLMP. *See* Papillary urothelial neoplasm of low malignant potential
Pure red cell aplasia (PRCA), CLL, 60
Pure seminoma, GCTs, 1086
Purinethol, Oncovin, methotrexate, and prednisone (POMP), ALL, 3, 8, 13
Purtill, D., 428
PV. *See* Polycythemia vera
PVB. *See* Cisplatin, vinblastine, and bleomycin
PVOD. *See* Pulmonary veno-occlusive disease
PVT. *See* Portal vein thrombosis
PVTT. *See* Portal venous tumor thrombus
Pyrophosphate analogs, bone cancer, 832

Q

QALYs. *See* Quality-adjusted life-years
Qiao, W., 1587
QT prolongation, 1448, 1449–1450, 1450t, 1451f, 1452t
  methadone, 1560
Quality-adjusted life-years (QALYs), 1604–1605
Quetiapine, delirium, 1568t
Quintas-Cardama, A., 32

R

Rabow, M. W., 1520
Radar charts, 1608, 1609f
Radiation fibrosis syndrome (RFS), 1538
Radiation necrosis, 1113f
Radiation recall pneumonitis (RRP), 1473
Radiation therapy (RT). *See also specific types*
  cardiovascular toxicity, 1455–1456, 1456f
  lung injury, 1472–1473, 1473f
  value-based oncology, 1611–1613
Radical cholecystectomy, gallbladder carcinoma, 651
Radical hysterectomy, cervical cancer, 966, 967f, 971, 975
Radical inguinal orchiectomy, GCTs, 1082
Radical nephrectomy, RCC, 1009
Radical orchiectomy, GCTs, 1086–1087
Radioactive iodine (RAI), DTC, 1193–1196, 1199
Radiofrequency ablation (RFA)
  ACC, 1217
  GISTs, 1172
  HCC, 689
  RCC, 1009
Radioimmunotherapy (RIT), FL, 174
Radiomics, 1593
Radon, NSCLC, 497
RAF. *See* Rapidly accelerated fibrosarcoma
RAI. *See* Radioactive iodine
Ramos, C. A., 372
Ramucirumab (Cyramza), 1292t
  CRC, 749
  HCC, 693
Randomized clinical trials, 1582–1583
RANK ligand (RANKL)
  giant cell tumor of bone, 1180
  hypercalcemia, 1426
  hypocalcemia, 1390
  MM, 343
Rapamycin. *See also* Mammalian target of rapamycin
  OP, 1465
Rapidly accelerated fibrosarcoma (RAF), 1323
Rapivab. *See* Peramivir
RAR. *See* Response-adaptive randomization
RARa. *See* Retinoic acid receptor a
RAS
  brain tumors, 1108
  CRC, 733, 748, 749
  DTC, 1190, 1192
  GISTs, 1171
  glial tumors, 1109
  HGGs, 1275
  MM, 342
  RAS-RAF-MEK pathway inhibitors, 1323–1327, 1326f, 1326t, 1327t
Rasburicase
  TLS, 1426
  tumor lysis syndrome, 38
RAS-RAF-MAPK, melanoma, 1133
RAS-RAF-MEK-ERK pathway, melanoma, 1135–1136
RAS-RAF-MEK pathway, targeted therapy, 1323–1327, 1326f, 1326t, 1327t
Ravandi, F., 42
RB. *See* Retinoblastoma
RB1, 1286
  parathyroid carcinoma, 1203
  prostate cancer, 1055
  sarcoma, 1175
RBCs. *See* Red blood cells
RCC. *See* Renal cell carcinoma
RCD. *See* Cyclophosphamide and dexamethasone
R-CHOP. *See* Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
RCM. *See* Red cell mass
R-CODOX-M/IVAC. *See* Cyclophosphamide, doxorubicin, vincristine, methotrexate/ifosfamide, etoposide, high dose cytarabine
R-CVP, FL, 171, 174
R-DHAP, MCL, 235, 237, 241
Reactive oxygen species (ROS), myocardial toxicity, 1440
Real-time PCR (RT-PCR)
  adenovirus, 1352
  AML, 43
  CML, 68, 69, 70, 78
  HHV-6, 1351

Receptor tyrosine kinase (RTK)
  glial tumors, 1109
  meningiomas, 1111
  NSCLC, 499
RECIST. *See* Response Evaluation Criteria in Solid Tumors
Recombinant human thyrotropin (rhTSH), DTC, 1194–1195
Rectal NETs, 788
Red blood cells (RBCs)
  bleeding, 1420
  hyperviscosity syndrome, 1416
  MDSs, 92, 94
  PV, 121
  transfusion
    MDSs, 105, 108
    PMF, 137
Red cell mass (RCM), PV, 121, 124
Reduced-dose whole-brain radiation therapy (rhWBRT), PCNSL, 211
Reduced-intensity conditioning (RIC)
  AHSCT, 401–402, 401f
  CBT, 432–433, 435t
  CLL, 59
  HaploSCT, 450, 450t
Reduction bilateral salpingo-oophorectomy (RRSO)
  breast cancer, 890
  EOC, 898
Reed-Stenberg cells
  ALCL, 258
  cHL, 311
  HL, 1241, 1273, 1305
  MCHL, 296
  PD-1, 315
  PEL, 200
  PMBL, 199
Refractory Ph-positive ALL, 17–18
Regimen-related toxicity (RRT), AHPCT, 383, 384, 385, 386
Regional lymph node (RLN), melanoma, 1137, 1140
Regorafenib (Sitara), 1292t, 1331
  CRC, 733, 747
  GISTs, 1172
  HCC, 691
  osteosarcoma, 1179
Rehabilitation, 1529–1548, 1531f, 1533f, 1539t, 1543f, 1544t, 1545t, 1547t
  amputation, 1529, 1537–1538
  asthenia, 1538–1540
  bone cancer, 1537
  brain cancer, 1532–1535
  deconditioning, 1538–1540
  exercise, 1540–1541, 1542f
  spinal cord injury, 1534–1537
Relatimab, LAG-3, 1308
Relenza. *See* Zanamivir
Renal cell carcinoma (RCC), 1005–1021, 1006f, 1007t, 1008t, 1012f, 1013t, 1015t–1018t, 1016f, 1018t
  brain tumors, 1106
  cancer genomics, 1297
  ICP, 1410
  lipid disorders, 1385
  PD-1 ICIs, 1303
  spinal cord compression, 1408
Renal mass biopsy (RMB), RCC, 1009
Renal medullary carcinoma (RMC), 1005, 1020
R-EPOCH, HGBL, 213
Repotrectinib, NSCLC, 540
R-ESHAP. *See* Etoposide, methylprednisolone, cytarabine, and cisplatin
Respiratory distress, GTD, 987
Respiratory syncytial virus (RSV), 1345, 1351, 1354t, 1355f, 1359
Response-adaptive randomization (RAR), 1583–1584
  Bayesian, 1588–1589
  patient heterogeneity, 1586–1587
Response Evaluation Criteria in Solid Tumors (RECIST), 1582
RET
  DTC, 1191
  mRCC, 1014
  MTC, 1200, 1201
  pheochromocytoma, 1205
  targeted therapy, 1340
Retinoblastoma (*RB*), 1284
  glial tumors, 1109
  MBC, 833
Retinoic acid receptor a (RARa), APL, 39
Retinoids, CTCL, 278
Retroperitoneal lymph node dissection (RPLND), NSGCT, 1093
Reverse phase protein array (RPPA), SCLC, 478
Revlimid, DVT and VTE, 1488
RFA. *See* Radiofrequency ablation
RFS. *See* Radiation fibrosis syndrome
R-GDP. *See* Gemcitabine, dexamethasone, and cisplatin
Rhabdomyosarcoma
  HCC, 685
  sarcoma, 1277
R-HCVAD, MCL, 237, 238t, 239
  triple-refractory relapsed, 244–245
Rheumatoid arthritis, B-NHL, aggressive, 192, 192t
Rhim, A. D., 639
Rhinovirus, 1345, 1355
RhTSH. *See* Recombinant human thyrotropin
RhWBRT. *See* Reduced-dose whole-brain radiation therapy
Ribavirin, 1346t
  PIV, 1355
  RSV, 1354
Ribociclib, 1334
  MBC, 833
Ribociclib and fulvestrant, MBC, 836
Ribociclib and goserelin, MBC, 836
Ribociclib and tamoxifen, MBC, 836
RIC. *See* Reduced-intensity conditioning
R-ICE. *See* Ifosfamide, carboplatin, and etoposide
Richter syndrome (RS), CLL, 61
Rickets, 1388–1889
Rimantadine, 1346t
Ripretinib, 1332
Risperidone, delirium, 1568t
RIT. *See* Radioimmunotherapy
Rituximab. *See also specific combination drugs*
  ALL, 11
  cHL, 309
  EBV, 1351
  FL, 174, 174t
  granulomatous pneumonitis, 1467
  HBV, 1356
  JC virus, 1357
  MALT, 186
  MCL, 235, 237
  OP, 1465
  primary cutaneous B-cell lymphomas, 284
  PTLD, 1477
  SMZL, 187
  WM, 335
Rituximab, cisplatin, dexamethasone, high-dose cytarabine (DHAP)
  B-NHL, aggressive, 214
  cHL, 312
Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)
  AHPCT, 383, 386
  B-NHL, aggressive, 208–209, 216t
  DLBCL, 191
    HIV/AIDS, 1235
    testes, 211
  DLBCL-CI, 211–212
  double-expressor DLBCL, 210
  EBVMCU, 212
  FL, 174
  HGBL, 213
  IVDLBCL, 212
  MCL, 237, 238t, 239t, 240
  NHL, 1235, 1237
  NLPHL, 303, 304
  PCDLBCL-LT, 211
  PMBL, 212
  WM, 335
Rivaroxaban, VTE, 1478, 1494
RLN. *See* Regional lymph node
RMB. *See* Renal mass biopsy
RMC. *See* Renal medullary carcinoma
Robot-assisted surgery, endometrial cancer, 938–939
Rogue chaperone activity, ET, 128
Romidepsin
  CTCL, 280–281
  PTCLs, 263, 264t
ROS. *See* Reactive oxygen species
ROS1
  NSCLC, 539–540
  targeted therapy, 1338
Rose, P. G., 974
Rosenberger, W. F., 1584
Ross, C. J., 1063
Rozlytrek. *See* Entrectinib
RPLND. *See* Retroperitoneal lymph node dissection
RPPA. *See* Reverse phase protein array
Rr-GZL, B-cell lymphoma, unclassified, 215
RRP. *See* Radiation recall pneumonitis
RRSO. *See* Reduction bilateral salpingo-oophorectomy
RRT. *See* Regimen-related toxicity
RS. *See* Richter syndrome
RSV. *See* Respiratory syncytial virus
RT. *See* Radiation therapy
RTK. *See* Receptor tyrosine kinase
RT-PCR. *See* Real-time PCR
Rubritz, J. E., 43
Rucaparib, 1336

EOS, 916–917
prostate cancer, 1049, 1064
Rummel, M. J., 240
Ruxolitinib (Jakafi), 1292t
CNL, 147, 148
ET, 134
PMF, 139, 140, 141
PV, 126

S
Sacituzumab govitecan (SG), 1339
bladder cancer, 1031
TNBC, 852
Saha, S. K., 648
sALCL. *See* Systemic anaplastic large-cell lymphoma
Samantas, E., 488
Sanger, F., 1284
De Santis, M., 1088–1089
SAP. *See* Amyloid P component
Sarcoid-like reactions, 1467, 1468f
Sarcoma, 1159–1181, 1160t, 1163t, 1164f, 1166f, 1172t, 1173t, 1174f, 1175t, 1176f, 1177f
esophageal cancer, 594
HCC, 685
pediatric cancer, 1277
spinal cord compression, 1408
Sarcomatoid bladder cancer, 1032, 1035
Sarcomatoid carcinoma, CUP, 1263
Sarcomatoid renal cell carcinoma (sRCC), 1019
SARS-CoV-2. *See* Severe acute respiratory syndrome coronavirus 2
Saunders, Cicely, 1511–1512
Sauter, C. S., 461
SBA. *See* Small bowel adenocarcinoma
SBRT. *See* Stereotactic radiotherapy
Scappaticci, F. A., 1447
SCARs. *See* Severe cutaneous adverse reactions
SCC. *See* Squamous cell carcinoma; Supportive Care Center
SCF. *See* Stem cell factor
Schaid, D. J., 1586
Schairer, C., 864
Scher, B., 1075
Schlecht, N. F., 960
Schlenk, R., 38
Schmeier, K. M., 920
Schmitz, R., 197
SCLC. *See* Small cell lung cancer
SCNSL. *See* Secondary CNS lymphoma
SCPC. *See* Small cell prostate cancer
Screener and Opioid Assessment for Patients with Pain (SOAPP), 1524, 1525
SCSTs. *See* Sex cord stromal tumors
SCT. *See* Stem cell transplantation
SCTAT. *See* Sex cord tumor with annular tubules
SDAC. *See* Standard-dose ara-C
SDH. *See* Succinate dehydrogenase
SDHB, pheochromocytoma, 1205, 1210
Seamless phase 2/3 design, 1586
Secondary CNS lymphoma (SCNSL), 372
g-secretase inhibitors (GSIs), 1339
Seizures, 1412–1413
bleeding, 1420
brain tumors, 1126
TLS, 1426
Selective estrogen receptor down-regulator (SERD), MBC, 838, 855
Selective estrogen receptor modulator (SERM)
MBC, 827, 838
osteoporosis, 1387, 1387f
Selective internal radiation therapy (SIRT)
HCC, 688, 689
NETs, 793–794
Selective serotonin reuptake inhibitors (SSRIs)
fatigue, 1563
methadone, 1560
SIADH, 1386
Selinexor
MM, 353
PTCLs, 263
Selpercatinib, 1340
DTC, 1199
NSCLC, 544
Selumetinib, LGGs, 1275
Seminomas, 1081, 1083–1089, 1084t–1086t, 1085f, 1086f, 1088f
Sentinel lymph node biopsy (SLNB)
breast cancer, 810, 824
cervical cancer, 966, 971, 971f, 972
DCIS, 885
endometrial cancer, 937
male breast cancer, 882
melanoma, 1140
PABC, 877
Sepsis, GTD, 983
Septin 9, CRC, 735
SERD. *See* Selective estrogen receptor down-regulator
SERM. *See* Selective estrogen receptor modulator
Serotonin, PNETs, 784
Sertoli-Leydig cell tumors (SLCTs), SCSTs, 923–924
Sertraline, depression, 1569
Serum protein electrophoresis (SPEP), WM, 334
SETD, pRCC, 1019
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), 1370
Severe combined immunodeficiency, B-NHL, aggressive, 192t
Severe cutaneous adverse reactions (SCARs), 1427, 1428
Severity-weighted assessment tool (SWAT), CTCL, 272–273, 273t
Sex cord stromal tumors (SCSTs), 923–925, 924t
Sex cord tumor with annular tubules (SCTAT), 924
Sex-determining regions-Y (SRY), MCL, 228
Sézary syndrome (SS), 269, 383
SG. *See* Sacituzumab govitecan
SHH. *See* Sonic Hedgehog
Shih, C., 1284
Shingles. *See* Varicella zoster virus
Shingrix, 1348
SIADH. *See* Syndrome of inappropriate antidiuretic hormone
Sickle cell disease, AHSCT, 398
Siddiqi, T., 372
Sidorkiewicz, I., 965
Sigmoidoscopy, CRC, 735
Signal transducer and activator of transcription (STAT)
CNL, 147
CTCL, 280
ET, 133
MPDs, 120
NLPHL, 295
NOTCH, 1338–1339
PMBL, 199
PMF, 135
PTCLs, 255
PV, 121–122
sALCL, 256
Signet ring
appendiceal tumors, 716
CRC, 737
DLBCL, 196
Siltuximab, ICANS, 1313
Simon, R., 1582, 1583, 1586, 1589
Simvastatin, lipid disorders, 1385
Single-nucleotide polymorphism (SNP)
biliary tract cancer, 650
MDSs, 97–98
Single-nucleotide variations (SNVs), 1285
Single-proton emission computed tomography (SPECT), brain tumors, 1114
Single-stage design, 1582
Sinusitis, aspergillosis, 1371
Sinusoidal obstruction syndrome (SOS). *See* Veno-occlusive disease-sinusoidal obstruction syndrome
Sinus tachycardia, 1449
Sipuleucel-T, 1313
Sirolimus, HCC, 688
SIRT. *See* Selective internal radiation therapy
Sitara. *See* Regorafenib
Sitravatinib, bladder cancer, 1031
Sjögren syndrome
B-NHL, aggressive, 192, 192t
FL, 165
SLCTs. *See* Sertoli-Leydig cell tumors
Sleep disturbances, 1461, 1485
SLL/CLL. *See* Small lymphocytic lymphoma/chronic lymphocytic leukemia
SLNB. *See* Sentinel lymph node biopsy
SLP. *See* Speech-language pathologist
SM. *See* Systemic mastocytosis
Small bowel adenocarcinoma (SBA), 707–716, 711t, 712t, 714t, 715f, 717f
Small cell cancer
bladder cancer, 1032
esophageal cancer, 594
Small cell lung cancer (SCLC), 475–491, 477f, 478f, 478t, 482f, 484f, 490t
PD-1 ICIs, 1304
SIADH, 1386, 1424
SVC syndrome, 1415
Small cell prostate cancer (SCPC), 1054–1055, 1064–1065
Small intestinal NETs, 786–788
Small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL), 187–188
MALT, 186
MCL, 228, 233

Small-medium pleomorphic lymphoproliferative disorder (SMPLD), 283
Small renal mass (SRM), RCC, 1009
SMARCB
  meningiomas, 1111
  RMC, 1020
SMM. *See* Smoldering multiple myeloma
SMO, meningiomas, 1111
Smoking
  anal cancer, 768
  bladder cancer, 1028
  brain tumors, 1108
  cervical cancer, 956
  ET, 132
  HNSCC, 555, 570
  NETs, 782
  NSCLC, 496, 498
  pancreatic cancer, 620
  SBA, 708
  SCLC, 476
Smoldering MCL, 236–237
Smoldering multiple myeloma (SMM), 341–344, 356
Smoldering SM (SSM), 148
SMPLD. *See* Small-medium pleomorphic lymphoproliferative disorder
Smudge cells, CLL, 50
SM with an associated hematologic neoplasm (SM-AHN), 148, 149, 151, 152
SMZL. *See* Splenic marginal zone lymphoma
SNP. *See* Single-nucleotide polymorphism
SNVs. *See* Single-nucleotide variations
SOAPP. *See* Screener and Opioid Assessment for Patients with Pain
SOAT. *See* Sterol-O-acyl transferase
Sokal, J. E., 77
Solitary plasmacytoma of bone, 356
Solitary pulmonary nodule, NSCLC, 503, 503t, 504f
Somatostatin
  appendiceal carcinoid tumors, 720
  diabetes mellitus, 1383t
  gastrointestinal bleeding, 1427
Somatostatin analogues (SSAs), NETs, 781, 792
Somatostatinoma, PNETs, 789
Somatostatin receptor scintigraphy (SRS), NETs, 785, 786f
Sonic Hedgehog (SHH), medulloblastoma, 1275
Sorafenib (Nexavar), 1292t
  arterial ischemia, 1446t, 1447
  cHCC-CC, 694
  DTC, 1199
  DVT and VTE, 1488
  HCC, 691, 694
  hypertension, 1454, 1454t
  hypothyroidism, 1394–1395
  mRCC, 1033
  parathyroid carcinoma, 1204
  RCC, 1010
  sarcoma, 1168
Sorafenib, lenvatinib, atezolizumab, and bevacizumab, HCC, 691
Sorafenib and midostaurin, AML, 33
SOX11, MCL, 228, 229f, 230, 233, 234–235
Spasticity, spinal cord injury, 1535–1536
SPECT. *See* Single-proton emission computed tomography
Speech-language pathologist (SLP), 1531
  aphasia, 1535
  RFS, 1538
SPEP. *See* Serum protein electrophoresis
Spinal cord
  compression, 1407–1409, 1409f
  injury
    bladder cancer, 1029
    rehabilitation, 1534–1537
Spindle cells, DLBCL, 196
Spleen volume reduction (SVR), PV, 126
Splenectomy
  CNL, 148
  PMF, 140
  SMZL, 186–187
Splenic lymphoma, MCL, 233
Splenic marginal zone lymphoma (SMZL), 186–187, 187f
Splenomegaly
  CLL, 50
  HCC, 683
  HHV8+ DLBCL, 200
  MM, 343
  PMF, 134, 141
  SLL/CLL, 187
  SM, 153
Sprycel. *See* Dasatinib
SPTCL. *See* Subcutaneous panniculitis T-cell lymphoma
Squamous cell carcinoma (SCC)
  anal cancer, 765–776, 766f, 770t, 771t, 773f, 774t
  biliary tract cancer, 648
  cervical cancer, 955, 956, 971
  CUP, 1257, 1260, 1261
  esophageal cancer, 594, 600, 601, 603
  gastric cancer, 579
  NSCLC, 500–501, 501f, 522
  penile cancer, 1071–1078, 1071t, 1074t, 1076t
Squamous cell carcinoma of the head and neck (HNSCC), 555–571, 557f, 558, 559t, 560t, 561f–563f, 564t, 567, 567t–569t
sRCC. *See* Sarcomatoid renal cell carcinoma
SRM. *See* Small renal mass
SRS. *See* Somatostatin receptor scintigraphy
SRY. *See* Sex-determining regions-Y
SS. *See* Sézary syndrome
SSAs. *See* Somatostatin analogues
SSM. *See* Smoldering SM
SSRIs. *See* Selective serotonin reuptake inhibitors
STAG2, bladder cancer, 1029
Stahl, M., 603
Stallard, N., 1586
Standard-dose ara-C (SDAC), AML, 29
Standard-dose chemotherapy, AHPCT, 384
Staphylococcus aureus, CTCL, 273, 285
STAT. *See* Signal transducer and activator of transcription
Statins, radiation-induced cardiovascular toxicity, 1456
Status epilepticus, 1413
Steatorrhea, GEP-NETs, 792
Stem cell factor (SCF), melanoma, 1136
Stem cell transplantation (SCT). *See also* Allogeneic hematopoietic stem cell transplantation; Allogeneic stem cell transplant; Autologous hematopoietic progenitor cell transplant; Autologous stem cell transplant; Hematopoietic stem cell transplantation
  acute pericarditis, 1451
  AML, 23, 37, 38, 38t
  CAR-T, 363
  CBT, 427–442, 430t, 434t, 435t, 436f, 437, 439t–441t
  CML, 74
  CNL, 148
  CTCL, 276, 282
  FL, 170, 171, 176
  MCL, 232, 235, 237
  MM, 347, 348
  myelofibrosis, 119
  SM, 153
  VTE, 1499
Stephenson, A. J., 1093
Stereotactic radiotherapy (SBRT)
  biliary tract cancers, 653
  GTD, 996
  HCC, 689
  HNSCC, 567
  ICP, 1410
  MBC, 831
  NSCLC, 507
  sarcoma, 1163
Steroids
  acute pericarditis, 1451, 1453f
  CMV, 1349
  COP, 1476–1477
  DVT and VTE, 1488
  EP, 1466
  hypertension, 1454, 1454t
  JC virus, 1357
  MM, 341
  PIV, 1355
Sterol-O-acyl transferase (SOAT), 1384
  primary adrenal insufficiency, 1396
Stevens-Johnson syndrome, 1427
STNI. *See* Subtotal nodal irradiation
Streptokinase, 1419t
Streptozocin
  diabetes insipidus, 1386
  diabetes mellitus, 1382
Subcutaneous panniculitis T-cell lymphoma (SPTCL), 284
Subtotal nodal irradiation (STNI), cHL, 304, 307
Succinate dehydrogenase (*SDH*), GISTs, 1171
Sugarbaker, P. H., 726
Sulindac, CRC, 736
Sunitinib. *See also specific drug combinations*
  arterial ischemia, 1446t, 1447
  DVT and VTE, 1488
  GEP-NETs, 794
  GISTs, 1172
  hypertension, 1454, 1454t
  hypothyroidism, 1394, 1395–1396
  mRCC, 1011, 1013–1014, 1018–1019, 1033, 1034
  nccRCC, 1019

pRCC, 1019
primary adrenal insufficiency, 1396
QT prolongation, 1450t
RCC, 1010
sarcoma, 1168
sRCC, 1019
TMAs, 1501
Sunitinib and pazopanib, mRCC, 1015
Superficial spreading melanoma, 1134, 1135t
Superior vena cava (SVC) syndrome, 1415, 1416f
NSCLC, 502
Supportive Care Center (SCC), 1523–1525, 1524f
Supraclavicular adenopathy, CUP, 1260
Supraventricular tachycardia (SVT), 1449
Surface antigen phenotype, CLL, 50
Surufatinib, PNETs, 794–795
Survivorship, 1545–1546
SVC. *See* Superior vena cava syndrome
SVR. *See* Spleen volume reduction
SVT. *See* Supraventricular tachycardia
SWAT. *See* Severity-weighted assessment tool
Sweet syndrome, 1427
Syndrome of inappropriate antidiuretic hormone (SIADH), 1385–1387, 1424–1425
SCLC, 478
Systemic anaplastic large-cell lymphoma (sALCL), 254, 256–258
Systemic light chain (AL) amyloidosis, 323–329, 325t–327t
MM, 341
Systemic mastocytosis (SM), 120, 148–153, 149t, 150t, 151f, 153

T

TAC. *See* Docetaxel, doxorubicin, and cyclophosphamide
TACE. *See* Transarterial chemoembolization
Tachyarrhythmias, 1449–1450
Tacrolimus
acute pericarditis, 1451
hypertension, 1454t, 1455
Tafinlar. *See* Dabrafenib
Talazoparib, 1336
MBC, 839–840
TALEN. *See* Transcription activator-like effector nucleases
Talimogene laherparepvec (TVEC), 1314
melanoma, 1141, 1150
T-ALL. *See* T-cell acute lymphoblastic leukemia
TAM. *See* Transient abnormal myelopoiesis
Tamiflu. *See* Oseltamivir
t-AML. *See* Therapy-related acute myeloid leukemia
Tamoxifen. *See also specific combination drugs*
anaplastic astrocytoma, 1122
breast cancer, 814
DCIS, 886–887
endometrial cancer, 941–942
ESS, 948
male breast cancer, 883
MBC, 827
osteoporosis, 1387
PABC, 878
thrombosis, 1502
VTE, 1417
Tandstad, T., 1093
TAP. *See* Paclitaxel, doxorubicin, and cisplatin
Tarceva. *See* Erlotinib
Tarextumab, 1339
Targeted therapy, 1323–1341, 1325t, 1326f, 1326t, 1327t, 1334f, 1340t, 1341f
DILI, 1464t–1465t
FL, 175–176
hypothyroidism, 1394–1395
ICIs, 1306–1307
lung cancer, 1585
NSCLC, 535–546, 536t, 538t, 543t
TAS-102. *See* Trifluridine/tipiracil
Tasigna. *See* Nilotinib
Tattersall, M. H. N., 1520
Taxanes
bladder cancer, 1040, 1041
LABC and IBC, 867
MBC, 842–843
PABC, 878
prostate cancer, 1063
Tazemetostat, FL, 176
TBG. *See* Thyroid hormone-binding globulin
TC. *See* Docetaxel and cyclophosphamide
TCC. *See* Transitional cell carcinoma
T-cell acute lymphoblastic leukemia (T-ALL), 3, 4–18
frontline therapy, 12
NOTCH, 1338
T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL), 197, 211
T-cell Ig and mucin domain-containing-3 (TIM-3), 1308
T-cell lymphoma, CAR-T, 372–373
gdT-cell lymphoma (GDTCL), 283
T-cell lymphomas (TCL)
central hypothyroidism, 1393
lipid disorders, 1384
T-cell PLL (T-PLL), 52
T-cell receptors (TCRs)
AITL, 256
CAR-T, 364, 374
CEL/HES, 144
CTCL, 274, 282
ICIs, 1298
immunotherapy, 1297
NOTCH, 1338
PTCL-NOS, 256
sALCL, 258
T-cell-rich B-cell lymphoma (TCRBCL), 295
NLPHL, 304
T-cells
CEL/HES, 144
DCs, 1314
LGLs, 63
LYG, 198
PLL, 63
TCF3. *See* Transcription factor 3
TCL. *See* T-cell lymphomas
TCRBCL. *See* T-cell-rich B-cell lymphoma
TCRs. *See* T-cell receptors
T-DM1. *See* Trastuzumab emtansine
TdT. *See* Terminal deoxynucleotidyl transferase
t-DxD. *See* Trastuzumab deruxtecan
TEC. *See* Paclitaxel, estramustine, and carboplatin
TEE. *See* Paclitaxel, estramustine, and etoposide
Teisberg, E. O., 1604
Telangiectasias, elevated erythropoietin and erythrocytosis, monoclonal gammopathy, perinephric fluid collection, and intrapulmonary shunting syndrome (TEMPI), 341
Teleglenastat and cabozantinib, mRCC, 1017
Teleglenastat and everolimus, mRCC, 1017
Telomerase, GTD, 985
Telomerase reverse transcriptase (*TERT*)
DTC, 1191
glioblastoma, 1110–1111
Telotristat ethyl, NETs, 795
Temel, J. S., 1520–1521
Temozolomide (TMZ)
glioma, 1121t
HGGs, 1275
melanoma, 1151
parathyroid carcinoma, 1204
PCNSL, 1125
SCLC, 485
Temozolomide and rituximab, PCNSL, 1125, 1240
TEMPI. *See* Telangiectasias, elevated erythropoietin and erythrocytosis, monoclonal gammopathy, perinephric fluid collection, and intrapulmonary shunting syndrome
Temsirolimus (Torisel), 1292t
Tenalisib, PTCLs, 263
Teniere, P., 604
Teniposide, extravasation injuries, 1424
Tenosynovial giant cell synovitis (TGCT), 1170
Teratoma, 1092, 1092f
Terazosin
pheochromocytoma, 1207
urinary tract obstruction, 1421
Terminal deoxynucleotidyl transferase (TdT), 5
PLL, 63
Terrault, N. A., 688
TERT. *See* Telomerase reverse transcriptase
Tesirine, ALL, 18
Testes
DLBCL, 211
GCTs, 1081–1099
Testosterone
ACC, 1212
fatigue, 1563
male breast cancer, 883
osteoporosis, 1387, 1387f
TET2, 1288–1289
TE/TP. *See* Paclitaxel and etoposide alternating weekly with paclitaxel and cisplatin
Tetracycline, MPE, 1484
TFE
pRCC, 1019
Xp11.2 translocation carcinoma, 1020

T-follicular helper (TFH)
AITL, 255–256
PTCLs, 253, 254
Tg. *See* Thyroglobulin
TGCT. *See* Tenosynovial giant cell synovitis
TGF-a. *See* Transforming growth factor a
TGF-b. *See* Transforming growth factor b
Thalassemia major, AHSCT, 398
Thalidomide
arterial ischemia, 1446t, 1447
CNL, 148
DVT and VTE, 1488
KS, 1230
PMF, 140
POEMS, 357
PTCLs, 263
VTE, 1477, 1478
Therapy-related acute myeloid leukemia (t-AML), 386
Therneau, T. M., 1586
Thiazide diuretics, SIADH, 1386, 1424
Thiotepa, LMD, 1412
THL. *See* Triple-hit lymphoma
Thoracic radiation therapy (TRT), SCLC, 483
THP. *See* Pertuzumab, trastuzumab, and docetaxel
THRLBCL, T–cell/histiocyte–rich large B–cell lymphoma
Thrombocytopenia. *See also* Essential thrombocytopenia; Immune thrombocytopenia
ACS, 1503–1504
anticoagulants, 1499
bleeding, 1419–1420
CNL, 148
FLHCC, 695
fungal infections, 1364
gastrointestinal bleeding, 1426
HCC, 683
LGLs, 63
MDSs, 93, 105
pericardial effusions, 1454
PMF, 135, 137, 140
rehabilitation, 1544–1545
SM, 120
tachyarrhythmias, 1449
VTE, 1477, 1499
VZV, 1348
Thrombocytosis
ET, 128, 129, 134, 154
PMF, 135
Thrombopoietin (Tpo)
MDSs, 105
MPDs, 120
PV, 121
Thrombosis, 1417–1419, 1418t, 1419t, 1493–1504. *See also* Deep vein thrombosis; Venous thromboembolism
ET, 131
PV, 122, 123t, 125, 126
Thrombotic microangiopathies (TMAs), 1499–1501, 1500f
Thrombotic thrombocytopenic purpura (TTP), 1430
TMAs, 1500
Thromboxanes
ET, 133
PV, 126
Thymidine phosphorylase (TP), 745
Thyroglobulin (Tg), DTC, 1197, 1197f
Thyroid cancer, 1189–1203, 1190t, 1191f, 1191t, 1192f, 1193t, 1194t, 1195f–1198f, 1200f, 1202f, 1394
brain tumors, 1106
RET, 1340
Thyroid disorders, 1400. *See also* Hyperthyroidism; Hypothyroidism
Thyroid hormone-binding globulin (TBG), 1396
Thyroid-stimulating hormone (TSH), 1391
central hypothyroidism, 1393
choriocarcinoma, 1091
DTC, 1195, 1196–1197
GCTs, 1083
hypothyroidism, 1394
MTC, 1201
Thyroid transcriptase factor 1 (TTF-1), 477, 489
CUP, 1257–1258, 1258f, 1262
NSCLC, 499
Thyrotoxicosis
co-twin pregnancy, 998
GTD, 991
Tichelli, A., 407
TILs. *See* Tumor-infiltrating lymphocytes
TIM-3. *See* T-cell Ig and mucin domain-containing-3
TIMPs. *See* Tissue inhibitors of matrix metalloproteinases
Tinnitus, PV, 122
Tinzaparin, DVT, 1418, 1418t
TIO. *See* Tumor-induced osteomalacia
TIP. *See* Paclitaxel, ifosfamide, and cisplatin
Tisagenlecleucel, 1312
ICANS, 1313
Tissue inhibitors of matrix metalloproteinases (TIMPs), brain tumors, 1111
Tizanidine, spasticity, 1536
TKIs. *See* Tyrosine kinase inhibitors
TLNs. *See* Total lymph nodes
TLRs. *See* Toll-like receptors
TLS. *See* Tumor lysis syndrome
T-lymphoblastic leukemia/lymphoma, 25t
TMAs. *See* Thrombotic microangiopathies
TMB. *See* Tumor mutational burden
t-MCL. *See* Transformed MCL
t-MDS. *See* Treatment-related MDS
TME. *See* Tumor microenvironment
TMPRSS2, prostate cancer, 1054
TMTV. *See* Total metabolic tumor volume
TMZ. *See* Temozolomide
TNBC. *See* Triple-negative breast cancer
TNC. *See* Total nucleated cell
TNF-a. *See* Tumor necrosis factor a
Tocilizumab
CAR-T, 367
ICANS, 1313
Toll-like receptors (TLRs)
CLL, 56
CTCL, 273
DCs, 1314
Topiramate, seizures, 1413
Topoisomerase, myocardial toxicity, 1441
Topotecan
cervical cancer, 976
LGSC, 920
MDSs, 107–108
SCLC, 485
Topotecan and paclitaxel, cervical cancer, 976
Topotecan, paclitaxel, and bevacizumab, cervical cancer, 976
Torisel. *See* Temsirolimus
Total lymph nodes (TLNs), SBA, 710
Total metabolic tumor volume (TMTV), cHL, 311
Total nucleated cell (TNC)
AHSCT, 402
CBT, 428, 431
Total-skin electron-beam therapy (TSEBT), CTCL, 277–278
Tournigand, C., 745
Toxic epidermal necrolysis, 1427
Toxic lung injury, 1423
Toxoplasmosis, AHSCT, 409
TP. *See* Thymidine phosphorylase
TP53, 1286
AML, 27, 34
appendiceal tumors, 723, 725
biliary tract cancer, 662
bladder cancer, 1029, 1031
breast cancer, male, 881
ccRCC, 1008
CLL, 50, 60
EOC, 898
gastric cancer, 580
glioblastoma, 1110
HGGs, 1275
HNSCC, 556
LABC and IBC, 870
MCL, 228, 230, 232, 234, 235, 244
smoldering, 236
MDSs, 96, 109–110
pancreatic cancer, 621
parathyroid carcinoma, 1203
prostate cancer, 1049, 1055
sALCL, 258
sarcoma, 1159, 1160
SBA, 709
SCLC, 477
sRCC, 1019
TP63
HNSCC, 556
PTCL-NOS, 256
TPEx. *See* Docetaxel, platinum, cetuximab
TPF. *See* Docetaxel, cisplatin, and 5-fluorouracil
T-PLL. *See* T-cell PLL
Tpo. *See* Thrombopoietin
Trabectedin
liposarcoma, 1169
sarcoma, 1165
Trametinib (Mekinist), 1292t, 1324
melanoma, 1146t, 1149
Transarterial chemoembolization (TACE)
FLHCC, 694–695
HCC, 688–689
Transcatheter arterial chemoembolization (cTACE), NETs, 793
Transcription activator-like effector nucleases (TALEN), 374
Transcription factor 3 (TCF3), BL, 203

Transcriptomes, MIBC, 1030
Transformed follicular lymphoma, 215
Transformed MCL (t-MCL), 232, 234
Transforming growth factor a (TGF-a), HNSCC, 556
Transforming growth factor b (TGF-b)
  MDS, 105–106
  osteoporosis, 1388
  PMF, 135
Transient abnormal myelopoiesis (TAM), 25t
Transitional cell carcinoma (TCC)
  bladder cancer, 1031, 1032, 1037, 1039
  EOC, 904
Transplant-related mortality (TRM)
  AHSCT, 458
  CBT, 428, 431
Transthyretin (TTR) amyloidosis, AL, 324
Transurethral resection (TUR), bladder cancer, 1034, 1035, 1036, 1037
Trastuzumab (Herceptin), 1292t, 1332
  atrial fibrillation, 1504
  breast cancer, 819–820
  esophageal cancer, 603
  gastric cancer, 606–607
  LABC and IBC, 868
  MBC, 846
  myocardial toxicity, 1442–1443
  PABC, 878
Trastuzumab and eribulin, MBC, 850–851
Trastuzumab and gemcitabine, MBC, 850–851
Trastuzumab and Iapatinib, MBC, 850–851
Trastuzumab and vinorelbine, MBC, 850–851
Trastuzumab deruxtecan (t-DxD), 544, 1333
  MBC, 850, 855
Trastuzumab emtansine (T-DM1), 608
  biliary tract cancer, 664
  breast cancer, 821
  MBC, 834, 849–851
Treatment-related MDS (t-MDS), 93
Tremelimumab
  biliary tract cancer, 669
  primary adrenal insufficiency, 1397
TRICOM, 1313
Tricyclic antidepressants, pain management, 1561, 1561t
Trifluridine/tipiracil (TAS-102), 610
  CRC, 747
Trimethoprim/sulfamethoxazole, AHSCT, 408–409
Tri-Mix-DC, 1314
Trimodality therapy, LABC and IBC, 867, 869
Triple-hit lymphoma (THL), 201–202, 201t, 202f
  CAR-T, 365
Triple-negative breast cancer (TNBC), 803, 805, 817–819, 818f, 819f
  LABC and IBC, 865
  MBC, 829, 830, 832, 851–854, 852f
  MRI, 1597
Triple-refractory relapsed MCL, 244–245
Trisomy 3, AITL, 256
Trisomy 5, AITL, 256
Trisomy 12, SLL/CLL, 188
Trisomy 13. *See* Patau syndrome
Trisomy 21. *See* Down syndrome
TRK. *See* Tropomyosin receptor kinase
TRM. *See* Transplant-related mortality
Tropomyosin receptor kinase (TRK)
  CUP, 1260, 1266
  DTC, 1191
  NTRK fusions, 544
Trousseau syndrome, 1503
TRT. *See* Thoracic radiation therapy
TSC. *See* Tuberous sclerosis complex
TSEBT. *See* Total-skin electron-beam therapy
TSH. *See* Thyroid-stimulating hormone
Tsiatis, A. A., 1585
TTF-1. *See* Thyroid transcriptase factor 1
TTP. *See* Thrombotic thrombocytopenic purpura
TTR. *See* Paclitaxel, topotecan, and rituximab
Tu, Y. H., 1586
Tuberous sclerosis, NET, 783
Tuberous sclerosis complex (*TSC*)
  parathyroid carcinoma, 1203
  RCC, 1006
  SCC, 502t
Tucatinib
  MBC, 834, 855
Tucatinib, trastuzumab, and capecitabine, MBC, 850
Tumor-induced osteomalacia (TIO), 1389
Tumor-infiltrating lymphocytes (TILs)
  ACT, 1311, 1312f
  ICIs, 1307–1308
Tumor lysis syndrome (TLS), 1425–1426
  AML, 38
  B-NHL, aggressive, 210
  hyperleukocytosis, 1417
  ICANS, 1313
Tumor microenvironment (TME)
  CRC, 741
  LABC and IBC, 868, 870
  pancreatic cancer, 622
Tumor mutational burden (TMB)
  PD-1 ICIs, 1305, 1307
  prostate cancer, 1064
Tumor necrosis factor a (TNF-a), 1311
  AHSCT, 458
  ARDS, 1423
  ICANS, 1313
  irAEs, 1431
  sarcoid-like reactions, 1467
Tumor suppressor genes, 1284
  GTD, 985
  pancreatic cancer, 621
  RMC, 1020
TUR. *See* Transurethral resection
Turcot syndrome, 1275
Turtle, C. J., 371
TVEC. *See* Talimogene laherparepvec
Twari, K. S., 910
Two-stage design, 1582
Tykerb. *See* Lapatinib
Typhlitis, 1427, 1427f
Tyrosine kinase inhibitors (TKIs)
  ACC, 1217
  AHSCT, 416
  ALL, 9–10, 11, 14
  ARDS, 1423
  arterial ischemia, 1446t, 1447
  ATC, 1203
  biliary tract cancers, 662–663
  bladder cancer, 1031
  breast cancer, 821
  CED/HES, 119
  CEL/HES, 145
  CML, 67, 68, 69, 70–84, 73t, 76t, 77t
  diabetes mellitus, 1382, 1383t
  DTC, 1199
  gastric cancer, 607, 609
  GISTs, 1171–1172
  hypertension, 1454, 1454t
  hypomagnesemia, 1390
  hypothyroidism, 1394
  mRCC, 1013, 1014, 1034
  MTC, 1202
  myocardial toxicity, 1443
  nccRCC, 1019
  NSCLC, 519, 535, 537–546
  oncocardiology, 1435, 1438
  OP, 1465
  osteoporosis, 1388
  osteosarcoma, 1179
  parathyroid carcinoma, 1204
  PH, 1469
  pleural effusions, 1467
  pRCC, 1019
  QT prolongation, 1450, 1450t, 1452t
  resistance, 79–80
  sarcoma, 1167, 1277
  second and third generations, 80–82
  SM, 152–153
  thrombosis, 1502
  thyroid disorders, 1400

U

UDSs. *See* Urine drug screens
UFH. *See* Unfractionated heparin
u5-HIAA. *See* Urine 5-HIAA
Ulcerative colitis, gallbladder carcinoma, 650
ULN. *See* Upper limit of normal
Ultrasound (US). *See also* Endoscopic ultrasonography
  anal cancer, 768
  co-twin pregnancy, 998
  DTC, 1197
  DVT, 1493
  EBUS, NSCLC, 503, 504
  GCTs, 1082
  GTD, 983, 985, 987, 989, 989f
  HCC, 685
  LABC and IBC, 867
  PABC, 876, 877, 879
  pancreatic cancer, 623
  parathyroid carcinoma, 1203
  prostate cancer, 1053
  SVC syndrome, 1415
  thyroid cancer, 1190
Ultraviolet radiation (UVR), melanoma, 1134, 1135
Umbralisib, MALT, 186
Undifferentiated carcinoma
  CUP, 1257
  EOC, 904
Undifferentiated endometrial sarcoma, 948
Undifferentiated pleomorphic sarcoma (UPS), 1172, 1175

Unfractionated heparin (UFH)
DVT, 1418, 1418t
Trousseau syndrome, 1503
VTE, 1494
Universal or switchable CAR-T cells, 375
Upper limit of normal (ULN), RCC, 1005
UPS. *See* Undifferentiated pleomorphic sarcoma
Ureterovesical junctions (UVJs), bladder cancer, 1035, 1037
Urinary tract infection, 1366–1367
Urinary tract obstruction, 1421–1422
Urine drug screens (UDSs), 1560–1561, 1561t
Urine 5-HIAA (u5-HIAA), NETs, 784
Urokinase, 1419t
Urothelial cancer. *See also* Bladder cancer
PD-1 ICIs, 1303–1304
US. *See* Ultrasound
USCs. *See* Uterine serous carcinomas
Uterine cervix. *See* Cervical cancer
Uterine corpus tumors. *See* Endometrial cancer
Uterine serous carcinomas (USCs), 933, 936–936
Uveal melanoma, 1134, 1135t, 1151
Uveitis, 1431
UVJs. *See* Ureterovesical junctions
UVR. *See* Ultraviolet radiation

V

VAC. *See* Vincristine, doxorubicin, and cyclophosphamide
Vaccination, 1313
ASCT, 350
DCs, 84
HCC, 694
HHV-8, 1230
HPV, 571, 765, 767, 776, 955, 957, 1078, 1244
ipilimumab, 1145, 1298
NSCLC, 514
pancreatic cancer, 639
prostate cancer, 1065
VZV, 140, 1348
VAD. *See* Vincristine, doxorubicin, and dexamethasone
Vaginal cancer
anal cancer, 767
GTD, 988
VAI. *See* Vincristine, doxorubicin, and ifosfamide
Valacyclovir, 1346t
CBT, 437
CMV, 1350
HSV, 1346–143
VZV, 1348
Valproic acid
brain tumor seizures, 1126
MDSs, 107
seizures, 1413
Value-based oncology, 1603–1614, 1607t, 1608f, 1609f
RT, 1611–1613
surgical oncology, 1613–1614
Vanbutsele, G., 1521
Vandetanib (Caprelsa), 1292t
hypertension, 1454, 1454t
hypothyroidism, 1394
MTC, 1202
parathyroid carcinoma, 1204
QT prolongation, 1450t, 1452t
Vannucchi, A. M., 138
Varicella zoster virus (VZV), 1345, 1346–1349, 1348f
vaccination, 140, 1348
Vascular endothelial growth factor (*VEGF*)
appendiceal tumors, 727
brain tumors, 1111
ccRCC, 1008
c-kit, 1331
CRC, 742, 749
DTC, 1192
EOC, 902, 918
GEJ cancer, 607
GEP-NETs, 794
GISTs, 1171–1172
HCC, 688
hypertension, 1454, 1454t
KS, 1230
mRCC, 1014, 1015, 1033
NSCLC, 520–521
oncocardiology, 1436–1437
osteosarcoma, 1179
PMF, 135
POEMS, 357
RCC, 1005, 1010
RMC, 1020
sarcoma, 1167, 1175
SBA, 715, 716
sleep disturbances, 1485
Xp11.2 translocation carcinoma, 1020
Vascular endothelial growth factor receptor (*VEGFR*)
ASPS, 1170
EOC, 902
HCC, 693
mRCC, 1014
targeted therapy, 1325t
Vascular signaling pathway inhibitors (VSPIs), 1446
hypertension, 1454, 1455
Vasoactive intestinal peptide (VIP), PNETs, 784
Vasopressin
gastrointestinal bleeding, 1427
SIADH, 1386
V/C. *See* Vemurafenib and cobimetinib
VC. *See* Virtual colonoscopy
V-domain Ig suppressor of T-cell activation (VISTA), 1308
Vectibix. *See* Panitumumab
VEGF. *See* Vascular endothelial growth factor
VEGFR. *See* Vascular endothelial growth factor receptor
VeIP. *See* Vinblastine, ifosfamide, and cisplatin
Vejpongsa, P., 1441
Vemurafenib (Zelboraf), 1292t, 1324
LGGs, 1275
melanoma, 1146t, 1149
QT prolongation, 1452t
sarcoid-like reactions, 1467
Vemurafenib and cobimetinib (V/C), melanoma, 1146t, 1150
Venetoclax. *See also specific drug combinations*
AML, 23, 32–33, 1273
CLL, 57
MCL, 236, 243
MDSs, 109
MM, 354
SLL/CLL, 188
WM, 336
Veno-occlusive disease-sinusoidal obstruction syndrome (VOD/SOS), 385–386
AHSCT, 401, 409–411, 410t
ALL, 13
Venous thromboembolism (VTE), 1417–1419, 1418t, 1419t, 1431, 1467–1468, 1477–1478, 1493–1494, 1495t–1498t, 1499
arterial ischemia, 1446
Ph-MPNs, 1502–1503
Verner-Morrison syndrome, pheochromocytoma, 1205
Vessel occlusion sign (VOS), fungal infections, 1364
VFLIP. *See* Viral FLICE-inhibitory protein
VGPCR. *See* Viral G protein-coupled receptor
VHL. *See* Von Hippel-Lindau syndrome/disease
Vickers, A. J., 1035
Vinatzer, U., 185
Vinblastine. *See also specific drug combinations*
bladder cancer, 1040
breast cancer, 1398
extravasation injuries, 1424
Vinblastine, ifosfamide, and cisplatin (VeIP), 923
Vincristine. *See also specific combination drugs*
CEL/HES, 145
Vincristine and carboplatin, LGGs, 1275
Vincristine, doxorubicin, and cyclophosphamide (VAC), 1179
Vincristine, doxorubicin, and dexamethasone (VAD), 348
Vincristine, doxorubicin, and ifosfamide (VAI), 1179–1180
Vincristine, doxorubicin, and prednisone, NHL, 1237
Vinorelbine
cervical cancer, 976
extravasation injuries, 1424
MBC, 839–840, 841t, 844–845
VIP. *See* Vasoactive intestinal peptide
VIPoma, PNETs, 789
Viral FLICE-inhibitory protein (vFLIP), KS, 1227
Viral G protein-coupled receptor (vGPCR), KS, 1227
Viral infections, 1345–1358, 1346t, 1347t, 1348f, 1350f, 1354t, 1355f, 1357f. *See also specific infections*
Viral-specific T cells (VSTs), 466
Virtual colonoscopy (VC), CRC, 735
Visco, C., 235
Vismodegib (Erivedge), 1292t
pancreatic cancer, 638
VISTA. *See* V-domain Ig suppressor of T-cell activation
Vitamin A, CTCL, 278
Vitamin B1 deficiency, altered mental status, 1413

Vitamin B12, fatigue, 1563
Vitamin D
  bone cancer, MBC, 832
  hypercalcemia, 1389
  hypocalcemia, 1390
  osteomalacia, 1388
  osteoporosis, 1388
  TIO, 1389
Vitamin K antagonists, VTE, 1478
Vitrakvi. *See* Larotrectinib
VOD. *See* Veno-occlusive disease
Vodobatinib, CML, 81–82
VOD/SOS. *See* Veno-occlusive disease-sinusoidal obstruction syndrome
Von Hippel-Lindau syndrome/disease (*VHL*)
  ccRCC, 1008
  mRCC, 1017
  NET, 783
  pheochromocytoma, 1205, 1206
  RCC, 1006
Von Willebrand factor (VWF), TMAs, 1500, 1500f, 1501
Von Willebrand syndrome, 1502
Voriconazole, 1368t
  AHSCT, 407
  aspergillosis, 1372
  candidiasis, 1368, 1369, 1369t
  CBT, 437
  coccidioidomycosis, 1377
  fusariosis, 1375
  QT prolongation, 1450t
Vorinostat
  CTCL, 280
  MM, 353
VOS. *See* Vessel occlusion sign
Votrient. *See* Pazopanib
VRD. *See* Bortezomib, lenalidomide, and dexamethasone
VSPIs. *See* Vascular signaling pathway inhibitors
VSTs. *See* Viral-specific T cells
VTE. *See* Venous thromboembolism
Vulvar cancer, anal cancer, 767
VWF. *See* Von Willebrand factor
VZV. *See* Varicella zoster virus

W
WAGR syndrome, WT, 1276
Waldenström macroglobulinemia (WM), 52, 333–337, 334t, 335t
  MM, 341, 345
Wang, S. K., 1585
Warde, P., 1087
Warfarin, atrial fibrillation, 1504
WAT. *See* White adipose tissue
WBCs. *See* White blood cells
WBRT. *See* Whole-brain radiation therapy
Wei, L. J., 1584
Wells syndrome, CLL, 50
Wenham, R. M., 918
Wernicke encephalopathy, fedratinib, 140
White adipose tissue (WAT), prostate cancer, 1051
White blood cells (WBCs)
  ALL, 4
  AML, 24, 28
  CNL, 147
  ET, 132
  fungal infections, 1377
  hyperleukocytosis, 1417
  MCL, 234
  PMF, 137
  PV, 122, 125
  urinary tract obstruction, 1421
Whole-brain radiation therapy (WBRT)
  CUP, 1260
  GTD, 996
  ICP, 1410, 1412
  PCNSL, 1125
  SCLC, 485–486
Wide local excision (WLE), anal cancer, 765–766
Wieand, S., 1586
Wilks, Samuel, 291
Wilms tumor (WT)
  CUP, 1262
  pediatric cancer, 1271, 1276–1277
Wilson, W. H., 213
Wilson disease, HCC, 682–683
Wiskott-Aldrich syndrome
  AHSCT, 398
  AML, 24
  B-NHL, aggressive, 192t
  LYG, 198
De Wit, R., 1088
WLE. *See* Wide local excision
WM. *See* Waldenström macroglobulinemia
Wolff's law, 1539
WT. *See* Wilms tumor

X
Xalkori. *See* Crizotinib
XELOX, CRC, 744, 749
Xiao, H., 1087
Xiao, Z. F., 604
X-linked immunoproliferative disorder
  B-NHL, aggressive, 192t
  LYG, 198
Xofluza. *See* Baloxavir
Xp11.2 translocation carcinoma, 1020
Xu, Y., 1585
XXY syndrome. *See* Klinefelter syndrome

Y
Yalin, Y., 1260
Yamada, R., 688
Yeh, E. T. H., 1441
Ying, Z., 375
Yizhak, K., 1289
Yolk sac tumors, 1090–1091, 1091f
Yuan, Y., 1585

Z
Zaino, R. J., 936
Zajkowska, M., 965
Zaltrap. *See* Ziv-afibercept
Zanamivir (Relenza), 1346t
  influenza, 1354
Zanubrutinib
  MCL, 243
  WM, 336
Zanubrutinib and rituximab (ZR), MCL, 241
Zelboraf. *See* Vemurafenib
Zhang, J., 1288
Zhang, Y., 461
Zheng, Z. H., 580
Zhou, X., 1585
Zidovudine, JC virus, 1357
Zimmermann, C., 1520
Zinzani, P. L., 171
Ziv-afibercept (Zaltrap), 1292t
Zoledronic acid
  bone cancer, MBC, 832
  hypercalcemia, 1426
  hypocalcemia, 1390
  prostate cancer, 1062
Zostavax, 1348
ZR. *See* Zanubrutinib and rituximab
Zydelig. *See* Idelalisib
Zykadia. *See* Ceritinib